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European Journal of Pharmacology 890 (2021) 173717

Contents lists available at ScienceDirect

European Journal of Pharmacology

journal homepage: www.elsevier.com/locate/ejphar

Full length article

# Hydroxychloroquine for the treatment and prophylaxis of COVID-19: The journey so far and the road ahead

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ARTICLE INFO

*Keywords:*
Novel coronavirus
SARS-CoV-2
COVID-19
Hydroxychloroquine
Prophylaxis
Drug safety
QTc prolongation

ABSTRACT

As mortality and morbidity from novel coronavirus disease (COVID-19) continue to mount worldwide, the scientific community as well as public health systems are under immense pressure to contain the pandemic as well as to develop effective medical countermeasures. Meanwhile, desperation has driven prescribers, researchers as well as administrators to recommend and try therapies supported by little or no reliable evidence. Recently, hydroxychloroquine-sulfate (HCQS) has got significant media and political attention for the treatment as well as prophylaxis of COVID-19 despite the lack of convincing and unequivocal data supporting its efficacy and safety in these patients. This has unfortunately, yet foreseeably led to several controversies and confusion among the medical fraternity, the patient community as well as the general public. Based on the available studies, many with high risk of bias, relatively small sample sizes, and abbreviated follow-ups, HCQS is unlikely to be of dramatic benefit in COVID-19 patients and yet has the potential to cause harm, particularly when used in combination with azithromycin or other medications in high risk individuals with comorbidities. Although definitive data from larger well-controlled randomized trials will be forthcoming in the future, and we may be able to identify specific patient subpopulations likely to benefit from hydroxychloroquine, till that time it will be prudent to prescribe it within investigational trial settings with close safety monitoring. Here we review the current evidence and developments related to the use of HCQS in COVID-19 patients and highlight the importance of risk-benefit assessment and rational use of HCQS during this devastating pandemic.

## 1. Introduction

The first case of novel coronavirus disease (COVID-19) caused by betacoronavirus - severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was reported from Wuhan city in the Hubei province of China in late December 2019. By the end of January 2020, World Health Organization (WHO) declared the outbreak as a global health emergency and by March 11, a global pandemic. (Wang et al., 2020). As of August 31, 2020, nearly 25 million cases of COVID-19 have been reported worldwide and more than 800,000 deaths have been recorded (WHO, Coronavirus Disease (COVID-19) Weekly Epidemiological Update, 2020). The primary target of the virus is the lung epithelial cells and the first step of viral infection involves its binding to angiotensin converting enzyme (ACE-2) receptors expressed on the host cells followed by fusion with the cell membrane (Hoffmann et al., 2020). Molecular analysis has demonstrated the involvement of several chemokines and cytokines associated with COVID-19 infection, which include tumour necrosis factor (TNF)-α, interleukin (IL)-6, IL-7, IL-8, IL-9, IL-10, IL-1, granulocyte colony stimulating factor (G-CSF), and interferon (IFN)-γ amongst others. The two most dreaded complications of COVID-19 - acute respiratory distress syndrome (ARDS) and multi-organ failure, are believed to be linked directly to the 'cytokine storm' and are usually associated with a poor prognosis in these patients (Huang et al., 2020). As on date, there is no specific pharmacological treatment or vaccine approved against COVID-19 infection in most parts of the world. According to WHO, it may take considerable time before safe and effective COVID-19 therapeutics or vaccines can be made available for the masses (Sohrabi et al., 2020). Currently, the cornerstone of management in these patients is symptomatic supportive treatment along with anti-inflammatory therapies including corticosteroids and few other investigational agents available through compassionate use and expanded access programs (Management of COVID-19,

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https://doi.org/10.1016/j.ejphar.2020.173717
Received 2 July 2020; Received in revised form 29 October 2020; Accepted 30 October 2020
Available online 3 November 2020

2020).

Use of broad-spectrum antiviral drugs like neuraminidase inhibitors, ribonucleic acid (RNA) synthesis inhibitors, nucleoside analogues, and human immunodeficiency virus (HIV)-protease inhibitors could possibly play a key role in the management of affected patients, although the current evidence base supporting their use is rather weak (Lu, 2020). Furthermore, a number of drugs have received emergency use authorization or are in pipeline such as – remdesivir, galidesivir, lopinavir/ritonavir combination, favipiravir, and several vaccines in both preclinical as well as early and late phase clinical trials (Pang et al., 2020). Recently, experimental use of hydroxychloroquine sulfate (HCQS) for treatment as well as prophylaxis of COVID-19 has led to several controversies and confusion among the medical fraternity as well as the lay public, often fuelled by political statements (Lowe, 2020; President's Tweet, 2020). In this review, we critically examine the current evidence and developments related to the usage of HCQS in COVID-19, controversies surrounding its use for prevention and treatment, and highlight the importance of rational use of HCQS to ensure its benefits outweigh the associated risks. A global timeline of significant developments related to the deployment of HCQS for the management of COVID-19 is outlined in Table 1.

For this study, an open search for pertinent publications was conducted through google search and MEDLINE using keywords like "hydroxychloroquine sulfate", "hydroxychloroquine", "chloroquine", "COVID-19", "SARS-CoV-2", "coronavirus", "2019-nCoV", "acute respiratory distress syndrome", and with their corresponding MeSH terms, if any, connected by OR, AND Boolean operators, wherever applicable. No search filters were applied. In addition, we used the snowball technique to gather further relevant papers from the reference lists of the initial search result articles.

### 1.1. Hydroxychloroquine: role in COVID-19 disease

Hydroxychloroquine sulfate is a chloroquine analogue, commonly used for malaria, rheumatoid arthritis (RA), and systemic lupus erythematosus (SLE). It possesses myriad anti-inflammatory and immunomodulatory properties, including inhibition of cytokine (IL-1 and IL-6) production, inhibition of phospholipase A2 and matrix metalloproteinases, and modulation of B and T cell function (Ben-Zvi et al., 2012). The potential role of HCQS against SARS-CoV-2 could be due to its ability to increase lysosomal pH, which modulates the cellular metabolism of iron, thereby decreasing its intracellular concentration, which in turn inactivates glycosyltransferases and glycosylating enzymes, further suppressing glycosylation of SARS-coronaviruses (Al-Bari, 2017; Vincent et al., 2005). Even though HCQS has been advocated as a potentially promising therapeutic option early in the course of the current pandemic, to date, we have limited clinical data to support its use for COVID-19 management (Yao et al., 2020). Even as low cost and easy availability of HCQS makes it a viable therapeutic intervention for COVID-19 patients, especially in low and middle-income countries (LMIC) settings, the molecular mechanisms underlying the protective effects of HCQS in COVID-19 remain to be fully elucidated (Gautret et al., 2020a; Singh et al., 2020).

Few in-vitro studies have evaluated the potential activity of HCQS and chloroquine in COVID-19 infections. A study conducted by Liu et al. investigated the antiviral effects of HCQS and chloroquine against SARS-CoV-2 and concluded that both the drugs showed similar cytotoxic concentration ($CC_{50}$) values (Liu et al., 2020). For certain multiplicities of infection, HCQS activity against SARS-CoV-2 was found to be less potent than that of chloroquine. Another study conducted by Yao et al. evaluated the antiviral activity of chloroquine and HCQS on Vero cells infected with novel coronavirus. They found that HCQS with a half maximal effective concentration ($EC_{50}$) of 0.7 μM was significantly more potent in inhibiting the virus as compared to chloroquine, whose $EC_{50}$ was 5.5 μM (Yao et al., 2020). It has been observed that $EC_{50}$ values of HCQS and chloroquine decrease with increasing incubation period.

**Table 1**
Timeline of major worldwide developments related to use of HCQS for the management of COVID-19.

| Date | Event | In text references |
|---|---|---|
| March 9, 2020 | Yao et al., demonstrate the efficacy of HCQS in an invitro study using SARS-CoV-2 infected vero-cells | Yao et al. (2020) |
| March 20, 2020 | First clinical study conducted by Gautret et al. on twenty-two patients concluded that adding azithromycin to HCQS has synergistic effect against SARS-CoV-2 infection | Gautret et al. (2020a) |
| March 21, 2020 | U.S President endorses HCQS by calling it a 'game changer' for COVID-19 treatment | President's Tweet (2020) |
| March 22, 2020 | ICMR recommends the prophylactic use of HCQS for healthcare providers & close contacts of COVID-19 patients | Advisory on the Empiric (2020) |
| March 28, 2020 | FDA allows emergency off-label use of HCQS and CQ for the treatment of seriously ill COVID-19 patients. | Lenzer (2020) |
| March 31, 2020 | Data from first RCT conducted in Wuhan using HCQS against COVID-19 were posted on MedRxiv.org | Chen J et al., (2020) |
| April 3, 2020 | Concerns are raised regarding the conduct and reporting of the study by Gautret et al. and International Society of Anti-microbial Chemotherapy (ISAC) released an official statement sharing their concern. | Joint ISAC and Elsevier Statement on Gautret et al. (2020a) |
| April 3, 2020 | American Thoracic Society suggests the use of HCQS in hospital admitted patients with COVID-19 pneumonia | COVID-19: Interim Guidance (2020) |
| April 11, 2020 | Infectious Disease Society of America (IDSA) recommends the use of HCQS & azithromycin in COVID-19 patients preferably in clinical trial settings. | Infectious Diseases Society of America Guidelines (2020) |
| April 24, 2020 | FDA cautions against the use of HCQS outside the ambit of clinical trials/hospitals due to safety concerns like cardiac arrhythmia | FDA (2020b) |
| May 22, 2020 | Mehra et al. publish a multinational registry analysis involving 96,000 patients and conclude that no beneficial effect of HCQS was observed with or without azithromycin in COVID-19. Treatment was associated with reduced survival and an increased frequency of ventricular arrhythmias. | Mehra et al. (2020a) |
| May 22, 2020 | ICMR expanded the prophylactic use of HCQS for asymptomatic healthcare providers as well as frontline COVID-19 workers. | Revised Advisory (2020) |
| May 25 | WHO suspends the HCQS arm in SOLIDARITY trial in COVID-19 patients following the paper published by Mehra et al. citing need for review of safety concerns | WHO Suspends Hydroxychloroquine Study (2020) |
| June 3, 2020 | Lancet editors express concerns over the questions raised about the validity of the study by Mehra et al. | Editors (2020) |
| June 5, 2020 | Lancet retracts the paper by Mehra et al. following authors' request. | Mehra et al. (2020b) |
| June 5, 2020 | WHO resumed HCQS arm in the SOLIDARITY trial following an independent review of the interim data | WHO Resumes Study (2020) |
| June 5, 2020 | RECOVERY trial investigators decide to halt enrolment into the HCQS arm based on an unblinded | Statement from the Chief Investigators (2020) |

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**Table 1** (*continued*)

| Date | Event | In text references |
|---|---|---|
| | analysis of the data from treated individuals. | |
| June 15, 2020 | FDA revokes emergency use authorization of HCQS and CQ in COVID-19 as it concludes that the drug is unlikely to be effective and potential risks outweigh the potential benefits. | Coronavirus (COVID-19) Update (2020) |
| June 17, 2020 | WHO announces the stoppage of HCQS arm enrollment in the SOLIDARITY trial following review of available data and concludes that HCQS doesn't reduce COVID-19 related mortality? | WHO Halts Trial (2020) |

**Abbreviations:** HCQS-Hydroxychloroquine, CQ-Chloroquine, SARS-CoV-2- severe acute respiratory syndrome coronavirus 2, COVID-19- Coronavirus disease 2019, FDA- Food and Drug Administration, ICMR-Indian Council of Medical Research, WHO-World Health Organization, RCT-Randomized controlled trial.

Since HCQS and chloroquine tend to get accumulated in tissues, there is a possibility that a longer incubation period may lead to increased intracellular drug concentrations resulting in augmented antiviral effects (Duvvuri and Krise, 2005; W. Wang et al., 2020).

## 2. Evidence from clinical studies: hope vs. hype

Currently, there is lack of unequivocal and convincing clinical data in support of using HCQS in the management of COVID-19 patients. Several studies published so far have been criticized for their methodology, small sample sizes, poorly defined outcomes, and lack of randomization, amongst other design flaws (Table 2).

The first clinical study which attracted the attention of clinicians, researchers, patients as well as health authorities was an open label non-randomized clinical trial conducted by Gautret et al. (2020a). They concluded that adding azithromycin to HCQS has a synergistic effect against SARS-CoV-2 infection as the combination significantly decreased the respiratory viral load. In this study, twenty-two patients were diagnosed with upper respiratory tract infections, eight patients with lower respiratory tract infections, and six patients were asymptomatic. Interestingly, the study demonstrated the efficacy of HCQS in reducing the viral load after 3–6 days of treatment. However, two patients also experienced failure of HCQS therapy in their investigation. The study raised the hopes of various stakeholders, however, few weeks later, it led to significant controversies related to its methodology and concerns regarding inclusion criteria amongst others (Molina et al., 2020; Retraction Watch, 2020). Consequently the journal instituted an additional independent peer review to clarify these concerns as per publisher policies and standards of the Committee on Publication Ethics (COPE) (Joint ISAC and Elsevier statement on Gautret et al, 2020; Gautret et al., 2020a; Statement on IJAA, 2020; Gautret et al., 2020b). In a randomized prospective pilot study reported by Chen J et al., 30 patients diagnosed with COVID-19 were included, and the efficacy and safety of HCQS were evaluated. Patients were randomized to either HCQS 400 mg once daily for five days in addition to conventional treatment or conventional treatment alone. On day 7, no significant difference was found in throat swabs negative patients in HCQS (86.7%) vs. control group (93.3%). In addition, no statistical difference was observed in the median time taken from hospitalization to virus nucleic acid negativity between the two study groups (HCQS group – 4 days; Control group – 2 days). Even temperature normalization and radiological progression were comparable. No significant benefit of using HCQS in COVID-19 was demonstrated in this study and the authors concluded that adequately powered studies are required to conclusively determine the efficacy of HCQS in the management of COVID-19 patients (Chen J et al., 2020).

In another randomized trial conducted by Chen Z et al., among 62 patients suffering from COVID-19, 31 were randomized to receive an additional five days therapy with HCQS 400 mg per day. All the study participants received the standard therapy consisting of oxygen, antimicrobial agents, and immunoglobulins, with or without glucocorticoids. The authors found that time to clinical recovery, temperature recovery, and remission of cough were significantly improved in patients receiving HCQS and also a greater number of these patients demonstrated improvement in pneumonia (81%) as compared to controls (55%). They concluded that HCQS could significantly shorten clinical recovery times and improve pneumonia in COVID-19 patients (Chen Z et al., 2020). Evidently, this randomized study had a better sample size as compared to the above two studies and a well-defined control group and inclusion criteria. However, the data are yet to be published after having undergone a rigorous peer review and the manuscript is currently available as a preprint version. Since this article is reporting a yet to be evaluated, new medical research, the results cannot be conclusively applied to clinical practice as yet.

In an another observational study done in France by Gautret et al., the efficacy of HCQS and azithromycin combination was evaluated in eighty patients diagnosed with COVID-19. The authors reported a substantial reduction in the viral load - 83% of the patients showed negative results on quantitative polymerase chain reaction (qPCR) on day 7 and 93% on day 8. They also reported that respiratory sample viral cultures were negative in nearly 98% of the patients on the fifth day, which helped patients to be discharged earlier (Gautret et al., 2020b). This data may be encouraging, but this study suffered from lack of a control group. Also, the early discharge and negative test status of the patients would depend on their individual baseline immune status, which has not been accounted for or adjusted for in the study results. The observational nature of the study, small sample size, and loosely defined inclusion and exclusion criteria are some of the major limitations of this study.

In a study by Million et al., data pertaining to 1061 patients diagnosed with COVID-19, who were treated with HCQS plus azithromycin for at least 3 days at IHU Méditerranée Infection, Marseille, France, were reported. The authors found improved clinical outcomes and virologic cure in 92% of the patients within ten days of hospitalization. A poor outcome was reported only in 4.3% of the patients, and mortality was reported in less than 1% of the patients. They did not report any cardiotoxicity among these patients, and poor clinical outcome was related to older age, disease severity and low hydroxychloroquine concentrations. Limitations of the study were the lack of control group as well as incomplete data for some patients, including computed tomography scans and serum HCQS levels (Million et al., 2020).

In a multicentric network cohort and self-controlled case series reported by Lane et al. nearly 310,000 users of HCQS and sulfasalazine, 323,000 users of HCQS and azithromycin, and 352,000 users of HCQS and amoxicillin were included. The authors did not find any increased risk of serious adverse events with 30-day HCQS versus sulfasalazine use. On the other hand, HCQS-azithromycin was associated with an excess risk of 30-day cardiovascular mortality, congestive cardiac failure and angina when compared to users of HCQS and amoxicillin. The authors concluded that while short-term therapy with HCQS is safe, azithromycin addition may lead to significant cardiovascular morbidity and mortality, possibly due to synergistic effects on QT interval, and hence a cautious approach is warranted (Lane et al., 2020). These data discourage the concomitant use of HCQS and azithromycin and are contrary to those of studies reported by Gautret et al., 2020a, 2020b. However, this study was not been done on actual COVID-19 patients; rather the safety data have been extrapolated given the potential use of HCQS and azithromycin in these patients.

A small study enrolling eleven COVID-19 patients assessed clinical and virological outcomes in individuals who received hydroxychloroquine and azithromycin. Within five days of treatment initiation, two patients were transferred to intensive care units (ICU), one reported prolongation of QT interval and one died. Repeat nasal swabs were still

**Table 2**
**Efficacy of HCQS in COVID-19: Evidence from earliest and major clinical studies.**

| Study Interventions | Study design | Drug regimens and/or doses | Results | Study limitations | Authors |
|---|---|---|---|---|---|
| HCQS -AZ or HCQS alone or None (control group) | Open-label, non- randomized study. The primary endpoint was virological clearance at day-6 post-inclusion. (N = 42) | 26 patients received HCQS 600 mg/day (of them 6 patients received HCQS-AZ), 16 patients were in the control group | At day 6 post-inclusion, 100% of patients treated with HCQS-AZ combination were virologically cured as compared to 57% treated with HCQS only, and 12.5% in the control group (P < 0.001) | Small sample size, no intention to treat analysis, other methodological issues. | Gautret et al. |
| HCQS in addition to conventional treatment or Conventional treatment alone | A randomized controlled study. The primary endpoint was negative conversion rate of COVID-19 nucleic acid in respiratory pharyngeal swab on days 7 after randomization. (N = 30) | Patients were randomized in 1:1 ratio to either HCQS 400 mg once daily for 5 days, or conventional treatment alone. | On day 7, no significant difference was found in throat swabs negative patients (87% cases in HCQS group and 93% cases in the control group, in the median duration from hospitalization test negative conservation, temperature normalization and radiological progression (P > 0.05). | Small sample size, full text in Chinese only | Chen J et al. |
| HCQS in addition to standard treatment or Standard treatment alone | A randomized controlled study. The primary outcome was time to clinical recovery and clinical characteristics of patients evaluated 5 days after HCQS administration. (N = 62) | Patients were randomized in1:1 ratio to receive either standard treatment or an additional 5 days therapy with HCQS 400 mg per day. | For TTCR, body temperature recovery time and the cough remission time were significantly abbreviated in the HCQS group and also a greater number of patients had improved pneumonia in the HCQS treatment group (81% vs. 55%). | Small sample size, not peer reviewed yet | Chen Z et al. |
| HCQS-AZ | Open label observational study. The main outcome measures were contagiousness as assessed by PCR and culture, and length of stay in the infectious disease ward. (N = 80) | A combination of 200 mg of oral HCQS, three times a day for ten days combined with AZ (500 mg on day 1 followed by 250 mg per day for 4 days) | There was a significant reduction in the viral load (83% patients showed negative results on qPCR at day 7, and 93% on day 8). Also, the virus cultures from patient respiratory samples were negative in 97.5% patients at Day 5 which helped patients to be discharged earlier with a mean length of hospital stay of five days. | Lack of control group, small sample size, not peer reviewed yet, other methodological issues. | Gautret et al. |
| HCQS-AZ | Retrospective observational study. Outcomes were death, clinical worsening – transfer to ICU, and hospitalization for more than 10 days) and viral shedding persistence (N = 1061) | The study cohort was treated with HCQS – 200 mg thrice a day for 10 days combined with AZ – 500 mg on day 1 followed by 250 mg daily for next 4 days | A good clinical outcome and virological cure was seen in 92% patients within 10 days. A poor outcome was reported only in 4% of patients and mortality was reported only in 0.75% of patients. Prolonged viral carriage was observed in 4% patients. | Observational nature of the study, absence of control group, complete data was not available for all participants. | Million et al. |
| HCQS -AZ or HCQS and sulfasalazine or HCQS and amoxicillin | Multinational, network cohort and self-controlled case series study to assess the safety of HCQS vs sulfasalazine and to evaluate the risk of add-on AZ as compared to amoxicillin among RA patients using HCQS. As a secondary analysis, self-controlled case series was used to analyse the safety of HCQS in the larger populations, including those with non-RA indications. (N = 956,374 HCQ and 310,350 sulfasalazine users) | 956,374 users of HCQS and 310,350 users of sulfasalazine, 323,122 users of HCQS -AZ and 351,956 users of HCQS and amoxicillin were included. | Short term HCQS treatment is safe and no excess risk of serious adverse events was identified. The results were confirmed in self-controlled case series. When AZ was added to HCQS, an increased risk for cardiovascular mortality, angina and heart failure was observed. Excess mortality could be likely attributed to synergism for QT prolongation. | The study is not done on actual COVID-19 patients, rather the data is extrapolated from other users with respect to safety in view of the potential use of HCQS alone or with AZ in COVID-19 patients. Risk for misclassification, lower HCQS doses in RA patients, not peer reviewed yet. | Lane et al. |
| HCQS | Observational study assessing post-exposure prophylaxis (PEP) using HCQS for COVID-19. (N = 211) | HCQS 400 mg daily until the completion of 14 days of quarantine. | PEP was completed in 97% patients and 95.5% health care workers. No serious adverse events were reported. Follow-up PCR tests were all negative at the end of 14 days. | Lack of control group; relatively higher doses used for prophylaxis | Lee et al. |
| HCQS in addition to SOC or SOC alone (control group) | Multicentre, open-label, randomized controlled trial done in 16 designated COVID-19 treatment centres in China. The primary endpoint was the | 75 patients were assigned to each study group. HCQS was administrated at a loading dose of 1200 mg daily for three days followed by a maintenance dose of 800 mg daily; Total | The overall negative conversion rate was not significantly different between the two groups. No significance difference was seen in 28-day symptoms improvement rate. | Open label study, concomitant medications in nearly 60% patients, groups were unbalanced in terms of baseline symptoms. | Tang et al. |

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**Table 2** (*continued*)

| Study Interventions | Study design | Drug regimens and/or doses | Results | Study limitations | Authors |
|---|---|---|---|---|---|
| | 28-day negative conversion rate of novel coronavirus-2. | duration for mild/moderate cases-2 weeks, severe cases- 3 weeks. | Adverse events were reported in 9% of SOC and 30% of HCQS group patients with two serious adverse events. | | |
| HCQS in addition to SOC or HCQS-AZ in addition to SOC or No HCQS; SOC alone | A retrospective data analysis from patients hospitalized with COVID-19 in US veteran health administration centres. The primary outcomes were death and the need for mechanical ventilation. (N = 807) | Patients were categorized into 3 groups: HCQS, n = 198; HCQS-AZ, n = 214; no HCQS, n = 395). | Rates of death in the HCQS, HCQS-AZ, and no HCQS groups were 19%, 23% and 9% respectively. Rates of ventilation in the HCQS, HCQS-AZ, and no HCQS groups were 19%, 20%, 20%, respectively. Compared to the no HCQS group, the risk of death was higher in the HCQS group (P = 0.009) but not in the HCQS-AZ group (P = 0.28). The risk of ventilation was similar in the HCQS and HCQS-AZ groups as compared to the no HCQS group. | Retrospective observational study, limited sample size, preponderance of male participants, non-randomization of treatments. | Magagnoli et al. |
| HCQS or No HCQS | Data collected during routine clinical care of COVID-19 patients in 4 French hospitals; Primary endpoint was survival without transfer to ICU at day 21 (N = 181) | 84 patients received HCQS 600 mg/day within 48 h of admission while 97 patients did not receive HCQS initially. | In the weighted analysis, survival without ICU transfer was recorded in 76% patients receiving HCQS vs 75% in the control group (HR-0.9, 95% CI 0.4–2.1). Overall survival at day 21 was 89% and 91% in the two groups, respectively. 10% patients in the HCQS reported ECG changes warranting HCQS discontinuation | Non-random treatment assignments, groups were unbalanced in terms of several prognostic variables, no power calculations, not peer reviewed yet. | Mahévas et al. |
| HCQS alone or Azithromycin alone or HCQS plus azithromycin or Neither drug | Retrospective multicentre cohort study that evaluated the effects of HCQS, AZ or their combination on COVID-19 clinical outcomes. Primary outcome was in hospital mortality (N = 1438) | HCQS doses ranged from 200 to 600 mg while for azithromycin the range was from 200 to 500 mg. For few patients the doses were unknown.<br>HCQS, n = 271; AZ, n = 211, HCQS-AZ, n = 735; neither drug, n = 221 | The adjusted HR for mortality was 1.08 for HCQS, 0.56 for AZ, and 1.35 for HCQS plus AZ group, none of the differences being significant. Cardiac arrest was more likely in individuals who received the combination therapy (adjusted OR 2.13, 95% CI 1.12,4.05). | Observational study design, mortality data limited only to in-hospital deaths, lack of definitive temporal association between adverse events and drug intake, residual confounders, and some underpowered study analyses. | Rosenberg et al. |
| HCQS or No HCQS | Observational study. Primary endpoint was a composite of intubation or death in a time to event analysis. (N = 1446) | N = 811 received HCQS in a dose of 600 mg twice on day 1 and then 400 mg daily for a median of 5 days and rest of the participants did not receive it. | No significant association was detected between HCQS use and intubation or death (HR, 1.04, 95% CI, 0.82 to 1.32). HCQS administration did not lead to either a greatly lowered or an increased risk of the intubation or death. | Observational study design, residual confounding, some missing data and potential for inaccuracies in the electronic health records. | Geleris et al. |
| HCQS **or** Placebo | Double-blind, placebo-controlled RCT. The primary outcome was the incidence of either laboratory-confirmed Covid-19 or illness compatible with Covid-19 within 14 days. Adult individuals who were either household or occupational close contacts of confirmed Covid-19 patients were enrolled. (N = 821) | HCQS dose was 800 mg once, followed by 600 mg in 6–8 h, then 600 mg daily for 4 additional days.<br>HCQS, n = 414, Placebo, n = 407 | 11 subjects in HCQS arm (2.7%) and 9 in placebo arm (2.2%) had laboratory confirmed COVID-19 (P = 0.82). No significant difference was found in the occurrence of COVID-19 compatible new illness; HCQS (11.8%) *vs.* placebo (14.3%), (P = 0.35). HCQS led to more adverse effects (40.1% vs. 16.8%), with no serious adverse effects as compared to placebo. | Use of a priori symptomatic case definition instead of universal laboratory confirmation; data were obtained by means of participant reports, and greater proportion of younger populations. | Boulware et al. |
| HCQS alone or HCQS + AZ or AZ alone or Neither of the two | Multicentric retrospective observational study. The primary outcome for this study was in mortality among hospitalized COVID-19 patients (N = 2541) | HCQS: 400 mg twice daily on day 1, followed by 200 mg twice daily from days 2–5. Azithromycin: 500 mg once daily on day 1 followed by 250 mg once daily for the next 4 days.<br>HCQS, n = 1202<br>HCQS + AZ, n = 783,<br>AZ, n = 147,<br>Neither, n = 409 | The overall mortality in this study was 18%; Mortality in the four study groups was found to be 13.5% (HCQS), 20% (HCQS + AZ), 22% (AZ) and 26% (Neither) (P < 0.001). There was a 66% (P < 0.001) mortality hazard ratio reduction in the HCQS group and 71% reduction in HCQS plus AZ group (P < 0.001). No episodes of torsades de pointes were recorded. | Retrospective, non-randomized, unblinded study design. Information on duration of COVID-19 symptoms prior to hospital admission was unavailable. Greater use of steroids in patients receiving HCQS | Arshad et al. |
| | Multicentric, randomized, open label, controlled clinical trial | HCQS was given in a dose of 400 mg twice daily for 7 days | The proportional odds of having a worse score on the 7 | Open label study; protocol deviations with respect to | Cavalcanti et al. |

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**Table 2** (*continued*)

| Study Interventions | Study design | Drug regimens and/or doses | Results | Study limitations | Authors |
|---|---|---|---|---|---|
| SOC alone or SOC + HCQS or SOC + HCQS + AZ | involving mild to moderate Covid-19 patients. The primary outcome was clinical status assessed using seven point ordinal scale at day 15 (N = 665) | while AZ was dosed at 500 mg once daily for 7 days. HCQS, n = 221 HCQS + AZ, n = 217 SOC alone, n = 227 | point ordinal scale on day 15 were not affected by study treatments (P = 1.00). Prolongation of QT interval and elevation of liver enzymes was more commonly reported in the HCQS alone and in combination therapy group as compared to the SOC alone group. | medication adherence, prior use of HCQS as well as AZ among trial participants; inclusion of patients upto 14 days after the onset of symptoms. | |
| HCQS or Placebo | Multicentric randomized, double-blind, placebo-controlled trial conducted in non-hospitalized adults with early COVID-19. The primary outcome was the change in overall symptom severity over 2 weeks. (N = 423) | HCQS: 800 mg once, followed by 600 mg in 6–8 h, thereafter 600 mg once daily for 4 days. HCQS, n = 212 Placebo, n = 211 | Change in overall symptom severity did not differ between the study groups over 2 weeks - absolute difference was −0.27 [95% CI, −0.61 to 0.07]; P = 0.117). Adverse effects occurred in 43% of HCQS recipients vs. 22% of those receiving placebo (P < 0.001). No difference was observed in the hospitalization rates between the study groups (P = 0.29) | Only 58% patients underwent PCR testing for COVID-19, | Skipper et al. |
| **HCQS or No antiviral therapy** | Multicentric, open label, randomized controlled trial in non-hospitalized adult COVID-19 patients with symptom duration of less than five days. Study outcomes were the reduction in viral RNA loads up to 7 days after initiation of treatment and time to symptom resolution. (N = 293) | HCQS: 800 mg on day 1, followed by 400 mg once daily for 6 days HCQS, n = 136 No antiviral therapy, n = 157 | No significant differences in the mean reduction in viral loads was found between the two study groups at day 3 or 7. HCQS did not reduce the risk for hospitalization or lead to early resolution of symptoms. | Open label design, fewer patients were analysed at day 7 for viral positivity; concomitant use of cobicistat-boosted darunavir in some patients; more than 4/5th of participants were healthcare workers | Mitjà et al. |

**Abbreviations:** HCQS-Hydroxychloroquine, HCWs- Healthcare workers AZ- Azithromycin, COVID-19- Coronavirus disease 2019, TTCR- Time to clinical recovery, PCR- Polymerase chain reaction, RA- Rheumatoid arthritis, ICU- Intensive care unit, PEP-Post exposure prophylaxis, SOC- Standard of care, QT - QT interval, ECG-Electrocardiogram, RR-Relative risk.

positive in 80% of the patients at day 5 and 6 post-initiation of treatment. The authors concluded that they could not replicate the previously reported antiviral effects and clinical benefits of this combination in severe COVID-19 patients (Molina et al., 2020).

HCQS has also been utilized for post-exposure prophylaxis against COVID-19 in a Korean study. This study conducted in a long term care hospital involved 211 participants, including 189 patients and 22 hospital workers. Post-exposure prophylaxis with HCQS 400 mg/day for 14 days was completed by more than 95% of the participants. Interestingly both the baseline as well as 14-day follow-up PCR tests for COVID-19 were negative in all individuals and none of the patients reported any serious adverse event during the study. The study did not have a control group, while 92 other hospital workers including clinicians and nurses who did not receive HCQS also tested negative at the end of the 14-day period. The choice of the dose also seems to be arbitrary and high, especially when compared to the approved dosage for malaria prophylaxis that is 400 mg per week (Lee et al., 2020).

Tang et al. conducted a randomized controlled trial to evaluate the effects of adding HCQS to standard care in 150 mild to moderate laboratory confirmed COVID-19 patients at 16 treatment centres across China. HCQS was administered as a loading dose of 1.2 g mg per day for 3 days, followed by 0.8 g per day for 2–3 weeks depending upon disease severity. The authors did not find a significant difference in the probability of SARS-CoV-2 negative conversion in HCQS group vs. standard care alone at 4 weeks (85.4% vs 81.3%). Thirty percent of the patients in the HCQS group reported adverse events, mostly gastrointestinal, versus 9% in the control group. The main limitations of this study were open label design and failure to achieve the predetermined sample size of 360 patients due to a rapid decline in the number of eligible participants following the control of outbreak (Tang et al., 2020).

In a retrospective analysis of 807 COVID-19 patients admitted to US Veterans Health Administration (VA) medical centres, comparisons were drawn between patients not receiving HCQS (n = 395), receiving HCQS alone (n = 198) or in combination with azithromycin (HCQS + AZ, n = 214). The mortality rates found were 19%, 23%, and 9% (P < 0.001) among patients who received HCQS alone, HCQS plus AZ, and no HCQS respectively. In contrast, the mechanical ventilation rates in the three study groups were 19%, 21%, and 20% respectively (P = 0.94). After propensity score adjustments, the authors found a significantly higher risk of mortality from any cause in the HCQS group as compared to non-users (adjusted hazard ratio (aHR) 1.8, 95%confidence interval (CI): 1.2–2.9, P = 0.009) but not in the combination therapy group (aHR 1.3, 95% CI 0.8–2.15, P = 0.28). The risk of ventilation as well as death after mechanical ventilation was comparable in the three study groups. Thus there was no significant reduction in the deaths or in the requirement for mechanical ventilation with HCQS±azithromycin treatment. Besides methodologic limitations such as retrospective analyses and non-randomized treatment allocations, the study results may have been biased by residual confounding and the use of codes for identification of patient characteristics and outcomes. Moreover, being a veteran study, there was a considerably high proportion of males (>95%) among the participants (Magagnoli et al., 2020). Mahevas et al. collected data from routine care of 181 COVID-19 patients requiring oxygen across four French hospitals. While eighty-four of them received HCQS 600 mg daily within 48 h of admission, 97 did not receive HCQS, and the patients were assessed for primary outcome of survival without intensive care unit transfer at 21 days of inclusion. A weighted analysis was done, and no significant difference was found for the primary outcome (76% in HCQS vs. 75% in non-HCQS group, weighted HR-0.9, 95% CI-0.4–2.1). The two groups were comparable in terms of overall survival as well as survival without acute respiratory distress syndrome at 21 days. Eight patients in the HCQS group were found to have electrocardiogram (ECG) changes requiring treatment discontinuation. Thus, their study results failed to support the use of HCQS for improving

outcomes in COVID-19 patients who require oxygen support. Although authors reported the use of robust statistical methods for adjustment, residual confounding could have biased the study results and four crucial prognostic variables-confusion at admission, liver cirrhosis, heart failure, and chronic kidney disease, could not be balanced in their propensity score model. The study did not include a power analysis and centre effect was not taken in the propensity score model (Mahévas et al., 2020).

In a retrospective cohort study including 1438 patients admitted across twenty-five hospitals, Rosenberg et al. found the adjusted HR for mortality to be 1.08 for HCQS alone, 0.56 for azithromycin alone, and 1.35 for HCQS plus azithromycin group as compared to treatment with neither agent, none of the values being statistically significant. Cardiac arrest, however, was more likely to occur in individuals who received the combination therapy (adjusted odds ratio (OR) 2.13, 95% CI 1.12–4.05). The authors concluded that treatment with any of three experimental regimens failed to improve mortality in COVID-19 patients. The main limitations of this observational study were mortality data limited only to in-hospital deaths, possible lack of temporal association of adverse events with drug intake, unmeasured residual confounders, and lack of power for some of the study analyses (Rosenberg et al., 2020).

In an observational study done by Geleris et al., more than 1400 COVID-19 patients were enrolled and the effect of HCQS administration on the risk of intubation or mortality was examined. The outcomes were compared among patients who were given HCQS (n = 811) at a dose of 600 mg twice on day 1 followed by 400 mg per day for a median period of 5 days vs. those who were not administered HCQS (n = 565). Out of 1376 patients (rest died or excluded), 811 received HCQS. The study authors did not find any significant relationship between HCQS use and intubation or mortality (HR-1.04, 95% CI-0.8, 1.3), and they concluded that HCQS administration did not lead to either a significantly higher or lower risk of death or intubation. The authors confirmed these results in multiple sensitivity analyses, although some degree of unmeasured confounding cannot be ruled out. Other limitations of this study include the involvement of single study centre, some missing data, as well as reliance on electronic health records (Geleris et al., 2020).

A double-blind, placebo-controlled randomized trial by Boulware et al. evaluated the role of HCQS in post-exposure prophylaxis (PEP) of COVID-19 with the primary outcome as the occurrence of COVID-19 within two weeks -either confirmed by laboratory testing or as a new compatible illness. Adult participants who were either household or occupational close contacts of diagnosed Covid-19 patients were enrolled in this trial. Individuals were randomized to receive either placebo (n = 407) or HCQS (n = 414) in a dose of 800 mg, followed by 600 mg within 6–8 h, followed by 600 mg per day for four more doses. Eleven subjects in the HCQS arm (2.7%) and 9 in the placebo arm (2.2%) developed lab-confirmed COVID-19 (P = 0.82) The study groups also did not differ in terms of new symptoms compatible with a diagnosis of COVID-19 (11.8% in HCQS vs. 14.3% in the placebo group). However, adverse events were reported in 40% of the subjects receiving HCQS compared to 17% in the placebo group. The study, although a randomized controlled trial, had some limitations such as use of symptomatic case definition for COVID-19, greater involvement of younger, healthier participants, and reliance on data from participant reporting (Boulware et al., 2020). A case-control study based on telephonic interviews with healthcare workers registered in the Indian Council of Medical Research (ICMR) data portal was reported by Chatterjee et al. The study enrolled 378 cases and 373 controls. The investigators collected data on the use of personal protective equipment (PPE), contact with suspected/confirmed COVID-19 patients on ventilators, involvement in aerosol generating procedures, and history of HCQS intake along with dosing details. The authors concluded that consumption of four or more HCQS doses had a protective effect (adjusted OR 0.44, 95% CI 0.22, 0.88) and the use of PPE such as masks, caps, gloves, and gowns was associated with reduced odds of novel coronavirus infection in healthcare workers. Notable limitations included an observational case-control study design, potential for recall bias, and failure to attain the desired sample size (Chatterjee et al., 2020).

Mehra et al. performed a multinational registry analysis of HCQS or chloroquine use with or without a macrolide in COVID-19 diagnosed patients. The study included more than 96,000 patients and concluded that the beneficial effects of these drugs in COVID-19, alone or in combination regimens, cannot be confirmed. The drugs were associated with reduced survival as well as increased incidence of cardiac arrhythmias. However, the article was later retracted when serious concerns were raised regarding the source, veracity, and analysis of data conducted by Surgisphere corporation, and the independent reviewers were unable to verify the primary data sources due to potential violation of confidentiality agreements with the clients (Editors, 2020; Mehra et al., 2020a; Mehra et al., 2020b).

More recent studies have demonstrated similar trends with observational studies reporting positive results while randomized controlled trials failing to replicate those significant benefits in COVID-19 patients. Arshad et al. conducted a multicentric retrospective observational study enrolling more than 2500 patients. These individuals were treated with HCQS alone, HCQS plus azithromycin, azithromycin alone, or neither of these agents. The overall mortality in these four study groups was found to be 13.5%, 20%, 22%, and 26%, respectively ($P < 0.001$). In the multivariable Cox regression model, the authors reported a 66% ($P < 0.001$) mortality hazard ratio reduction in the HCQS alone group and a 71% reduction in HCQS plus azithromycin group ($P < 0.001$). No episodes of torsades de pointes were recorded in the study participants (Arshad et al., 2020). A multicentre, randomized, open label trial conducted across 55 hospitals in Brazil randomized 667 adults into three groups – standard care alone, standard care with HCQS, standard care with HCQS plus azithromycin. This study evaluated the role of HCQS and azithromycin in mild to moderate COVID-19. The proportional odds of having a worse score on a 7 point ordinal scale on day 15 were not affected by any of the experimental treatments ($P = 1.00$ for both intervention groups). Moreover, the incidents of QT prolongation and elevation of hepatic enzymes were more commonly reported in the HCQS alone and in the combination therapy group as compared to the control group (Cavalcanti et al., 2020).

Two recently reported randomized controlled studies evaluated the role of HCQS in patients with mild COVID-19. Skipper et al. conducted a double-blind, randomized, placebo-controlled study across US and Canada and included nearly 420 symptomatic, non-hospitalized adults who received either oral hydroxychloroquine or placebo. The primary end point was change in the overall severity of symptoms over two weeks using a ten point visual analogue scale. The study failed to detect a significant improvement in symptom severity ($P = 0.12$). Importantly, the number of patients reporting drug related adverse events were nearly double in the HCQS group (43%) as compared to placebo (22%) ($P < 0.001$). The number of patients undergoing hospitalizations did not differ between the two study groups (Skipper et al., 2020). Mitja et al. conducted a multicentric, open label study in Catalonia to assess whether early intervention with HCQS was effective in reducing the viral RNA load or shortening the time to symptom resolution in patients with mild COVID-19. Their study enrolled 293 patients who were randomized to either of the two study groups: HCQS for one week or no antiviral treatment. They found no statistical differences in the mean reduction in viral loads at day 3 or 7 in the two study groups. HCQS also did not reduce the risk for hospitalization or lead to early resolution of symptoms. No major HCQS related adverse events were recorded in their study (Mitjà et al., 2020).

Current clinical evidence does not seem to be definitive enough to support or refute the use of HCQS for COVID-19 management. Several preprint studies are yet to be peer reviewed and the global investigative efforts are probably not well coordinated. Given the equivocal data on safety as well as efficacy for HCQS especially in combination therapy,

the prevailing benefit-risk dilemma can only be resolved by data derived from further well designed, adequately powered, randomized, and controlled clinical trials. Currently, more than 200 studies involving hydroxychloroquine alone or in combination with other experimental therapies are registered on *clinicaltrials. gov* (Search of: Hydroxychloroquine).

## 3. Response by the governments, healthcare authorities, and scientific community across the globe

Considering the immediate and dire need for safe and effective therapies to combat the ongoing coronavirus disease-2019 pandemic, several developments have taken place across the globe with the bid to safeguard public health. At the outset, several health authorities across the globe had placed significant faith in the role of HCQS as a medical countermeasure against COVID-19, although based on little and equivocal evidence.

The United States Food and Drug Administration (USFDA) had issued an emergency use authorization (EUA) allowing temporary off-label use of HCQS and chloroquine for the managment of seriously ill patients diagnosed with COVID-19 during the pandemic. According to the FDA, these drugs should be employed when enrolment in clinical trials is not possible or available and benefits outweigh the risks of therapy in the opinion of the prescriber. It also required that necessary information regarding known adverse effects and drug interactions related to the use of chloroquine and HCQS in treating COVID-19 should be provided to prescribers as well as patients. However, no guidance on the prophylactic use was given and it only recommended the use of HCQS among serious COVID-19 patients. The healthcare professionals were also expected to report serious adverse events and patient outcomes associated with the use of HCQS and chloroquine in COVID-19 patients (HHS Accepts Donations, 2020; Hinton DM, 2020; Lenzer, 2020).

In April 2020, the FDA issued a safety warning against the use of these medicines outside the ambit of clinical trials or hospitals due to the possible risk of arrhythmias, including prolongation of QT interval and ventricular tachycardias. The agency particularly highlighted a heightened risk in patients using concomitant azithromycin or those with cardiac or renal comorbidity (FDA, 2020b). In an alert issued on June 15, the FDA rescinded the EUA for both the drugs based on the ongoing review of available evidence. The agency determined that HCQS and chloroquine are not likely to be efficacious in treating COVID-19 patients, and the potential benefits of treatment no longer outweigh the attending risks from serious cardiac and other adverse events (Coronavirus (COVID-19) Update, 2020).

World Health Organization (WHO) has also taken the initiative to test the effectiveness and safety of potentially useful therapeutic agents against COVID-19, including HCQS. The international study known as "Solidarity" trial, has been launched by WHO and partners and is a large adaptive clinical study that allows dropping of ineffective therapy arms and including other potentially useful drugs. In this trial, the study subjects are allocated to either standard of care alone group or standard of care plus one out of HCQS, chloroquine, remdesivir, lopinavir/ritonavir or lopinavir/ritonavir plus interferon beta-1a. This multicentric trial aims to identify therapies that can slow down the disease progression or improve survival among affected patients. Given the lack of sufficient evidence presently, WHO has warned physicians, medical authorities as well as the common public likely to be engaged in self-medication, about the risk of using unproven treatments for COVID-19 as this can lead to more harm rather than benefit (WHO, 2020a). In response to the large observational study published by Mehra et al. (Mehra et al., 2020a), WHO suspended the HCQS arm of the Solidarity trial (WHO Suspends Hydroxychloroquine Study, 2020). However, following the review of the trial mortality data, the data safety and monitoring committee recommended the continuation of all treatment groups, including the resumption of the HCQS arm (WHO Resumes Study, 2020). Subsequently, on June 17th, WHO announced the stoppage of HCQS arms of the trial based on the review of data from the study itself, the Recovery trial, and a Cochrane review of the available evidence. The agency concluded that HCQS treatment does not lead to reduction in mortality in COVID-19 inpatients (WHO Halts Trial, 2020).

American Thoracic Society led task force in their empiric guidance related to COVID-19 management, suggested the use of HCQS and chloroquine in hospitalized patients with evidence of pneumonia on a case-by-case basis (COVID-19: Interim Guidance, 2020). They also recommended that the condition of the patients should be sufficiently severe to warrant the use of investigational therapy. Nearly three-fourths of the experts agreed on this. However, only 18% and 8% of the experts respectively agreed to the use of HCQS in COVID-19 outpatients and for hospitalized COVID-19 patients without pneumonia, respectively. The guidelines formulated by the Infectious Disease Society of America (IDSA) recommended using HCQS and Azithromycin in COVID-19 patients, preferably in the context of a clinical trial. This was deemed to meet the overarching goal of devising evidence-based treatment recommendations and careful monitoring of the safety and efficacy of HCQS therapy. In situations where the conduct of clinical trials was not feasible, the guidelines recommended alternate methods of data collection such as local or collaborative prospective outcome registries (Infectious Diseases Society of America Guidelines, 2020).

The Indian Council of Medical Research was one of the first medical councils worldwide that issued the recommendation of deploying HCQS prophylaxis among health care providers and close contacts involved in the care of COVID-19 or suspected patients ("Advisory on the Empiric", 2020). Given the absence of any conclusive evidence, the ICMR also warned against the misuse of the drug by the lay public. The advisory was expanded in late May to include asymptomatic healthcare workers deployed in non-COVID areas and hospitals, asymptomatic frontline personnel such as those involved in surveillance, police, and paramilitary services as groups eligible for HCQS chemoprophylaxis (Revised Advisory, 2020). To avoid the misuse of HCQS, likely hoarding by the general public, and possible toxicity concerns, Indian government included HCQS in Schedule H1 of the Drugs and Cosmetics Rules, 1945 with the aim to regulate and restrict the sale and distribution of HCQS and its preparations (Ministry of Health and Family Welfare, 2020).

RECOVERY (Randomized Evaluation of COVID-19 Therapy) trial is one of the largest randomized clinical trials designed to evaluate various experimental treatments for COVID-19 including: HCQS, azithromycin, dexamethasone, lopinavir-ritonavir, tocilizumab, and convalescent plasma. Recently, the investigator team for this study decided to halt enrolment into the HCQS arm of the trial based on an unblinded analysis of the data from HCQS treated individuals. They analysed data from 1542 subjects who received HCQS and compared it with 3132 recipients of usual care alone. They failed to detect any significant effect of HCQS treatment on the primary end point of 28-day mortality (26% vs. 24% in usual care group; HR 1.1, 95% C.I, 0.9–1.3; P = 0.10). HCQS was also not able to demonstrate any beneficial effect on the duration of hospital stay or associated outcomes. The trialists were convinced of the lack of mortality benefit of HCQS in COVID-19 patients (Statement from the Chief Investigators, 2020).

### 3.1. Concerns regarding toxicity, controversies, and rational use of HCQS

So far, HCQS has not been conclusively shown to be safe and effective for the treatment or prophylaxis of COVID-19. However, amidst the speculation regarding its beneficial role based mainly on *in vitro* and patchy clinical data, its use amongst diagnosed or suspected patients is expected to cause potential safety concerns, some of which are already well known from the previous experience with this drug.

Use of HCQS in people with glucose-6-phosphate dehydrogenase (G6PD) deficiency is linked to an increased risk of haemolytic anaemia. Therefore, screening of G6PD deficiency is crucial before administering HCQS (Mohammad et al., 2018). It is possible that in this pandemic situation, it will be difficult to obtain a detailed history of all patients

and there is a significant concern of misuse of HCQS as self-medication among lay public, especially in developing countries where the drug sales and availability are loosely regulated. Such scenarios can lead to increased incidence of haemolysis in individuals at risk, thus causing harm rather than any significant benefit. National Institute for the Infectious Diseases – Italy has recommended the evaluation of G6PD deficiency in patients before administering HCQS in its guidelines for the management of patients with COVID-19 (Nicastri et al., 2020).

Cardiac toxicity is a serious concern with HCQS. It can result in cardiomyopathy leading to heart failure, which could be fatal in some cases and the drug should be discontinued if such symptoms develop. It can also lead to conduction defects like bundle branch block or atrioventricular heart block and biventricular hypertrophy (Chatre et al., 2018; Hydroxychloroquine, 2020; Plaquenil®,). Its use has been associated with QT prolongation, raising concerns of fatal ventricular arrhythmias. The risk of cardiotoxicity increases significantly when HCQS is used in combination with other cardiotoxic drugs. Concurrent use of HCQS and azithromycin can lead to QT prolongation and ventricular arrythmias, and therefore, these drugs should be cautiously used, and close clinical monitoring is required Drug Interactions Checker, 2020 (Drug Interactions Checker, n.d.). In such situations, ECG assessments should be done at baseline and regularly during treatment with HCQS. When consumed in unsupervised situations, for example self-medication for prophylaxis of COVID-19, the possibility of widespread harm cannot be ruled out.

Chorin et al. reported changes in the corrected QT interval (QTc) interval based on chart reviews of 84 COVID-19 patients treated with HCQS-Azithromycin combination. Maximum prolongation of QTc interval was observed at a mean of 3.6 days post initiation of therapy with a maximal average value of 463 ±32 millisec. Notably, 11% of their patients had severe QTc interval prolongation of more than 500 millisec (Chorin et al., 2020). Routine examination of ECG has been recommended to rule out the incidence of QT interval prolongation or bradycardia. Along with this, it has also been recommended to avoid the concurrent use of drugs that cause QT interval prolongation such as - macrolides, quinolones, anti-psychotic, anti-arrhythmic and anti-depressants (Multicenter Collaboration Group, 2020). Notably, a parallel group, randomized, double-blind Brazilian study where 81 hospitalized COVID-19 were receiving either low dose (total dose 2.7 g) or high dose (total dose 12 g) chloroquine in addition to oseltamivir and azithromycin, was recently stopped due to safety concerns in the higher dose group. Greater incidence of corrected QT interval by Fridericia's method (QTcF) > 500 ms (19%) and deaths (39%) were reported in high dose chloroquine group as compared to lower dosage arm (11% and 15% respectively), leading to immediate termination of recruitment in the high dose arm (Borba et al., 2020). In a cohort of 90 COVID-19 patients, over a 4-week study period, nearly 25% patients treated with HCQS alone or with azithromycin had either significant QTc prolongation or delta QTc of 60 ms or more (Mercuro et al., 2020).

Apart from cardiac side effects, HCQS can also lead to retinal toxicity and sometimes irreversible retinal damage can occur in patients who receive high doses of HCQS, especially for prolonged periods. A thorough discussion regarding possible ocular toxicity of HCQS with prospective recipients is must before commencing treatment within this agent (Hydroxychloroquine, 2020; Plaquenil®,).

HCQS is also known to cause hypoglycaemia that can lead to loss of consciousness and can be dangerous in diabetic individuals treated with or without antidiabetic drugs (Hydroxychloroquine, 2020; Plaquenil®,). Treating clinicians must take a thorough history of COVID-19 patients and discuss the risks of hypoglycaemia and ways to avoid such situations. Many geriatric patients with COVID-19 may have diabetes as comorbidity, which itself is a risk factor for severe disease and increased mortality among COVID-19 patients (Jordan et al., 2020). Thus, the uninformed use of HCQS can further complicate the clinical situation in these patients.

Other adverse reactions include hematologic effects like neutropenia, hypersensitivity reactions, dermatologic adverse effects, and hepatotoxicity, amongst others (Makin et al., 1994; Murphy and Carmichael, 2001). Possible immune suppression effects, along with neutropenia can be dangerous in those who are likely to take HCQS for prophylaxis against COVID-19 (FDA, 2020b). Since healthcare providers and close contacts of COVID-19 patients are at an increased risk of contracting the infection, use of HCQS at this time can potentially suppress their immunity and increase their susceptibility to COVID-19 infection. Unsupervised use of HCQS for COVID-19 may also lead to an increased incidence of allergic reactions including anaphylaxis in vulnerable subjects (Hydroxychloroquine, 2020;Plaquenil®,). Recently FDA has also warned against a possible drug interaction between HCQS and remdesivir – the antiviral drug that has received emergency use authorization for the treatment of adult as well as paediatric COVID-19 patients. In vitro studies have shown that HCQS might interfere with the metabolic activation and hence the antiviral activity of remdesivir leading to reduction of its efficacy (FDA, 2020a).

Hydroxychloroquine use for its labelled indications – malaria, SLE, and RA is well known and for SLE it is one of the most effective therapies. The drug offers several advantages including effective management of joint pains and rashes, reducing flare ups, organ damage, osteoporosis and thrombotic events, sparing glucocorticoids use, and prolonging life expectancy in these patients. Given the current hype around HCQS being one of the promising therapies against COVID-19, acute shortages are already being experienced by both prescribers as well as patients who are prescribed HCQS for its labelled indications. This is a rather unfortunate and unprecedented situation where off label drug use is depriving such users of a low cost, efficacious and well tolerated therapy (Jakhar and Kaur, 2020; Yazdany and Kim, 2020). Widespread use of HCQS for COVID-19 prophylaxis, could also lead to a false sense of security among users who, in turn might neglect proven effective measures including social distancing and hand and respiratory hygiene. This might lead to more harm than benefit for the individuals as well as for the society at large.

In an editorial by Ferner and Aronson, it was highlighted that it is premature and potentially harmful to use HCQS and chloroquine in COVID-19 patients. They stressed more on the need for treatments or vaccines targeting specific structures in the virus rather than relying solely on older repurposed medicines. Despite the promise shown in laboratory studies, these drugs lack supporting data for their clinical use, and thus eventually may lead to more harm than good (Ferner and Aronson, 2020).

## 4. Conclusions

Hydroxychloroquine has received significant attention from clinical experts, politicians, media as well as the lay public ever since the pandemic flared up in most parts of the world and reports of its efficacy in *in vitro* experiments and early observational studies were published. Although the initial findings were mostly positive, these studies had several methodological flaws and were subject to numerous biases and confounders. They employed diverse dosing regimens, outcomes assessed were variable, and many of them lacked comparative control groups. In contrast, the accumulating evidence from randomized controlled trials has failed to maintain this hype. Given the lack of clinical meaningful reduction in mortality based on evaluation of interim data, several large multicentric clinical trials have been either terminated or have stopped further recruitment of participants in the HCQS arms of the study. In addition, emergency use authorization for HCQS has been withdrawn, highlighting the lack of unequivocal benefit and risk of toxicity especially in unsupervised settings. A survey of *clinicaltrials. gov* registry reveals several ongoing studies that continue to investigate the role of HCQS in the treatment as well as prophylaxis of COVID-19. The emerging data from high quality clinical studies are expected to further shape our understanding, and these may identify relevant subgroup(s) that might benefit from the use of HCQS. Till that

time, it will be prudent to administer HCQS to COVID-19 patients as per national, regional, or local treatment guidelines; however, strictly under investigational settings followed by close monitoring of patients.

It should be ensured that the use of HCQS for the purpose of treatment and research related to COVID-19 must not hamper its availability for patients with SLE and rheumatic diseases. Restricting unnecessary and unreasonable hoarding of HCQS by the masses will likely require intervention by the regulatory authorities, especially in the developing countries, besides vigilant monitoring for off label drug use as well as drug safety. In addition, active efforts are warranted to educate the public, patients as well as healthcare providers to avoid the irrational use of HCQS and the likely health hazards due to its clinically important adverse effects.

## Funding sources

None.

## CRediT authorship contribution statement

**Harmanjit Singh:** Conceptualization, Methodology, Writing - original draft, preparation, Investigation. **Prerna Chauhan:** Data curation, Investigation, Writing - review & editing. **Ashish Kumar Kakkar:** Conceptualization, Methodology, Investigation, Writing - review & editing, Supervision.

## Declaration of competing interest

None, for all authors.

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