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# A SYSTEMATIC REVIEW OF TREATMENT OUTCOME OF ANTIMALARIAL DRUGS AGAINST SARS-COV-2

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## ABSTRACT

**Objective:** The pandemic of the coronavirus disease (COVID-19) has become a public health emergency of international concern. There is no effectual drug at this time, although there is a dire need for an effective treatment against severe COVID-19. The purpose of this systematic review was to summarize the evidence regarding chloroquine (CQ)/hydroxychloroquine (HCQ) for COVID-19 treatment. **Methods:** We searched EMBASE, PubMed and three trial Registries for studies on the use of CQ/HCQ against COVID-19. **Results:** We included 12 articles (two narrative letters, two in-vitro studies, three editorial, two expert consensus paper, two national guideline documents, one complete study) and 41 ongoing clinical trials worldwide. CQ/HCQ seems to be effective in limiting the replication of SARS-CoV-2 (the virus causing COVID-19) in vitro. **Conclusions:** Even though the safety of CQ/HCQ has been established in clinical practice and there is also sufficient pre-clinical rationale and evidence for its effective use in other conditions that validate clinical research on CQ/HCQ against COVID-19. Moreover, the recent results of the trials are also not in favor of HCQ use against covid-19. However, clinical use against COVID-19 should either adhere to the MEURI framework or only after ethical approval after clinical trials as specified by WHO. The current situation holds an urgently needed safety data from high-quality clinical trials.

**KEYWORDS:** SARS-CoV-2, COVID-19, Chloroquine, Hydroxychloroquine, Pneumonia, Coronavirus.

## Abbreviations

COVID-19, coronavirus disease; CQ, chloroquine; HCQ, hydroxychloroquine; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; MEURI, Monitored Emergency Use of Unregistered Interventions; WHO, World Health Organization; MERS-CoV, Middle East Respiratory Syndrome related coronavirus; BID, twice per day; RCT, Randomized controlled trial; pts, patients; ICU, intensive care unit.

## 1. INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causing coronavirus disease (COVID-19), has spread rapidly around the globe with approximately 11,500,302 reported cases including at least 535,759 deaths reported across at least 180 countries by July 7, 2020.[1] It was declared as a global pandemic by the World Health Organization on March 11, 2020.[2] With the rapidly increasing number of positive cases and deaths, it has become a public health emergency of international concern. There is a dire need for effective treatments against severe COVID-19.[3] As of this time, there is no known specific, effective and proven pharmacological treatment. In-vitro studies have suggested that CQ/HCQ is effective against viral infections, including the SARS-associated coronavirus (CoV) and Middle East Respiratory Syndrome related

coronavirus (MERS-CoV).[4],[5] HCQ is an analog of CQ with more solubility and has less toxicity than CQ.[6]

CQ/HCQ has been used worldwide against antiprotozoal infections, and it is part of the World Health Organization (WHO) model list of essential medicines. It is also inexpensive and has a clinical safety profile.[5] However, the efficacy and safety of CQ/HCQ for treatment of SARS-CoV-2 (the new virus causing COVID-19) pneumonia is still uncertain.

## 2. METHODS

We performed a systematic review of the EMBASE and PubMed databases from inception to 25-March-2020 to find articles providing information on the efficacy and safety of CQ/HCQ and its related formulation in patients with SARS-CoV-2 pneumonia and articles relating in-vitro studies. Language restrictions were not imposed (see detailed search strategy in supplement 1). We expanded the search using a snowballing method and applied it to the references of published papers. We also searched the Chinese Clinical Trial Registry, Clinicatrial.gov, and the International Clinical Trials Registry Platform (WHO, ICTRP) to find ongoing trials. Three authors independently screened the databases and the trial registries and extracted relevant information. Doubts and incongruities about the relevance of the sources were solved by consensus with three more authors. We did not register the systematic review protocol because we expected the very limited available data and evidence on the topic and due to the urgency of the matter.

## 3. RESULTS

The initial search identified 87 sources (56 from PubMed, 29 EMBASE and 2 from other sources). We evaluated 21 articles in the full text following the screening of titles and abstracts. We also removed duplicates. Among these, we found 12 relevant articles (two narrative letter, two research letter, three editorial, two expert consensus paper, two national guideline documents, one completed study).[5-16] 21 trials were found in the clinical trial registries (Table 1). CQ/HCQ seems to be effective in limiting the replication of SARS-CoV-2 (the virus causing COVID-19) in vitro.

**Table 1: Characteristics of clinical trials studying CQ/HCQ or related formulation in patients with new coronavirus, pneumonia (COVID-19).**

| ID | Recruiting status | Population (n) | Intervention Groups (s) | Comparison groups | Primary outcome |
|---|---|---|---|---|---|
| ChiCTR2000030054 | Pending approval | Mild and common COVID-19 pneumonia(n = 100) | Hydroxychloroquine sulfate<br>Chloroquine phosphate | Standard treatment | Clinical recovery time |
| ChiCTR2000030031 | Recruiting | Mild and common COVID-19 pneumonia (n = 120) | Chloroquine phosphate | Placebo | Time of conversion to be negative of novel coronavirus |
| ChiCTR2000029992 | Pending approval | Severe COVID-19 pneumonia (n = 100) | Chloroquine phosphate<br>Hydroxychloroquine sulfate | Standard treatment | Clinical recovery time; Changes in viral load of upper and lower respiratory tract samples compared with the baseline |
| ChiCTR2000029988 | Recruiting | Severe COVID-19 pneumonia (n = 80) | Chloroquine phosphate | Standard treatment | Time to clinical recovery |
| ChiCTR2000029975 | Pending approval | COVID-19 pneumonia (n = 10) | Chloroquine phosphate | No comparison group | Viral negative-transforming time; 30-day cause-specific mortality; Co-infections; Time from severe and critical patients to clinical improvement |
| ChiCTR2000029939 | Recruiting | COVID-19 pneumonia (n = 100) | Chloroquine phosphate | No comparison group | Length of hospital stay |
| ChiCTR2000029935 | Recruiting | COVID-19 pneumonia (n = 100) | Chloroquine phosphate | No comparison group | Length of hospital stay |
| ChiCTR2000029899 | Recruiting | Mild and Common COVID-19 pneumonia (n = 100) | Hydroxychloroquine | Phosphate chloroquine | Time to Clinical Recovery |
| ChiCTR2000029898 | Recruiting | Severe COVID-19 pneumonia (n = 100) | Hydroxychloroquine: | Phosphate chloroquine | Time to Clinical Improvement |
| ChiCTR2000029868 | Recruiting | COVID-19 pneumonia (n = 200) | Hydroxychloroquine sulfate | Standard treatment | Viral nucleic acid test |
| ChiCTR2000029837 | Pending approval | Mild and common COVID-19 | Chloroquine phosphate | Placebo | Negative conversion rate of COVID-19 nucleic acid |

| | | | | | |
|---|---|---|---|---|---|
| | | pneumonia (n = 120) | | | |
| ChiCTR2000029826 | Pending approval | Critically ill COVID-19 pneumonia (n = 45) | Chloroquine phosphate | Placebo | Mortality rate |
| ChiCTR2000029803 | Pending approval | COVID-19 pneumonia(n = 320) | Hydroxychloroquine, small dose; Group A2: Hydroxychloroquine, high dose | Group B1: Abidol hydrochloride low dose; Group B2: Abidol hydrochloride high dose | Progression to suspected or confirmed disease |
| ChiCTR2000029762 | Recruiting | COVID-19 pneumonia (n = 60) | Hydroxychloroquine tablet | Standard treatment | Negative conversion rate of COVID-19 nucleic acid; |
| ChiCTR2000029761 | Recruiting | Common COVID-19 pneumonia (n = 240) | Low-dose hydroxychloroquine; Medium-dose hydroxychloroquine; High-dose hydroxychloroquine | Standard treatment | Negative conversion rate of COVID-19 nucleic acid; |
| ChiCTR2000029741 | Recruiting | Mild and common COVID-19 pneumonia (n = 112) | Chloroquine phosphate | Lopinavir/Ritonavir | All-cause mortality; length of stay; oxygen index during treatment; blood cell count; inflammation serum factors; coagulation indicators |
| ChiCTR2000029740 | Recruiting | COVID-19 pneumonia (n = 78) | Hydroxychloroquine 0.2 g BID | Standard treatment | Negative conversion rate of COVID-19 nucleic acid; prognosis; oxygen index; respiratory rate; lung radiography; |
| ChiCTR2000029609 | Pending approval | COVID-19 pneumonia (n = 205) | Mild-moderate Chloroquine group: oral Chloroquine phosphate; Mild-moderate combination group: Chloroquine phosphate plus Lopinavir/ritonavir; Severe Chloroquine group: oral Chloroquine phosphate | Mild-moderate Lopinavir/Ritonavir group: oral Lopinavir/Ritonavir; Severe Lopinavir/Ritonavir group: oral Lopinavir/ritonavir | Negative conversion rate of COVID-19 nucleic acid |
| ChiCTR2000029559 | Recruiting | COVID-19 pneumonia (n = 300) | Group 1: Hydroxychloroquine 0.1 g oral BID; Group 2: Hydroxychloroquine 0.2 g oral BID | Placebo control group: Starch pill oral BID | Negative conversion rate of COVID-19 nucleic acid; T cell recovery time |
| ChiCTR2000029542 | Recruiting | COVID-19 pneumonia (n = 20) | Oral chloroquine | Standard treatment | Negative conversion rate of COVID-19 nucleic acid; 30-day cause specific mortality |
| NCT04307693 | Recruiting | (SARS-CoV-2) (n=150) | Lopinavir/ritonavir Hydroxychloroquine | No intervention | Viral load |

For data entry, we used the definitions and the information provided by the investigators in the trial registries, if available. The number of patients in the Population columns refers to the reported sample size. ; BID: twice per day; in the 'Primary outcomes column' we reported only the primary outcomes, as described by the investigators.

## 4. DISCUSSION

The role of HCQ in reducing the viral load in COVID-19 patients was reported by a study done in France where 42 patients of age >12 years with Polymerase Chain Reaction (PCR) documented SARS-COV-2 carriage in the nasopharyngeal sample were included, with 26 patients receiving HCQ and 16 patients being placed in the control group. Six patients in the HCQ group received Azithromycin as well. 70% of HCQ treated patients were virologically cured vs 12.5% in the control group (p=0.001) at day 6 post inclusion while 100% patients treated with HCQ plus Azithromycin were virologically cured vs 57.1% in patients receiving HCQ alone. The limitations of this study were small sample

size, limited follow-up duration and dropout of 6 patients from the study.[7]

A group of Chinese researchers studied the effect of CQ in vitro in a research letter. They used Vero E6 cells infected by SARS-CoV-2 at a multiplicity of infection (MOI) of 0.05. The study showed that CQ was found to be highly effective in reducing viral replication, with an Effective Concentration $(EC)_{90}$ of 6.90 μM that can be easily achievable with standard dosing, due to its favorable penetration in the lung.[8] The authors described that immunomodulant effect of the drug and its ability to block virus infection by increasing endosomal pH and by interfering with the glycosylation of cellular receptors of SARS-CoV, may enhance the antiviral effect in vivo.[8] Though chloroquine (CQ)/HCQ has shown in vitro antiviral effects, it did not show efficacy in inhibiting viral replication in a mouse SARS-CoV model. Since the pathogenesis of COVID-19 is still not fully understood, they point out that the immune effects of CQ/HCQ administration in these patients are unpredictable and hence CQ/HCQ may be harmful, if not just useless when administered to these patients.[9]

An editorial was written by French researchers highlighted the in-vitro efficacy of CQ in other viral infections, especially SARS. They also conferred the possibly favorable risk-benefit balance, the high safety, and the low cost of such treatment in the context of the current COVID-19 outbreak.[5] HCQ has been proven to have much less (~40%) toxic effects based on animal study. Liu et al reported that HCQ can efficiently inhibit SARS-Cov2 infection in vitro. It also has anti-inflammatory effects which can be useful to treat COVID-19 patients where cytokine storm has been reported to be associated with disease severity.[6] HCQ is also more soluble and has toxicity than CQ and has additional effects of downregulating the expression of TLRs (Toll-like Receptors) and decreases the IL-6 production. A safe dose of HCQ is 6.5mg/kg of ideal body weight and 5mg/kg of actual body weight.[6] Since cases were reported in 180 countries so, the low cost of CQ/HCQ is a major benefit for both the highly stressed healthcare systems of involved developed countries and the underfunded healthcare system of underdeveloped counties.[10]

An expert consensus was published on 20th February by a multi-center collaboration group of the Department of Science and Technology of Guangdong Province specifically related to the use of chloroquine phosphate.[11] No information was provided on the method used to achieve consensus. Based on in vitro evidence and still unpublished clinical experience, it is recommended the use of chloroquine phosphate tablet, at a dose of 500 mg twice per day for 10 days, for patients with mild, moderate and severe cases of SARS-CoV-2 pneumonia, provided that there were no contraindications to the drug. Diarrhea and vomiting are the most common adverse effects of these two drugs. Long term exposure to CQ can result in retinopathy, bull's eye maculopathy and cardiomyopathy. It is also recommended to use several precautions, including complete blood testing to rule out the serum electrolyte disturbances, hepatic and renal function dysfunction and/or development of anemia, thrombocytopenia or leukopenia along with They also routine electrocardiography and patient interviews to seek the appearance of visual and/or mental disturbance/deterioration.[11-13]

The Dutch Center of Disease Control (CDC), in a public document, suggested the use of CQ in ICU patients with COVID-19.[14] However, the document also described that treating patients only with appropriate supportive care is still a reasonable option, due to lack of supportive evidence. The suggested regimen in adults consists of 600 mg of CQ base (6 tablets A-CQ 100 mg) followed by 300 mg after 12 hours on day 1, then 300 mg ×2 on 2–5 days. After that treatment should be stopped to reduce the risk of side effects.[14] Another guideline recommends the use of CQ 500 mg × 2/die or HCQ 200 mg die for 10 days, although the treatment may vary from 5 to 20 days depending on clinical severity. The suggested target population ranged from patients with mild respiratory symptoms and comorbidities to patients with severe respiratory failure.[15] Based on in-vitro study, Yao et al. reported that an oral loading dose of 400mg twice daily of HCQ followed by a maintenance dose of 200mg twice daily for 4 days for SARS-COV-2 infection. Also, a longer incubation period may provide more time for the drug to accumulate intracellularly resulting in better antiviral effects in such patients with a longer incubation period.[16]

Our search also identified ongoing 21 trials worldwide (Table 1). The trial registrations varied in quality of the reported information. These trials also varied in study structure, the severity of the disease in the target population and in dosing and duration of the treatment. That so many such studies are in parallel, suggests that the scientific research community is making a huge effort to explain this question, but this effort is probably insufficiently coordinated. In support of this observation, Authorities have recently issued a directive to regulate and coordinate clinical trials studying potential pharmacological treatments for COVID-19.[17] The results of these trials will be the first accessible on humans since studies published to date on the features and management of patients with COVID-19 did not provide any information about CQ/HCQ use [[3],[18-21]

The vivacious ethical issue is whether administration of CQ/HCQ in the setting of COVID-19 is experimental, and therefore needs ethical trial approval, or off-label (i.e. ethically justifiable as the best available treatment). Additional information on CQ/HCQ will soon be released in the context of the evolving outbreak. Timely release of this data can be of importance due to the growing number of diseased patients, and the absence of

licensed specific drugs. Meanwhile, the recommendations for "Clinical management of SARS-COVID-19 when novel coronavirus (2019-nCoV) infection is suspected", published by the WHO, approve that there is currently no evidence from RCTs to inform on specific drug treatment of COVID-19 and those unlicensed treatments should be used only in the context of ethically-approved clinical trials or the Monitored Emergency Use of Unregistered Interventions Framework (MEURI), under strict monitoring.[22] The WHO, therefore, seems to view CQ/HCQ as experimental. The authors tend to agree with this perspective. But even off-label use of CQ/HCQ may be accompanied by several concerns; the first is patient safety. Such use should be accompanied by close monitoring. A pandemic is hardly the ideal setting to do this. The ethical approach to off-label drug use also differs between countries, raising questions regarding fairness. Finally, CQ/HCQ remains an essential drug in the treatment of Malaria in many places in the world. Off label drug use can create major drug shortages.[23]

## 5. CONCLUSION

Even though the safety of CQ/HCQ has been established from long time use in clinical practice for other indications and there is also sufficient pre-clinical rationale and evidence for its effective use for the treatment of COVID-19. However, recent data does not favor the use of antimalarial drugs against COVID-19. A wide range of data is needed to determine the efficacy of antimalarial drugs against COVID-19. However, its use for COVID-19 may be supported by expert opinion, use of this drug to treat COVID-19 patients should adhere to MEURI framework or only after ethical approval as a trial as stated by WHO. The current situation holds an urgent need for data from high quality, coordinated, clinical trials related to its efficacy and safety from worldwide.

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