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Expert Opinion

Is it worth the wait? Should Chloroquine or Hydroxychloroquine be allowed for immediate use in CoViD-19?

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ABSTRACT

The growing CoViD-19 pandemic and the number of deaths is becoming a big concern across the world. There is a need for an immediate therapeutic solution to prevent the spread of the disease further and prevent the number of CoViD-19 associated deaths across the world. The healthcare professionals and the public at large are asking questions about the evidence surrounding the use of chloroquine (CQ) and hydroxychloroquine (HCQ) in the prevention and management of CoViD-19. Both CQ and HCQ had been recently used clinically across the world to treat severe pneumonia associated with COViD-19 however the evidence is very weak due to the lack of randomised clinical trials and misinterpretation of clinical evidence by the non-scientific community. This article critically reviewed the clinical and scientific evidence around the use of CQ and HCQ in CoViD-19 available so far and highlighted the issues concerning the safety and toxicity of CQ/HCQ if permitted for general use by the public. Due to lack of evidence around CQ/HCQ in preventing the CoViD-19, its potential risk of fatal cardiac arrhythmia, and great risk of self-use and harm in developing world, it is recommended that use of CQ/HCQ should only be initiated by specialist clinician dealing with CoViD-19 outbreak to treat CoViD-19 associated pneumonia under close cardiac monitoring.

INTRODUCTION

In December 2019, a novel coronavirus, identified as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has caused an outbreak of the novel coronavirus disease 2019 (CoViD-19), starting in Wuhan, China and spreading quickly to the rest of China and to more than 190 countries worldwide. As of 30 March 2020, more than 700,000 confirmed cases of CoViD-19, including more than 30,000 deaths, had been reported worldwide (CSSEE, 2020). Europe and the US have since replaced China to be the epicentre of the disease with several countries observed rapidly growing CoViD-19 cases, including Italy, Spain, and Germany (CSSEE, 2020).

Currently, clinical management of CoViD-19 involves only supportive care, including supplementary oxygen and mechanical ventilatory support when indicated, along with strict infection prevention and control measures (WHO, 2020). The use of antimicrobials is also common in clinical practice for severely ill CoViD-19 patients for prophylaxis and treatment of secondary infections of the respiratory tract. There is an urgent need to identify safe and effective treatment to curb the disease among symptomatic patients and to limit the transmission of the disease by decreasing viral load among asymptomatic carriers. A range of drugs including various protease inhibitors (remdesivir, lopinavir, ritonavir) (Cao et al., 2020; Martinez, 2020) and novel IL-6 receptor antibody (sarilumab) (Clinical Trials 2020a) have been under investigation to treat critically ill CoViD-19 patients. Remdesivir, despite showing good clinical efficacy in trials on CoViD-19 patients, is a new drug candidate and will require significant safety and efficacy trials before it can be made available in time for the current outbreak to the public at large. Recently, on 25th March 2010, the FDA also approved convalescent plasma from CoViD-19 recovered patients as a source of antibodies for investigational use to treat CoViD-19 patients under

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21 CFR 312 (FDA, 2020a). The convalescent plasma has already been trialled in China in critically ill CoViD-19 patients with acute respiratory distress syndrome. Shen et al., (2020) recently reported that transfusion of plasma containing antibodies (neutralisation titre>40) successfully neutralised the SARS-CoV-2 in five critically ill patients. Nevertheless, the availability of enough 'healthy' donors to obtain the therapeutically effective antibody titre in time will be difficult to deal with the current scale of this global pandemic. In this connection, repositioning of existing drugs such as antimalarials (chloroquine and hydroxychloroquine) has also been investigated in clinical trials. These antimalarials are promising candidates for CoViD-19 due to their costs, availability and proven safety.

Use of chloroquine and hydroxychloroquine in CoViD-19

Chloroquine (CQ) and hydroxychloroquine (HCQ), which has long been indicated for the chemoprophylaxis and treatment of malaria and as a disease-modifying antirheumatic drug for rheumatoid diseases, has a history of being safe and well-tolerated at typical doses (Ruiz-Irastorza et la., 2020). The antiviral effects of CQ/HCQ were investigated after the first SARS-CoV infection recognising the lack of therapeutic management. The antiviral mechanism of CQ/HCQ involves interfering with the glycosylation of angiotensin-converting enzyme (ACE) 2, thereby reducing the binding efficiency between ACE2 on the host cells and the spike protein on the surface of the coronavirus (Zhou et al., 2020). Besides, CQ/HCQ could also increase the pH of endosomes and lysosomes, and thus prevent the fusion of the coronavirus with host cells and its subsequent replication since endosomes serve as the cellular entry mechanism of coronavirus (Vincent et al., 2005). It is also hypothesised that CQ may prevent the virus entry into host cells by inhibiting clathrin-mediated endocytosis of SARS-CoV-2 (Hu et al., 2020). In addition to the direct antiviral effects, CQ/HCQ due to their weak basic nature, may accumulate in acidic compartments of inflamed lung tissues of severely ill CoViD-19 patients and potentially help in reducing inflammation of CoViD-19 associated pneumonia, which is primarily responsible for the CoViD-19 associated deaths (Schrezenmeier & Dörner, 2020).

CQ & HCQ have also been known to possess *in vitro* antiviral activity against coronaviruses (Biot et al., 2006; Vincent et al., 2005). Specifically, both drugs have demonstrated *in vitro* antiviral activity against SARS-CoV-2 (Liu et al., 2020; Wang et al., 2020; Yao et al., 2020). In the recent SARS-CoV-2 outbreak, therefore, HCQ & CQ attracted the attention of clinicians to trial in severely ill CoViD-19 patients. In addition, pharmacological modelling based on observed drug concentrations and *in vitro* drug testing suggests that prophylaxis with HCQ at approved doses could prevent SARS-CoV-2 infection and reduce viral shedding (Tett et al., 1989; Yao et al., 2020). The first report of clinical use of chloroquine in the treatment of CoViD-19 associated pneumonia in China was reported by Gao et al., (2020). Cortegiani and colleagues systemically reviewed the currently available evidence of CQ in the treatment of CoViD-19 and reported that 23 clinical trials involving the administration of chloroquine in the setting of CoViD-19 are ongoing in China (Cortegiani et al., 2020). The detailed results of these studies have not been published yet, however; it has been reported that data from at least 100 patients exhibited a superior response of CQ/CHQ than control in inhibiting the exacerbation of pneumonia. This has led to the inclusion of CQ/CHQ in the federal guidelines for the 'Prevention, Diagnosis, and Treatment of Pneumonia Caused by CoViD-19' by the National Health Commission of the People's Republic of China CoViD-19 in the People's Republic of China (Gao et al., 2020).

For HCQ, encouraging results have been observed in a preliminary trial in France involving thirty-six patients with CoViD-19 (Gautret et al., 2020). Among the patients in this trial, six were asymptomatic, twenty-two demonstrated symptoms of upper respiratory tract infections, while eight presented with symptoms of lower respiratory tract infections. Twenty patients were being treated with HCQ with a daily dose of 600 mg. At 6th day post-therapy, the virus was no longer detectable in 70% of the samples taken from patients who were treated with hydroxychloroquine. Noteworthily, six of the twenty patients in the hydroxychloroquine arm also received azithromycin (AZT) and they appeared to have more rapid eradication of the virus as compared to the monotherapy. In contrast, only 12.5% of patients who did not receive the hydroxychloroquine treatment had cleared the virus in the same timeframe. The synergistic effect between HCQ and AZ is interesting and attracted the attention of various clinicians across the world dealing with CoViD-19 crises. The exact mechanism behind the synergism is not yet known, however, it may be attributed to the secondary bacterial lower respiratory tract infections among patients with CoViD-19. These results are preliminary, and thus should be taken with caution due to a small number of CoViD-19 subjects treated with HCQ (n=14), and even smaller (n=6) in the combination intervention group (HCQ+AZT); as well as potential selection biases due to the open-label, non-random nature of the study. At least four randomized controlled trials (Trial identifiers:

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(NCT04307693, NCT04261517, NCT04304053 and NCT04321616) to evaluate the efficacy of HCQ as a potential treatment for CoViD-19 have recently been started including a multicentre Solidarity trial from WHO (Clinical Trials 2020b-e). HCQ & CQ have also been recently listed under potential therapeutic options for the clinician treating CoViD-19 patients by the United States Centre for Disease Control and Prevention (CDC 2020). FDA has also issued an Emergency Use Authorisation for CQ/HCQ for the treatment of CoViD-19 when administered by healthcare provider pursuant to a valid prescription of a licensed practitioner provided that clinical trials are not available or participation of such a patient into a trial is not feasible (FDA, 2020b).

Impact of (social) media on CQ/HCQ supply and use

The recent reports associated with efficacy and clinical effectiveness of HCQ/CQ in CoViD-19 patients have attracted press and public attention and led to an 'excitement' leading to a shortage of supply of both drugs. There have also been deaths reported in Nigeria attributed to inappropriate self-use of CQ by the public (Soto, 2020). Therefore, before more evidence becomes available, we have to warn that the enthusiasm for general use in prevention and treatment of CoViD-19 is premature and should be prohibited, due to severe concerns about drug-misuse and unnecessary hoarding of HCQ/CQ by the public who do not have an immediate need for the treatment (Bebinger, 2020). As of 20 March 2020, four manufacturers of HCQ in the United States are already facing shortages of this drug following the United States government's plea to expedite the approval of HCQ as a potential treatment of CoViD-19 (ASHSP 2020). The shortage of CQ/HCQ in other countries is also inevitable although it has not been reported officially. Unnecessary hoarding of hydroxychloroquine will not only cause problems with drug supply to treat severely ill CoViD-19 patients if approved but would also affect patients needing regular supply for treating rheumatoid arthritis and the demand for the prophylaxis and treatment of malaria (Lecrubier, 2020).

Safety issues concerning the use of CQ/HCQ

While CQ/HCQ has a good safety record, it is not devoid of side effects. Vision-threatening toxic retinopathy is one of the severe adverse effects associated with CQ/HCQ use (Yusuf et al., 2017). It has been hypothesized that CQ/HCQ binds to melanin in the retinal pigment epithelium, thereby damaging the overlying photoreceptors and subsequently leads to permanent vision loss (Rosenbaum et al., 2016). The risk of retinopathy is increased with long term therapy, and since CoViD-19 pandemic is likely to persist, there will be a greater potential for CQ/HCQ-related retinopathy (Wolfe & Marmor, 2010). Moreover, the drug also requires a close cardiac monitoring while treating CoViD-19 associated pneumonia due to its ability to prolong QTc interval, which may lead to fatal arrhythmia and torsade de points (Costedoat et al., 2007; McGhie et al., 2018). This risk can be further augmented if CoViD-19 patients were also receiving antibiotics such as azithromycin in preventing or treating secondary bacterial respiratory tract infections. Moreover, the poor selectivity index of HCQ during *in vitro* studies also warrant large cohort studies to assure HCQ/CQ safety and efficacy in humans (Yao et al., 2020). Recently on 25th March 2020, the government of United Kingdom also issued a warning that 'CQ/HCQ is not licensed in the UK to treat CoViD-19 related symptoms or prevent infection' and advised that 'until we have clear and definitive evidence that these treatments are safe and effective for the prevention/treatment of CoViD-19, they should only be used for this purpose within a clinical trial' (GOV.UK, 2020).

CONCLUSION

We appreciate the effort of clinicians across the world dealing with severe medical emergencies associated with CoViD-19, the urgent call for therapeutic options and a public outcry for a 'magic bullet' to prevent and cure the infection. However, care should be taken to avoid exaggerating the preliminary safety/efficacy evidence of CQ/HCQ treatment in prevention and treatment of CoViD-19 as it can lead to potential self-harm. An unnecessary hoarding of the drug by the public is also possible due to undue publicity in the press and social media. We, therefore, urge for the responsible dispensing of CQ/HCQ by pharmacists across the world and strictly follow the prescription-only restrictions in respective jurisdictions as the law prohibits the over the counter supply of these drugs in most of the countries. While laws in some countries do permit the over-the-counter supply of CQ/HCQ in pharmacies, it is the duty of pharmacists and other healthcare professionals to monitor the proper usage of these antimalarial drugs. As the evidence currently stands, the CQ/HCQ use cannot be generalised for all CoViD-19 positive cases and its use should be restricted for the treatment of CoViD-19 associated pneumonia in severely ill patients only under clinical supervision of a licensed practitioner and close cardiac monitoring.

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Key points and recommendations for CQ/HCQ use in CoViD-19

- There is no evidence to support the mass use of CQ/HCQ to prevent the infection in public at large therefore these drugs cannot be recommended for general use by the public to protect from acquiring CoViD-19 infection. Social isolation and quarantine measures are still appropriate to control the infection until a reliable preventive therapeutic option becomes available, for instance, a vaccine.
- There is very limited use of CQ/HCQ in clinical settings, where most of the evidence has emerged from its clinical use in CoViD-19 emergency centres as life-saving measures in critically ill CoViD-19 patients. There are no random controlled trials available to date.
- There is a need for an open-access central repository where clinicians can record the use/outcomes of CQ/HCQ or other pharmacological interventions for the thorough scrutiny of the data by the global scientific community.
- There is a risk of fatal cardiac arrhythmias associated with CQ/HCQ use. There are other safety concerns in patients with other pre-existing chronic conditions, in particular cardiovascular diseases. Therefore, CQ/HCQ use cannot be generalised for all CoViD-19 positive cases. It is advised that the use of CQ/HCQ should be restricted for the treatment of CoViD-19 associated pneumonia in severely ill patients only under clinical supervision and close cardiac monitoring.
- The responsible pharmacist must strictly follow the prescription-only restrictions in their respective jurisdictions, discourage the over-the-counter supply of CQ/HCQ in pharmacies, and monitor the proper usage of these drugs.

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