CURRENT HIGHLIGHT

Perspectives on repositioning chloroquine and hydroxychloroquine for the treatment of Covid-19

Ahmed Awad Adeel (1,2)

(1) Independent Consultant in Malaria and Tropical Diseases, Lawrenceville, GA

(2) Formerly, Professor, Department of Pathology, College of Medicine, King Saud University, Riyadh, Saudi Arabia

ABSTRACT

Coronavirus disease 2019 (COVID-19) is now spreading as a pandemic ravaging the whole world. In the absence of a vaccine and an effective antiviral chemotherapy, there is currently an intense global interest in repositioning chloroquine (CQ) and its derivative hydroxychloroquine (HCQ) to combat the pandemic. CQ has been used for decades for the treatment and prophylaxis against malaria in endemic countries. It is readily available and has also been manufactured in these countries. CQ is cheap, stable under field conditions and has been well tolerated as an antimalarial. This experience could be adapted to deploy CQ or HCQ for prophylaxis or treatment of COVID19 if strong evidence could be generated for these uses. We believe that well-designed drug trials should be initiated in malaria-endemic countries, taking into account the local context of the epidemic and the capacity of the health system in combating it. In this paper, we are presenting the current status of evidence for using CQ and HCQ against COVID19.

KEYWORDS

Coronavirus disease 2019; COVID-19; Treatment; Prophylaxis; Chloroquine; Hydroxychloroquine; Malaria.

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARSCoV-2) is spreading rapidly around the world in a devastating pandemic with deaths from its associated disease, corona virus disease 2019 (COVID-19). There is currently an intense interest in deploying chloroquine (CQ) and its derivative hydroxychloroquine (HCQ) to combat the pandemic. CQ as sulphate or phosphate and HCQ as sulphate are better known as antimalarials [1]. CQ was discovered in 1934 at the Bayer laboratories, it was named Resochin [2]. However, Bayer shelved the drug for more than 10 years because it was thought to be too toxic, a decision that would come to be known as ‘the Resochin error.’ During World War II, clinical trials on the drug were conducted jointly by French and German scientists in Tunisia in 1941–1943, with very impressive results. Resochin was then handed over by the French authorities to the Allied

Correspondence to:

Ahmed Awad Adeel
Independent Consultant in Malaria and Tropical Diseases, Lawrenceville, GA
Email: aaadeel@yahoo.com

Received: 20 April 2020 | Accepted: 30 April 2020

How to cite this article:

Adeel AA. Perspectives on repositioning chloroquine and hydroxychloroquine for the treatment of Covid-19. Sudan J Paediatr. 2020;20(1):4–9.
<https://doi.org/10.24911/SJP.106-1587122398>

Forces. During the following years, Resochin was rediscovered; it was given the name 'chloroquine' by E. K. Marshall in 1945 [3]. Afterwards, it was field-tested against vivax malaria with successful results [4]. Alexander Surrey and Henry Hammer synthesised hydroxychloroquine sulphate in 1946, they reasoned that the introduction of a hydroxy group into one of the N-ethyl groups of chloroquine phosphate should significantly reduce CQ toxicity [5]. HCQ was demonstrated to be much less toxic than CQ in animals [6]. HCQ was also reported to be less active than CQ against chloroquine-resistant *Plasmodium falciparum* owing to its physicochemical properties. However, HCQ had the advantage that it could be used in high doses for long periods with very good tolerance compared to CQ and this led to its use against chronic conditions like autoimmune diseases and rheumatoid arthritis [7]. Due to its efficacy against malaria, CQ came to be favoured as an antimalarial treatment and it became the first-line antimalarial therapy for many years. In the 1990s, it was the most frequently used in the treatment of malaria. This was because of its low cost, low toxicity and high efficacy against all forms of malaria. Moreover, CQ was relatively easy to manufacture and chemically stable, and thus is readily stored and transported, even under extreme climatic conditions. CQ was also commonly used for self-treatment, chemoprophylaxis and for trial treatment of cases of fever whether they are malarial or not [8,9]. In 2001, the consumption of chloroquine phosphate preparations in Sudan was 75,132,040 tablets (150 mg base), 20,690,308 ampules (200 mg/ml) and 1,118,186I syrup bottles (50 mg/5 ml) [10]. As is the case for most antimicrobial drugs, resistant strains of the target organism eventually emerged. With the onset and spread of chloroquine resistant *P. falciparum* at the turn of the century, chloroquine was largely replaced in sub-Saharan Africa by artemisinin-based combination therapies [11].

Repositioning of old drugs

Recently, a movement has evolved to encourage repositioning of old drugs. This meant to find new applications for old drugs has been gaining grounds [12]. Attempts to reposition CQ and HCQ were already underway to utilise these drugs for

the treatment of intracellular viral, bacterial and fungal infections [13]. The antiviral action for CQ and HCQ was assessed by *in vitro* studies and *in vivo* in laboratory animals [14–17].

More recently, *in vitro* studies demonstrated effectiveness of CQ and HCQ in suppression of 2019 novel coronavirus SARS-CoV-2 [18,19]. However, animal models using mice did not demonstrate significant *in vivo* suppression of viral multiplication by CQ [20].

The mechanism of the antiviral effect of CQ is mainly by inhibiting pH-dependent steps of the replication of several viruses including members of the flaviviruses, retroviruses and coronaviruses. Moreover, chloroquine has immunomodulatory effects, suppressing the production/release of tumour necrosis factor and interleukin 6, which mediates the inflammatory complications of several viral diseases [21,22]. In spite of *in vitro* evidence, *in vivo* studies and clinical trials have not confirmed any significant beneficial effects in a number of viral infections, including Ebola virus disease, chikungunya, influenza, HIV infection and dengue [23–27].

Clinical studies

Based on *in vitro* evidence of the efficacy of CQ against Coronavirus 2 [28–30], the first clinical studies of CQ against COVID-19 were conducted by Chinese investigators who reported the findings of 15 Chinese trials in more than 10 hospitals [31]. They reported that in more than 100 patients, chloroquine phosphate had a significant beneficial effect in reducing symptom duration, exacerbation of pneumonia, radiological improvement and lead to virus-negative conversion. The dose of CQ used was not given. An expert consensus in China recommended CQ for treatment of novel coronavirus pneumonia. The dose initially recommended was chloroquine phosphate tablet, 500 mg twice per day for 10 days for patients diagnosed as mild, moderate and severe cases of novel coronavirus pneumonia and without contraindications to CQ [32].

A randomised clinical study involving 62 COVID-19 patients in China included 31 cases treated with HCQ and 31 patients given standard treatment as controls. The treatment group

received oral HCQ (hydroxychloroquine sulphate tablets) 400 mg/d (200 mg/bid) between days 1 and 5, the patients in the control group received the standard treatment only. They concluded that among patients with COVID-19, the use of HCQ could significantly shorten the time to clinical recovery and promote the absorption of pneumonia [33].

HCQ was also tested in a preliminary randomised clinical trial in 30 patients in China [34]. The study did not show a demonstrable effect with HCQ. A much larger study is needed to show a significant effect, but the negative outcome of this small study could mean that if HCQ has an effect it is likely to be small. Another unpublished multicentre, open-label, randomised controlled trial was conducted in 16 government-designated COVID-19 treatment centres in China from 11 to 29 February 2020. This study covered 150 patients hospitalised with COVID-19. Patients were assigned to HCQ treatment group (75 patients), treated with loading dose of 1,200 mg daily for 3 days followed by a maintained dose of 800 mg daily for the remaining days (total treatment duration: 2 or 3 weeks for mild/moderate or severe patients, respectively). Controls were 75 not treated with HCQ. Results: HCQ did not result in a higher negative conversion rate but more alleviation of clinical symptoms than in controls in patients hospitalised with COVID-19, possibly through anti-inflammatory effects. Adverse events were significantly increased in HCQ recipients but no apparent increase of serious adverse events [35]. In France, Gautret et al. [36] reported an open label non-randomised control trial, including 36 patients with COVID-19. Twenty patients were given hydroxychloroquine at a dose of 600 mg daily along with azithromycin. The authors showed significant reduction in viral load on day 6 of the treatment compared to the control group [36].

It goes without saying that the current pandemic of COVID-19 is in desperate need for a therapeutic tool for prevention of transmission and cure of the disease. Although the possible beneficial effect of CQ and HCQ in suppression of viral multiplication has been supported by some *in vitro* studies, the published clinical trial on CQ HCQ have so far failed to provide sufficient evidence of the safety and efficacy of these drugs for use against

COVID-19. This led to calls for more elaborate clinical trials that provide more strong evidence [37–44]. As of the preparation of this manuscript (16 April 2020), the United States National Institutes of Health (NIH) clinical trials registry site (<https://clinicaltrials.gov/ct2/home>) shows 95 registered clinical trials on hydroxychloroquine and 37 trials for chloroquine against COVID19. The site also links to additional trials registered in the WHO database and the Chinese clinical trials registry. Some of the trials in the Chinese registry have been cancelled, probably because the epidemic has subsided in China.

CONCCLUSIONS AND RECOMMENDATIONS

Given the long experience in the use and manufacturing of CQ in malaria endemic areas, it would be the time to encourage researchers in these countries to engage in trials of these drugs against COVID-19 [41]. In designing these trials, the first issue is how to mitigate possible serious side-effects through careful patient selection and careful monitoring [45]. The toxicity with CQ occurs at relatively low levels of the drug [46]. We should note that both CQ and HCQ interfere with ventricular repolarisation, leading to prolongation of the QTc interval and an increased risk of torsades de pointes [45]. Moreover, we need to assess whether the immunomodulator effect of these drugs could actually be harmful to patients with COVID-19 [47].

Although CQ as sulphate and phosphate salts has been used for decades against malaria in endemic areas, the doses used for malaria treatment and prophylaxis were much lower than the doses tested so far against COVID-19. For this reason, there was a call to switch from CQ to HCQ in China [48]. Iran is another country where HCQ was preferred over CQ for COVID [49].

Another issue that has been frequently overlooked was: What exactly are we assessing in these trials? In India, CQ has already been used as prophylaxis [50]. In designing these trials, we should have clear research questions that could help interpretation of the results and translation of the generated evidence to policies [51,52].

Some of the possible research questions include:

- Does it work as preventive treatment to protect case contacts?
- Does it prevent progression of infection to severe disease in at risk patients?
- Would it be a curative treatment for severe cases?
- Does it affect the rate of hospitalisation, intubation or mortality?

CONFLICT OF INTERESTS

The author declares that there are no competing interests.

FUNDING

None.

ETHICAL APPROVAL

Not applicable.

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