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Mini Review

Is Hydroxychloroquine an Effective Drug Against COVID-19?

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ABSTRACT

The coronavirus (COVID-19) outbreak was declared a Public Health Emergency of International Concern (PHEIC) on 30 January 2020 and a pandemic on 11 March 2020 by the WorldHealth Organization (WHO). By 16 June 2020, COVID-19 has affected more than 7.82 million people worldwide and caused more than 432,000 deaths. The scientific community works relentlessly to invent vaccines, drugs and establish effective therapeutics for the COVID-19 pandemic. However, a well-known antimalarial drug Hydroxychloroquine (HCQ) has recently received enormous attention and given an emergency use authorization from the FDA as of 3 April 2020. But, there are several concerns about the appropriate dosage and possible side effects of HCQ during COVID-19 treatment. Here we reviewed the HCQ mechanism of action against the virus and its clinical studies in COVID-19 therapy.

Keywords: Hydroxychloroquine; Chloroquine; Drug; COVID-19; Clinical studies

INTRODUCTION

Human coronaviruses were first discovered in the mid-1960s. Coronaviruses belong to the Orthocoronavirinae subfamily within the Coronaviridae family, the Nidovirales order and the Riboviria domain. These are enveloped viruses with a single-stranded, positive-sense RNA genome and a helical symmetry nucleocapsid. Coronavirus genome size ranges from 26 to 32 kilobases and is one of the largest among RNA viruses [1]. Previously, six coronaviruses have been known to cause disease in humans. SARS-CoV-2 is the seventh member of the coronavirus family that causes mild to fatal respiratory illness in humans after SARS-CoV and MERS-CoV [2]. SARS-CoV-2 has a (COVID-19) is highly contagious, primarily through respiratory droplets, aerosol from infected individuals, and the WHO has notified the current pandemic of COVID-19 as an international public health emergency. By 16 June2020, COVID-19 has to they affected more than 7.82 million people worldwide and caus1ed more than 432,000 deaths [3]. The World Health Organization (WHO), the US Food and Drug Administration (FDA), the European Medicines Agency (EMA), the Chinese government and drug manufacturers have been coordinating with academic and industrial researchers to speed up rapid diagnosis kit development, vaccine development, antiviral drugs and post-infection therapy development [4]. The aim WHO International Clinical Trials Registry Platform (ICTRP) has recorded 536 clinical studies for the development of post-infection treatments for COVID-19 infections with many established antiviral compounds for the treatment of other infections to be replicated in clinical studies8. Interestingly, as of 3 April 2020, Hydroxychloroquine (HCQ) received an emergency use authorization from the FDA. However, there are still a number of concerns about the appropriate dosage and treatment procedures for COVID-19. In this mini-review, we discuss the HCQ mechanism of action and its effectiveness on COVID-19 treatment.

HCQ a less toxic derivative of Chloroquine (CQ)

HCQ was synthesized in 1946 by adding hydroxyl(-OH) group to CQ and reported to be less toxic in animal studies than CQ9. HCQ belongs to 4-aminoquinoline families, predominantly used in malaria treatment. In 1955, HCQ was approved for medicinal use in the United States. The WHO lists necessary medicines that are the safest and effective medicines needed in the health system. In 2017, it was the 128th most widely prescribed drug in the United States, with more than five million prescriptions [5]. HCQ is also used for the treatment of rheumatoid arthritis, lupus and porphyria cutaneatarda. The common side effects are vomiting, migraine, vision changes and muscle weakness [6]. HCQ is water-soluble white crystalline powder and insoluble in chloroform, ether and alcohol. The chemical name for HCQ is,

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with molecular weight 433.95 and the molecular formula is $C_{18}H_{26}ClN_3O.H_2SO_4$. HCQ tablets contain 200 mg HCQ as sulfate, equivalent to 155 mg base, and are for oral use. The inactive ingredients in the tablet include corn starch, crospovidone, lactose monohydrate, magnesium stearate, hydroxypropyl methylcellulose, polyvinyl alcohol, polyethylene glycol, titanium dioxide and talc. HCQ is sold under there are a brand name Plaquenil and is available as generics.

CQ has shown promising antiviral activity against numerous viruses *in vitro*, including EBOV, Nipah, Hendra influenza, to a Dengue and CHIKV. Unfortunately, this antiviral activity has not always been studied in vivo efficacy models or clinical trials. CQ block viral infection by increasing endosomal pH needed for viral fusion, as well as interfering with the glycosylation of cellular receptors of the virus [7]. The virus needs a fusion mechanism to transmit the viral genome when attached to the cells. Preventing this action by fusion inhibitors has been an effective approach in HIV antiviral therapy. CQ inhibits both on *in vitro* and *in vivo* replication of HIV-1 and has been suggested that it changes the glycosylation pattern of the gp120 envelope. The modulators of the gp120 envelope protein structure enable the generation of broader Ab neutralizing reactions. Alkaline HCQ and CQ increase the pH in acidic vesicles, which source several enzymes interruption. Mechanism of action of CQ, and HCQ against virus includes gp120 expression alteration and intracellular iron restriction [8].

Clinical studies of HCQ

The first study reported by Philippe Gautret and colleagues is non-randomized with 36 COVID-19 positive patients (HCQ and they 16 controls) by nasopharyngeal sampling for the first six to a days of treatment. The author demonstrated that HCQ treatment was superior to control patients in eliminating SARS-CoV-2 from the nasopharynx [9]. Further, in the HCQ treatment group, six patients were prescribed HCQ plus azithromycin, and the investigators found that viral eradication was statistically superior in this subgroup compared with HCQ alone and control group. The authors concluded that HCQ plus azithromycin treatment reduced the viral load in COVID-19 patients. Following this Gautretet al. study, another group justify from France [10]. Reported that they treated 11 COVID-19 patients using the same dosing regimen 600 mg HCQ per day for 10 days and 500 mg azithromycin on day one followed by 250 mg up to 5 days. The clinical outcome showed that HCQ plus azithromycin have no vigorous antiviral activity in COVID-19 patients. Till now, 6 clinical trials have been registered in China to test the efficacy and safety of HCQ in the treatment of COVID-19. In a study performed in 30 patients with COVID-19, Jun Chen and colleagues observed no substantial difference in nasopharyngeal viral transmission on day 7 when HCQ treatment (400 mg per day for five days plus conventional treatments) was compared to the standard treatment.Zhaowei Chen and colleagues, another Chinese group study from 62 COVID-19 patients in Wuhan, revealed that HCQ (200 mg twice daily for five days on admission in addition to standard treatment) treatment reduced the symptoms and shortened the recovery time [11]. In another Chinese study, a multicenter, parallel, open-label randomized clinical trial that included 150 COVID-19 hospitalized patients. Clinicians were a reported that HCQ administration (loading dose of 200 mg daily for three days, followed by a maintained dose of 800 mg daily for the remaining days) with standard care did not show significant recovery of COVID-19 patients compared to the standard care in 28 days treatment. They suggested that HCQ may be considered for treatment in symptomatic patients to prevent the progression of the disease, particularly high-risk patients. On 9 April 2020, at Henry Ford Hospital, started the first large-scale study in the US on volunteered to test the effectiveness of HCQ in preventing COVID-19. Similarly, The Spanish Government has announced the start of a large-scale clinical trial to determine whether HCQ can prevent frontline health workers from contracting COVID-19. Columbia University trail involves nearly 1400 patients, of 1,376 patients in the final trial, 811 were treated with hydroxychloroquine and 565 patients did not receive the drug. Finally, 346 patients developed respiratory insufficiency, 180 were intubated and 166 died without intubation. Their findings indicated that hydroxychloroquine patients had the same risk of intubation or death as those who were not treated with the drug [12]. On 17 June 2020, WHO announced that the hydroxychloroquine was ineffective in the in the reduction of mortality of hospitalised COVID-19 patients, when compared with the standard treatment. Data from Solidarity (including the French Discovery trial data) and the UK's Recovery trial both showed that hydroxychloroquine was ineffective.

CONCLUSION

In vitro experiments of HCQ's antiviral activity against the main COVID-19 show promising results, it does not turn up to the mark in clinical trials. The current clinical reports are too poor to justify a significant resource shift in this direction. However, a large-scale clinical study from various regions of the world, especially malaria-risk zones and fundamental research are very much required. This will help not only to understand HCQ's physiological function but to refine the treatment plan continuously.

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