

Hydroxychloroquine for COVID-19: A Review

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Abstract: *In dealing with the COVID-19 pandemic, hydroxychloroquine (HCQ) as a drug captured serious worldwide attention. Some in-vitro and in-vivo studies recently showing possible inhibition of SARS-CoV-2 by the use of HCQ. At same time, however, a few cases research demonstrating NO medical benefit/ poor clinical result with major adverse effects through the use of HCQ in coronavirus disease-2019 treatment. Therefore, the use of HCQ (in treatment with COVID-19) is of considerable international concern, although a consensus has not yet been reached. Further proof to prove HCQ 's efficacy against COVID-19 is still needed. In view of this, the current analysis illustrates the ongoing work on use of HCQ in the management of coronavirus disease-2019. The present analysis will address the potential in-vitro study of HCQ's anti-viral function, prophylaxis strategy and impact of HCQ on SARS-CoV-2 viruses. This review also sums up and discusses all clinical practice trials / HCQ use research studies against COVID-19 (with clinical results). Finally, considering the public health and pharmacovigilance concerns, possible detrimental effects are also discussed.*

Keywords: hydroxychloroquine; COVID-19; Coronavirus disease-2019; Clinical trials; SARS-CoV-2; adverse effects of hydroxychloroquine; Pharmacovigilance concern.

1. Introduction

The novel 2019 coronavirus disease (COVID-19), announced a pandemic began in 2020 [1]. It is the third highly pathogenic and infectious coronavirus that has emerged in humans after endemic SARS-CoV and MERS-CoV [2]. The specific source, propagation, processes of SARS-CoV-2 are not yet established and explicit, but its genomic composition is closely associated with the coronavirus of SARS-CoV (76-80 percent) [2]. As of now (25 June 2020), about 29, 01, 305 cases have been reported to have COVID-19 infection worldwide (212 countries) with 2, 00, 082 deaths [3]. A notorious anti-malaria product to be investigated and used against possible COVID-19 in random clinical trials and clinical case studies around the world to alleviate symptoms, or as a preventive measure to stop people from being infected with COVID-19 [5-10] Some findings indicating possible use of HCQ in coronavirus disease treatment 2019 (with limited side effects) [5, 6, 9] . Around the same time, some studies are not all that supporting HCQ for COVID-19 [7, 8, 10], while they increase alertness adverse effects by COVID-19 patient use of HCQ [10]. Therefore, in view of the pharmacovigilance issue, there are many toxic effects of HCQ which are required to resolve the use of prophylaxis [7, 8, and 10]. It could be dangerous enough for many people to suffer excessively or even die during care because of cardiac problems [10]. Therefore a really careful review of the usage of HCQ in the management of coronavirus disease-2019 is still needed [7, 8, 10]. Therefore, the discussion on the use of HCQ against COVID-19 is of great importance and requires urgent attention to recognize the actual power of HCQ toward COVID-19 [5-10].

4-Aminoquinolines and its use in anti-viral therapies:

Hydroxychloroquine and chloroquine are variants of the 4-aminoquinoline. The improvement in CQ's N-diethyl side chain by the Nethyl hydroxyl group at HCQ provides further solubility. In addition, HCQ showed strong bioavailability and immunomodulatory impacts by trying to interfere with the interleukin-6 synthesis (IL-6), that plays an important function in chronic inflammation and autoimmunity [11-13]. In addition, HCQ develops fewer toxic compounds, less

harmful effects and thus considers a drug safer than CQ [11-14]. In addition to this, HCQ also demonstrated antiviral activity by enhancing the IFN- β pathway by phosphorylation [11, 12]. HCQ is primarily an anti-malarial drug that is also utilized in autonomic dysfunction [11-13], sarcoidosis [14], rheumatoid arthritis [15], alopecia areata [16], lupus erythematosus [17], anti-thrombotic therapy [18], and antineoplastic therapy [19]. In addition, HCQ demonstrates possible antiviral and therapeutic activity against Ebola [20], Marburg [20], Zika [21], HIV-1 [22], Dengue [23], Chikunguniya [24], Hepatitis C [25], MERS-CoV [26] and SARS-CoV [27] virus treatment.

HCQ impact on the immune response, and COVID-19:

During COVID-19, during critical patients that are specifically related to a cytokine surge, the lung damage becomes more evident. The prognosis was influenced by the pro-inflammatory cytokine storm with serious illness. To combat the cytokine wind, various IL-6 antibody blockers and convalescent plasma therapies were added. Therefore, HCQ is predicted to be used against COVID-19, taking into account its antiviral activity. Excessive cytokine development contributes to an obstruction of the innate immune response [1113]. The HCQ regulates or modulates the production of the various cytokines (such as IL-6, IL-1, IL-2) involved in the cytokine storm [11]. The HCQ also exhibited antiviral activity by activating the IFN- β pathway by phosphorylation [11, 12]. Furthermore, HCQ supports post-translational adaptation of signaling proteins to modulate innate immune responses and hence it is presumed that HCQ's antiviral and immunomodulatory effects can synergetically combat COVID-19 infection [11, 12, 28]. HCQ may therefore have an evolving role in controlling and reducing the immune response of the host against COVID-19, but further investigation is required to verify the appropriate position of HCQ against COVID-19 in considering the innate immunity factor [11, 12, 28].

In vitro repression of HCQ and CQ against SARS-CoV-2:

Currently several studies have been available that showed invitro [27, 29] (Table 1, entries 1-8) and in-vivo [5-10] suppression of SARS-CoV-2 virus by HCQ usage. Liu et al.,

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[29] researched antiviral activity of HCQ and CQ toward infection with the SARS-CoV-2 virus at different infection multiplicities (MOI). They assessed HCQ and CQ cytotoxic effects in vitro in the Vero-E6-cells of African monkey kidney [29].

Table 1: In vitro Hydroxychloroquine and chloroquine inhibitory activity against SARS-CoV-2 virus

S.n.	Drug	Time	CC50 (μ M)	EC50 (μ M)	Ref
1	Chloroquine	48	ND	5.47	27
2	Hydroxychloroquine	48 h	ND	0.72	27
3	Hydroxychloroquine (0.02 MOI)	48 h	249	4.06	29
4	Chloroquine (0.02 MOI)	48 h	273	3.81	29
5	Hydroxychloroquine (0.01 MOI)	48 h	249	4.51	29
6	Chloroquine (0.01 MOI)	48 h	273	2.71	29

HCQ: Potential method for fighting COVID-19:

On the basis of an initial evaluation of HCQ as a drug against SARS-CoV-2 virus, a potential mechanism is proposed [27, 29]. It is believed that, HCQ acts against the SARS-CoV-2 virus in three separate ways [29-33]. The angiotensin converting enzyme-2 (ACE-2), which was considered to be a potential binding receptor for SARS-CoV, is now known as a potential SARS-CoV-2 receptor considering the homology of amino acids [30]. It is known that SARS-CoV-2 has 76 per cent homology of amino acids to SARS-CoV [2, 3]. Therefore, SARS-CoV-2 virus can adopt similar mechanisms to invade the host cell as SARS-CoV virus [2, 3]. SARS-CoV-2 has spike protein involving the two subunits [2, 3, 30], namely S1 and S2. The first S1 subunit demonstrates binding capability against the ACE-2 receptor (in adipose tissues); while the second S2-subunit requires membrane fusion and RNA penetration into the cell [27, 29, 30]. In the research on the antiviral activity of HCQ that influences the viral entrance cascade; different interventions have been posited by reducing the glycosylation of ACE-2 [27, 29, 30]. Since, virus is believed to bind to the ACE-2 receptor to reach the host cell within. HCQ is a poor base that can be stored inside acidic organelles (endosomes, vesicles of Golgi, and lysosomes) where the actual pH is low. After aggregation, the HCQ induces an effect on acid organelles as well as some acid hydrolase enzymes to act by expanding the pH of organelles [31]. Some viruses join by mechanism of endocytosis, wherein the virus attacks the lysosomes [31]. These low pH lysosomes and viral particle enzymes are disrupted by the action of acid hydrolase which releases various viral contents (material infections, nucleic acid, and enzymes) needed for viral replication [31]. The accumulated HCQ in acid organelles has been found to inhibit the endocytosis cycle and subsequent replication of viruses by increasing the pH level of lysosomes. Accordingly, HCQ is thought to influence the viral input [31]. Virus is transferred to endosome in some cases and is replicated in it [32]. Such endosomes are ruptured by low pH acid intracellular lysosome enzymes and allow the viral contents and replicated viruses to relive [32]. Accumulation of HCQ is believed to increase the pH level of the endosome as well as the Golgi network and interfere with the processing of numerous essential acid hydrolase enzyme which impede the formation protein modification and the mechanism of viral indoor entry [32]. In addition, such HCQ modify the pH of cell organelles and prevent the mechanism of viral fusion,

replication, glycosylation of viral proteins, endocytosis, transport of viron and release of viron [27, 29, 30-32].

Prophylaxis use of HCQ:

Funnily, HCQ may be used as prophylaxis to avoid potential COVID-19 infection [27, 36, 37]. Given many negative impacts and absence of proof, the question arises about the use and dosage of HCQ in prophylactics. Most recently, the HCQ dosing analysis is optimized by Yao et al. [27], who reported EC50 values (for HCQ) of 6.14 and 0.72 μ M respectively at 24 and 48 hours [27]. Based on physiologically-based pharmacokinetic models, the dosage of 400 mg BID (on day 1) and 200 mg BID (from day 2 to day 5) offers 21 and 83 times higher concentrations of lung tissue than the EC50 value at day 1 and day 10 respectively [27]. This analysis may suggest successful usage HCQ as a prophylactic drug based on model and in-vitro analysis to prevent potential COVID-19 infection [27]. In addition, HCQ's immunomodulatory action can control the cytokine storm (in the COVID-19 infection) [11-13]. However, there is an urgent need for more confirmatory evidence [510, 33-35] to look to contradictory case results of use of HCQ against COVID-19. HCQ may look like a promising life-saving drug for coronavirus inhibition in vitro, but it has failed to reduce the actual effective load of corona virus in mice [38] in practice. But it is not confirmative that something that works in-vitro will work well in-vivo, so there is an urgent need to review clinical trials [38-42].

Approach to Pharmacovigilance when using HCQ:

Studies showing multiple adverse effects linked to HCQ usage. Though HCQ is somewhat harmful and healthier than CQ, it also has certain negative impacts that are not insignificant and cannot be disregarded.

Table 2: HCQ Adverse effects

S.N	Adverse effects	References
1	General major side effects: Thrombocytopenia, hypoglycaemia, obnubilation, weight loss, appetite loss.	[48, 50]
2	Cardiac complications: QT prolongation, ventricular hypertrophy, ventricular arrhythmias, hypokinesia, cardiac arrest, pulmonary arterial hypertension, ventricular arrhythmias, valvular dysfunction, heart failure.	[43]
3	Cutaneous/allergic side effects: Erythema multiforme, exanthematic pustulosis, Stevens-Johnson syndrome, allergy, rashes.	[47, 49]
4	Ocular side effects: Retinopathy, blurred vision, blindness, corneal deposition	[44]
5	Gastrointestinal side effects: Diarrhoea, vomiting, abdomen cramping, nausea, abnormal liver function	[46]
6	Neuro/muscular side effects: Signal conduction disorders, convulsion, myopathy, vertigo, psychrosis, ataxia, nightmare, depression	[45]

2. Conclusion

In summary, HCQ demonstrates antiviral effects toward various viruses, as well as having demonstrated immunomodulatory effects. HCQ could be safe to use and necessary to inhibit viral load at lower dosages than CQ, to control cytokine storm and viremia time-span based on in-vitro analyses. However, further clinical trials / testimonies

still are expected and appropriate to confirm HCQ's in-vivo effectiveness toward COVID-19. Actually clinical studies and case reports reported using HCQ to counter COVID-19 found the clinical result conflicting. Extension of QT is a big issue when combining HCQ with drugs that combat lower respiratory tract infections (e.g. AZT). The adverse consequences of using HCQ toward COVID-19 could not be ignored. Therefore, the usage of HCQ (in treatment with COVID-19) is of considerable international concern, since a majority has not yet been reached. Special caution in expectant mothers, pediatric patients and patients with comorbidity in the COVID-19 coronavirus disease is needed for HCQ treatment. Misuse of HCQ as a COVID-19 prophylaxis (without guidance from a physician) should be avoided due to lack of good evidence that may lead to one or more adverse side effects. Usage of HCQ can only be done following medical advice.

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