



## **Optimizing the Use of Hydroxychloroquine in the Management of COVID-19 Given Its Pharmacological Profile**

**Ahmed S. Ali<sup>1\*</sup>, Mahran S. Abdel-Rahman<sup>2</sup>, Riyadh S. Almalikil<sup>3</sup>,  
Abir S. Mohamed<sup>4</sup>, Khalid A. Alfaifi<sup>5</sup>, Abdelbabgi El. Fadil<sup>6</sup>,  
Nagla A. El-Shitany<sup>7,8</sup> and Huda M. Alkreathy<sup>1</sup>**

<sup>1</sup>Department of Pharmacology, Faculty of Medicine, King Abdulaziz University, KSA.

<sup>2</sup>Department of Pharmacology, Faculty of Medicine, Assiut University, Egypt.

<sup>3</sup>Department of Pharmacology, Faculty of Pharmacy, Umm Al-qura University, KSA.

<sup>4</sup>Department of Internal Medicine, Faculty of Public Health and Tropical Medicine,  
Jazan University, KSA.

<sup>5</sup>Department of Pharmacy, Medical Services Directorate, Taif, KSA.

<sup>6</sup>Department of Medical Microbiology and Parasitology, Faculty of Medicine,  
King Abdulaziz University, KSA.

<sup>7</sup>Department of Pharmacology and Toxicology, Faculty of Pharmacy,  
King Abdulaziz University, KSA.

<sup>8</sup>Department of Pharmacology and Toxicology, Faculty of Pharmacy, Tanta University, Tanta, Egypt.

### **Authors' contributions**

All authors actively participated in this reference research and major work. Author ASA designed the idea in cooperation with author MSAR. Author RSA early joined the team to organize communication between researchers. He prepares the introduction. Author ASA assumed full supervision of the research with the assistance of all colleagues author MSAR prepared the side effects of the drug he also reviewed all that colleagues author ASM reviewed all clinical issues related to COVID 19 patients and their management she described in details cardiac toxicity of HCQ. Author AEF revised all sections related to the novel virus description and epidemiology. Author KAA collected and reviewed the pharmacokinetics of HCQ and its integration with the efficacy and safety issues. Author NAES participated actively in explaining the mechanism of HCQ. She also provided the summary and conclusion. Author HMA provided huge effort to edit the review, in a professional way regarding all aspects, language, reference and connoting ideas etc.

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## ABSTRACT

After the global pandemic of the new coronavirus, its rapid spread and many victims, it is necessary to find an effective vaccine or drugs to overcome it. Most specialists consider that repositioning some medications is the best, fastest and most reliable option for treating patients with the new coronavirus without delay. One of these drugs was an old antimalarial drug, hydroxychloroquine. The current review aimed to explore its potential mechanism, as well as its pharmacokinetics and toxicity, in an attempt to suggest a treatment protocol for its use in treating the COVID-19 virus effectively and safely. This study reviewed the published references on the popular search engines as well as the reference books regarding the pharmacological effects of HCQ. The results of this study suggested the following practical guidelines to optimize HCQ efficacy and safety in the management of COVID-19. HCQ should be used as early as possible, i.e., once the viral infection is confirmed or suspected. A loading dose is recommended to be given in 3-4 divided doses to minimize cardiac toxicity. Maintenance daily dose (divided into two doses), should be continued until complete remission. Precautions, drug-interaction, contraindications, variable metabolic pathways in the particular population should be considered. This study suggests more clinical trials regarding the use of HCQ in the management of early identified COVID-19 patients under close medical observation to minimize HCQ cardiac toxicity.

*Keywords: Hydroxychloroquine; antimalarial drugs; COVID-19; SARS-CoV-2; clinical trials; pharmacokinetics; cardiac toxicity.*

## 1. INTRODUCTION

In December 2019, the authorities in Wuhan, Hubei Province, China, reported that there was an epidemic in progress, with a growing number of individuals suffering from pneumonia, which was linked to a novel type of coronavirus, over the next few weeks, the infection spread outside China to most countries worldwide. Experts list fever, tiredness, and dry cough as the most common symptoms, but some infected individuals have also presented with aches and pains similar to flu, congestion, and a runny nose, a sore throat, or diarrhea. Approximately 80 percent of those who get the virus recover independently. However, some 16 percent of those who get COVID-19 have severe respiratory issues and become so ill they need hospitalization. On 11 February the International Committee on Taxonomy of Viruses, officially named the novel virus as severe, acute respiratory syndrome coronavirus 2 [1], based on its phylogeny, taxonomy and recognized practice. The WHO subsequently named the illness Covid-19. At present the exact origin of this virus is unknown, no vaccine is available, but many drugs are under investigations [2,3].

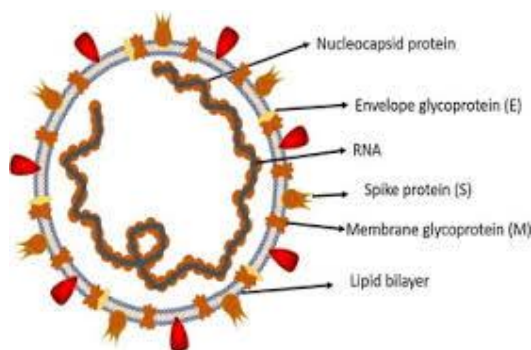
We realized improper use of antimalarial drugs in the management of covid 19 likely because of inadequate awareness about their unique features, specially pharmacokinetics. The present review aimed to integrate the

pharmacological characteristics of these drugs and pathophysiological changes associated with COVID-19 to optimize their use. It hoped to provide a platform for critical knowledge required to design and conduct clinical trials about the use of antimalarial as treatment or prophylaxis against COVID-19.

## 2. SARS-CoV-2 CHARACTERISTICS

SARS-CoV-2 is classified as  $\beta$ -coronavirus [4]. It is an enveloped virus that has a nano-size (65-125 nm), It has (26-32 Kb) single-stranded, positive-sense RNA. At a nucleotide level, it is very close to SARS-CoV (about 80 % similarity). The entry of the virus into the host cell involves the interaction of its spike protein (S protein) with angiotensin-converting enzyme 2 (ACE2) receptors [5]. These receptors are located on the surface of lung alveolar epithelial cells and enterocytes of the small intestine and many other tissues [6,7]. SARS-CoV-2 was considered highly infectious as it remains viable in aerosols for 3 hours, stable on plastic and stainless steel, up to 72 hours [8]. It is transmitted from human to human mainly by droplet infection; however, in certain circumstances, the airborne transmission is possible. WHO (Organization, 2020).

The virus could be found on many surfaces like door handles and light switches. SARS-CoV-2 viral RNA has been found in nasopharyngeal



**Fig. 1. SARS-CoV-2**

swabs, faces and blood [9]. Its R0 (primary reproductive number) was reported between 2-3 [10,11].

Some epidemiological studies have recorded that most patients show symptoms during two weeks, while the average incubation period is approximately 4-6 days [12]. Risk factors for severe illness and worse outcomes include advanced age; the presence of co-morbidities including diabetes, cerebrovascular disease, chronic kidney disease, chronic obstructive lung disease, pregnancy [13].

A meta-analysis reported the Case fatality rate (CFR) as 4.3% [14]. More detailed data can be retrieved in these publications [15-17].

### **2.1 Pathophysiological Changes in Covid-19**

The severe cases of Covid-19 were associated with many pathophysiological changes in most organs and systems [1]. Of particular importance pathophysiological changes in lung tissues which include various degrees of lung consolidations. Serous fluid, fibrous protein exudate and hyaline membrane formation were seen in alveoli; [18].

In general pathological changes in critically ill adults are expected to alter drug pharmacokinetics (ADME) and drug response [19].

### **3. PHARMACOTHERAPY OF COVID 19 AND DRUG REPURPOSING**

Numerous efforts have been paid to discover and evaluate the effectiveness of already known antivirals, immunotherapies, monoclonal antibodies, and vaccines in Covid-19. At the time

of presenting this review, no vaccine is available, but several drugs are under investigation which includes antiviral drugs, e.g. remdesivir, lopinavir-ritonavir, and interferon- $\alpha$  2b [20,21]. Using Plasma donated by recovered COVID-19 patients to treat other patients represent a promising approach [14].

Repurposing (using a known drug for indication) some existing therapeutic agents initially developed for other viruses or infections, the disease seemed at present an optimal realistic approach for the management of the emerging pandemic [22]. These agents can be classified according to their pharmacological targets. For example, a large scale drug repositioning survey among antiviral drugs suggested 30 compounds as a candidate to be studied as antiviral drugs against SARS-CoV-2, these drugs have known targets such as cysteine protease inhibitors [23]. These drugs suggested by computational approaches can be further screened given pharmacological rationale to select few to be tested *in vitro* and animal models [24,25]. At present, more than a hundred drugs with known targets against SARS-CoV-2 life cycle were allowed for researchers through a free access database (Excelera 2020).

Many of these suggested drugs now undergo clinical trials [26]. Moreover, some of these drugs have multiple targets and benefits. A comprehensive list of these drugs which can be retrieved from these publications [14,17,22].

Reviews of clinical trials and a brief pharmacological profile of selected drugs were assessed [27,28]. Among these repurposed drugs are antimalarial drugs Chloroquine [29] and its less toxic metabolite hydroxychloroquine (HCQ) [30,31].

This review will focus on (HCQ), based on its unique pharmacological profile, *in vitro* effectiveness against closely related virus SARS-CoV-1 and early promising clinical results suggesting hope for a role in the management of Covid-19. Regardless of current conflicting results and debates regarding its efficacy or safety [32]. Many clinical trials are going on to evaluate the utility of CQ or HCQ in the management of Covid-19. It is too early to provide a final decision. The authors of this review recognized that the use of HCQ could be optimized given an understanding of its unique pharmacological characteristics, They emphasize that using HCQ at the early stage of infection under close medical follow up can enhance safety and efficacy. These will be explained in the following sections.

#### 4. HYDROXYCHLOROQUINE (HCQ) AND ITS UTILITY IN COVID-19

HCQ was given primarily to prevent malaria. It is also given, in combination with other drugs, to treat several autoimmune diseases, such as lupus [33] and rheumatoid arthritis. Sometimes, it is also used to treat other infectious diseases, such as endocarditis and Q fever. FDA allowed its use among other drugs in clinical trials for the management of Covid-19. The following sections focus on fundamental characteristics relevant to its use in the management of Covid-19, Hydroxychloroquine FDA 2020 [34].

##### 4.1 As an Immunomodulatory Drug

HCQ is a less toxic metabolite of Chloroquine [35] (Fig. 2).

HCQ and CQ are considered immunomodulatory rather than immunosuppressant drugs [36]. HCQ inhibits major histocompatibility complex (MHC)

class II-mediated autoantigen presentation to T cells. This effect can be explained by its efficacy in the suppression of lysosomal activity in antigen-presenting cells (APCs). These events eventually suppress the expression of inflammatory cytokines such as type I interferons, IL-1 and TNF, etc... [37]. *In vitro* studies also showed that HCQ effectively inhibits the production of IL-6, IL-17, and IL-22 [38].

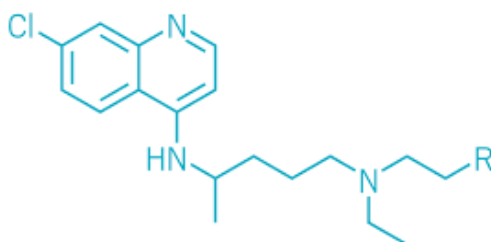
These immunomodulatory mechanisms of HCQ/CQ provided the basis of their utility to prevent cytokine release syndrome (CRS) [39]. This assumption was based on the fact that. One of the major fatal complications of COVID -19 is cytokine storm mediated by the uncontrolled release of cytokines especially IL-6 [40]. However, other authors raise a concern that HCQ possibly suppress certain immune components which are essential to identify or kill the virus [41].

##### 4.2 Prophylaxis against Lung Thrombosis

Evidence is emerging that COVID-19 is associated with an increased risk of thromboembolic disease. Interestingly, HCQ was suggested as a valuable drug for prophylaxis against lung thrombosis [42]. Multiple lung micro thrombi was reported as one of the severe complications of COVID-19 [43].

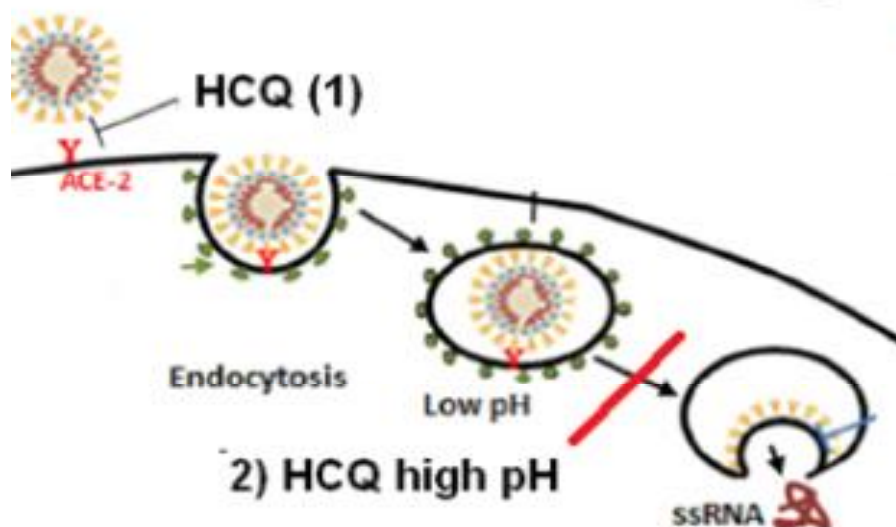
##### 4.3 Multiple Mechanisms against Viral Infections

Recall that HCQ and CQ are weak bases and exhibited unique ability to be entrapped in the organelles with acidic pH, (i.e. endosomes, Golgi vesicles, and lysosomes) and make these structures basic [44].



Chloroquine, R = H  
Hydroxychloroquine, R = OH

Fig. 2. Structure of hydroxychloroquine and chloroquine



**Fig. 3. Simplified mechanism of hydroxychloroquine against SARS-CoV-2**

1. Inhibit entry (interfere with the glycosylation of, ACE2); 2. Inhibit replication (increasing endosome/lysosome pH)

Fig. 3 shows the suggested site of action of antimalarial drugs against the novel virus. Coronaviruses entry to host cells involve two sequential steps, 1) binding of the viral spike to angiotensin-converting enzyme 2 (ACE2) cell surface receptors, 2) membrane fusion [5]. ACE2 requires glycosylation to be active. CQ has been shown to inhibit these Lysosomal step proteases (LP) activate the fusion process between host and viral membranes by cleaving coronavirus surface spike proteins [45], increasing the pH of the lysosome prevents LP. In other words, the viral fusion process is disrupted, and its replication is blocked [46,47]. Other mechanisms were suggested, such as enhancing the antiviral activity of Zn, this makes investigators suggest the use of zinc formulation to enhance HCQ/CQ efficacy against the SARS-CoV-2 [48]. HCQ was also shown *in vitro* to suppress endocytosis of nanostructures in cell culture [49].

#### 4.4 Demonstrated Efficacy *in vitro* and Animal Model

In cell culture, CQ showed an ability to suppress replication of SARS-CoV; the results are similar when the cells were treated either before or after exposure to the virus. These observations suggesting the feasibility of antimalarial to be of

value in the treatment and prophylactic of viral infection [50].

*In vitro* studies showed that HCQ is more potent than CQ against SARS-CoV-2 (EC<sub>50</sub> of 0.72  $\mu$ M for HCQ & 5.47  $\mu$ M, for CQ) [51].

Moreover, the efficacy of CQ as a potent broad-spectrum antiviral drug was demonstrated in an animal model infected with avian influenza A H5N1 virus I [52]. More details about the efficacy of antimalarial drugs against other viruses were reported [53].

#### 4.5 Limited Clinical Trials Suggested Promising Efficacy and Safety

Few promising clinical trials demonstrated the effectiveness of both CQ and HCQ in the early management of COVID-19 [54]. First clinical trial in China, (about 100 patients with COVID 19), brief results indicated that chloroquine phosphate resulted in clinical improvement of viral pneumonia and marked reduction in the duration of illness, no serious adverse effects were reported [55]. A limited non-randomized clinical trial (36 patients diagnosed with SARS-CoV-2). The treatment group received HCQ 200 mg three times a day for ten days. The control group received usual supportive care (few patients in the treatment group also received azithromycin). The authors suggested that these empirical

findings suggested the promising effectiveness of HCQ and a potential synergistic effect with azithromycin [56].

A recent meta-analysis concluded that HCQ is a promising treatment for COVID-19 patients, good safety profile, clinical improvement based on radiological findings but more data still needed to provide the conclusion [57].

#### **4.5.1 Debates and criticism about its use in COVID-19**

Some authors provided criticism for these studies, and focused on considerable limitations, regarding statistical power or insufficient data, which lacks medium and long-term follow-up among other [58]. For example, the authors of a study reported a lack of evidence of clinical benefit after treatment of severe cases of COVID-19 with hydroxychloroquine plus azithromycin [59]. Other publications raise concern reading the COVID-19 patients are at high risk for cardiac toxicity [60]. More about the limitations of *in-vitro* and clinical studies are presented in several reviews [61].

#### **4.5.2 Explanation of unfavourable results of HCQ in severe Covid-19**

The authors of this review explained the lack of effectiveness or increased cardiac toxicity in case of late use of antimalarial drugs likely due to neglecting its pharmacokinetic (PK) unique features that will be reviewed and integrated with pathophysiological changes in the following sections.

### **4.6 PK (ADME) Profile of HCQ**

Brief PK summary is presented below [62].

#### **4.6.1 Absorption**

Variable absorption of HCQ after oral administration was reported (~70% [range: 25 to 100%]).

#### **4.6.2 Distribution**

HCQ reaches the peak shortly after the absorption phase and decreases relatively quickly due to rapid partitioning into organs. Accumulation in lysosomes appears to drive the large volume of distribution in plasma, whereas

binding to melanin contributes to the long terminal half-life ( $t_{1/2}$ ) and can deposit in melanin-containing tissue such as the eyes and the skin, which might explain certain tissue-specific mechanism such as retinopathy [63,64]. With long-term use of HCQ, peak plasma levels occur 3 to 4 hours after each dose, with a terminal half-life of 40 to 50 days [37,65]. HCQ protein binding is approximately 50%, primarily albumin [66]. Hydroxychloroquine can be detected in the placenta at delivery in concentrations similar to those in the maternal serum [67].

#### **4.6.3 Metabolism**

HCQ metabolism occurs in the liver through CYP2C3, CYP 2D6, 2C8, 3A4 and 3A5 into the metabolites desethylhydroxychloroquine, desethylchloroquine and bisdesethylchloroquine HCQ can interfere with several drugs metabolized by these enzymes; polymorphism in these enzymes would affect its disposition [68].

#### **4.6.4 Elimination**

HCQ excreted in urine (15% to 25%); as metabolites and unchanged drug up to 60%, can be enhanced by urine acidification. Renal clearance is an important clinical consideration, especially in the patient with renal impairment. HCQ has a long terminal half-life ranged from 40 to 50 days [69]. HCQ is expected in breast milk [67,69,70].

### **4.7 Clinical Implication of HCQ PK in Management of Covid-19**

The high volume of distribution, and trapping within the endosome explain its potential efficacy in viral pneumonia. Slow accumulation (Fig. 3) suggests that use HCQ as early as possible likely to enhance efficacy in the management of viral infection. Screening for drug interaction should be manipulated to ensure its optimal use in the management of COVID-19, and therapeutic drug monitoring is highly recommended. We used the Henderson-Hasselbalch equation: [71] to estimate % mono-protonated CQ<sup>+</sup> at different pH. (Table 1). We realized there is a significant reduction of CQ<sup>+</sup> (lipid-soluble form) in acidic pH likely to be encountered in viral infections [13].

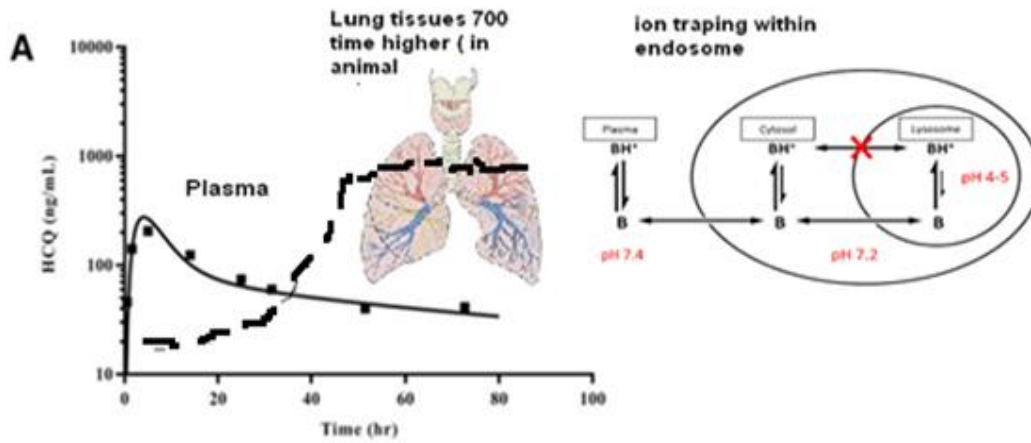


Fig. 4. Hypothetical illustration of the correlation between plasma and lung tissue level of HCQ (trapping within cells due to protonation)

Table 1. Ionization of HCQ as a function of blood pH

pH	% CQ+	pH	% CQ+
7.4	20.0	6.9	6.3
7.3	16.0	6.8	5.0
7.2	12.6	6.7	4.0
7.1	10.0	6.6	3.2
7	7.9		

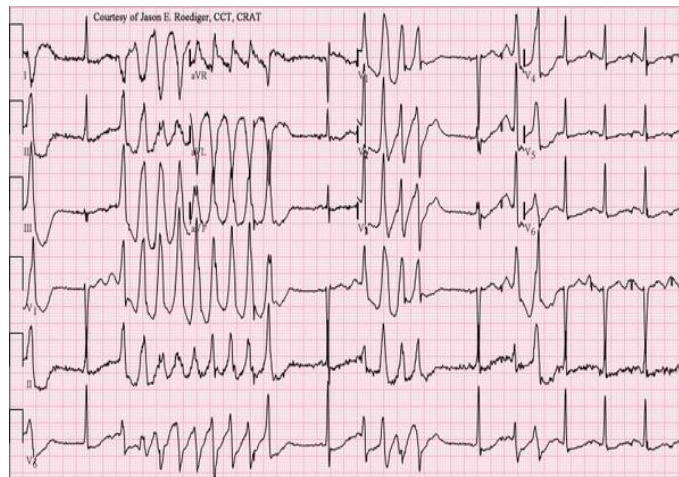


Fig. 5. QT prolongation and torsade de pointes (Tsp.)

#### 4.8 Approaches for Optimizing the Use of HCQ

A pharmacokinetic model approach was suggested to enhance our confidence in the utility of model g to optimize HCQ use [58]. A physiological pharmacokinetic model was recently developed to support,

whether HCQ lung concentration levels will be sufficiently high enough to treat SAR-COV2-infection or not. A population-based pharmacokinetic model (PBPk) model they which simulate HCQ lung concentrations with multiple dosing regimens was suggested to provide an optimal dosing regimen [72].

#### 4.8.1 Therapeutic Drug Monitoring (TDM)

TDM involves measuring the drug level at the specified time (e.g. trough level) to guide the dosage regimen on an individual basis. It is applied for drugs with a narrow therapeutic range or complicated pharmacokinetics [73]. Estimation of the HCQ blood level was suggested to optimize its uses in management systemic lupus erythematosus [74]. The currently published clinical trials reading HCQ adopted different regimens, and conflicting results were demonstrated, therefore. PK studies were suggested to define the optimal level of HCQ in management of COVID-19 [75].

#### 4.8.2 Pharmaceutics technology and Nano delivery system

Nano drug delivery system process several advantages, including enhanced biocompatibility, targeted delivery, reduced drug toxicity. This approach showed promising results regarding the optimal use of antimalarial drugs in the management of malaria [76] and autoimmune diseases [77]. These approaches provided an excellent platform to explore the utility of Nano delivery system to optimize the use of HCQ in management of Covid-19 (i.e. the design of formulation suitable to administer HCQ by inhalation).

#### 4.9 Side Effects of CQ/HCQ an Overview

The safety profile of CQ/HCQ is well documented. These include gastrointestinal side effects, retinal toxicity associated with prolonged use of CQ and HCQ or overdose. There is a list of precautions and contraindications of both drugs, for example, CQ is contraindicated in patients with porphyria (Both drugs should be used cautiously in patients with liver or renal failure) [78]. The clinician should also consider the reported possibility of the liver and renal impairment, induced by COVID-19 [79].

Focusing on particular adverse effects of HCQ likely relevant with short courses (7-10 days) likely to be applied in COVID-19.

##### 4.9.1 Cardiotoxicity of HCQ: [80,81]

It has been noticed that HCQ can lead to QT prolongation and torsade de pointes (Tsp) is a specific type of abnormal heart rhythm that can lead to sudden cardiac death (Fig. 4) development in susceptible individuals [82].

However, there is no strong correlation between the risk of Tsp development and drug-prolongation of QT intervals by drugs since not all patients with drug-induced QT prolongation will develop Tsp. However, despite this cardiotoxic effect HCQ is rare, co-prescription of azithromycin in Covid-19 could amplify this risk with HCQ [81].

##### 4.9.1.1 Suggested cardiac monitoring of COVID 19 patients on HCQ [83]

The baseline ECG allows for documentation of the QT (and corrected QTc) interval. Importantly, QTc will need to be monitored as chloroquine therapy can cause QT prolongation especially if used with azithromycin.

Overall, the average QTc in healthy persons after puberty is 420±20 milliseconds. In general, the 99th percentile QTc values are 470 milliseconds in post pubertal males and 480 milliseconds in post pubertal females [83].

In general, patients with the following QTc intervals are at low risk for significant QT prolongation and polymorphic VT:

- QTc <460 milliseconds in pre-pubertal males/females.
- QTc <470 milliseconds in post pubertal males.
- QTc <480 milliseconds in post pubertal females.

A QTc >500 milliseconds is considered highly abnormal for both men and women.

In such patients, efforts should be made to correct any contributing electrolyte abnormalities (e.g., hypocalcaemia, hypokalaemia, and/or hypomagnesemia), with goal potassium of close to 5 mEq/L.

Even in those with a normal QT interval, there should be a review and discontinuation of any QT-prolonging medications that may not be essential to the immediate care of the patient (e.g., proton pump inhibitors, etc.) [58].

#### 4.10 Ocular Toxicity of HCQ

Ocular side effects of HCQ include retinal toxicity (which can lead to permanent visual impairment) and deposition of the drug in the cornea [84]. HCQ appears to be considerably less toxic to the retina than chloroquine, possibly because



chloroquine crosses the blood-retinal barrier more easily. HCQ ocular toxicity depends critically on daily dosage and duration of use, as well as other risk factors. With attention to dosage and other factors, and with proper screening for early signs of toxicity. Risk factors include a daily dose of hydroxychloroquine >5.0 mg/kg (body weight), severe renal impairment, concomitant use of tamoxifen, and duration of use of about five years [85,86].

We suggest that identifying abnormalities with screenings and examination before the patient's visual complaints is essential when HCQ is suggested to be used in Covid-19, especially in the elderly.

#### **4.11 Hypoglycaemic Effects**

HCQ-induced hypoglycaemia is well documented in the literature [87]. Interestingly, this hypoglycaemic effect was suggested to be of clinical value as add on the drug to control T2DM in patients not adequately controlled on multiple medications [88]. Concerning the use of HCQ in COVID-19 patients, careful follow up of glucose level should be implemented. In the case of diabetic patients. Antidiabetic drug regimen should be tailored and individualized to each patient to avoid serious hypoglycaemia.

### **5. HCQ USE IN SPECIAL POPULATION**

#### **5.1 Use in Pregnant Women and Breastfeeding**

Pregnant women have changes in their bodies that may increase their risk of some infections and have a higher risk of severe illness when infected with viruses as COVID-19. Safety of hydroxychloroquine in pregnant patients with connective tissue diseases has been studied on one hundred thirty-three cases compared with a control group there was no statistical difference between HCQ and control groups and the authors considered HCQ is a safe drug [89]. However, its safety in pregnant females with COVID-19 so far is not clear and needs to be clarified. Chloroquine was also showed no appreciable teratogenic effect in pregnant women, administered the drug for chemoprophylaxis of malaria [88]. Fortunately, in COVID-19, HCQ is used for a short period of a low dose for prophylaxis. It is likely if no other risk factors in pregnant women the benefit of using HCQ in management of COVID

19 outweigh its low potential risk of teratogenicity.

Infants exposed to hydroxychloroquine during breastfeeding receive only small amounts of the drug in breastmilk [90]. A recent study in Chinese women taking HCQ for connective tissue disease indicated that HCQ is not likely to be harmful to infants on breastfeeding [91]. Concerning Covid-19, a low dose for prophylaxis not likely to be harmful to infants > 1month. For confirmed cases, the baby is thought to be isolated away from his mother.

#### **5.2 Use in Elderly**

There are no studies that have been done on this population of older Covid-19 patients. However, as a consequence of aging, it has been established from basic pharmacological sciences that the potential harms of medications in aging populations increased as a result of diminished elimination pathways. [92]). Therefore, great cautions must be considered when HCQ is given to elderly populations with COVID-19, and suspicion of toxicity is expected. Accordingly, patient monitoring is essential [93].

#### **5.3 Use in Children**

HCQ is approved for the treatment of malaria, rheumatoid arthritis, juvenile idiopathic arthritis, lupus erythematosus, and dermatological conditions caused or aggravated by sunlight [94]. Due to the assumed various immunomodulatory mechanisms of HCQ it has been used frequently for more than 40 years off-label for different autoimmune diseases (e.g., Sjögren's syndrome and inflammatory osteoarthritis) in a wide range of clinical conditions and, in particular, in chronic or acute and often very severe paediatric diffuse parenchymal lung diseases. Liccioli et al reported the first case of Acute Generalized Exanthematous Pustulosis (AGEP) caused by HCQ in a child affected by juvenile Sjögren syndrome [95].

#### **5.4 Liver and Kidney Impairment Patient Use**

When it comes to the impacts of different organs' ischemia/reperfusion (I/R) impairments, HCQ has been showcased to wield highly valuable impacts [96-98]; indeed, via the decreasing of inflammatory cytokine production, Fang et al. (2013) have stated that liver I/R injuries can be

amended via CQ treatment. Furthermore, whilst Tang et al. (2018) have garnered novel understandings of HCQ's anti-inflammatory impact in AKI treatment, they have also pinpointed that renal injury has been decreased by HCQ via cathepsin's reduction in regulation (CTS) B, as well as through CTSL-mediated NLRP3 inflammasome activation [99].

### **5.5 Drug Interactions and Contraindications**

When it comes to sufferers of neurologic, hematologic, and liver issues, chloroquine should be administered; and, when it comes to HCQ (cautioned against for sufferers of porphyria and psoriasis), this should largely be avoided for those with myopathy or visual field impairments. Further, going back to chloroquine, this is largely regarded as safe for administration to young children and pregnant women, although calcium and magnesium antacids—as well as kaolin, an anti-diarrheal agent, this should not be prescribed.

Demonstrating specifically via the debrisoquine recovery ratio that CYP2D6's activity is hindered by chloroquine, Adedoyin et al. [100] have underlined the finding that this can hinder metabolizing enzymes' activities in selective fashions, taking a large toll on some whilst leaving others completely. In this light, they additionally showcased a possible situation whereby drugs could interact whenever CYP2D6's substrates and chloroquine are provided, alongside one another, *in vivo*—something that may prove to be popular, considering its fairly lengthy 40-year half-life for those who have undergone long-term treatments of high chloroquine levels. Here, according to Chen et al., Eichelbaum et al. and Otton et al. a highly notable interaction in terms of medicine has the potential to come about with drugs that are either triggered by the impacted enzyme (e.g., hydrocodone; codeine), or possess limited therapeutic indices [101-104].

Being a harmless and low-cost drug that has been trusted for approximately seven decades, chloroquine phosphate has been at the center of the bulk of recommendations concerning remedying pneumonia that often accompanies Coronavirus [105].

### **6. CONCLUSION**

It was clear from this review of the possible mechanism of action of HCQ that the drug works

to inhibit the entry of the virus into the cell and also retard its reproduction, which enhances the use of HCQ to treat the virus in early phases of the disease. On the contrary, the use of HCQ in late cases of the disease may be useless as the late infections may lead to an increase in acidity of the blood, lung inflammation, other pathological changes which may negatively affect the distribution of the drug and predispose the patient for higher risk cardiac toxicity. Full care and treatment should be carried out under medical supervision for possible cardiac toxicity and many drug interactions and precautions.

Our review suggests that clinical studies must be conducted on a large number of COVID-19 patients using HCQ with other relevant medications in the early phases of the disease in agreement with published data [106].

### **DISCLAIMER**

This article is intended for education and research purposes only. It is not a substitute nor aimed to change recommendations provided by national or international guidelines for the management of COVID-19. Information is provided to illustrate concepts but not aimed to be used for any kind of intervention in clinical. Authors tried to do their best but do not guarantee, the accuracy, reliability, completeness of the information provided in this review.

### **CONSENT**

It is not applicable.

### **ETHICAL APPROVAL**

It is not applicable.

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### COMPETING INTERESTS

Authors have declared that no competing interests exist.

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