Chapter 8

Myth surrounding the FDA disapproval of hydroxychloroquine sulfate and chloroquine phosphate as drugs for coronavirus disease 2019

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Chapter outline

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Letter from the editor

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This chapter presents the therapeutic potentials of hydroxychloroquine (HCQ) and chloroquine (CQ) as therapeutic options for the novel coronavirus disease 2019 (COVID-19), a pandemic disease that has claimed the lives of tens of thousands of people just within few months of emergence.

Myths about COVID-19 and hydroxychloroquine

COVID-19 is a disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), characterized by fever, tiredness, dry cough, acute respiratory distress syndrome, shortness of breath, loss of speech, movement, among other symptoms. SARS-CoV-2 is a very deadly novel coronavirus with no universally accepted treatment regimen as at the time of writing this chapter.

The period of writing this chapter coincided with when the COVID-19 pandemic is at its peak while wreaking havoc in many countries of the world, like the United States, United Kingdom, Italy, France, Spain, Brazil, Russia, Iran, China, and the world at large, with some countries recording more than 1000 deaths in 1 day due to COVID-19. The situation was so chaotic that it turned out to be the greatest crisis man has ever faced since World War II. The situation was also worsened by the lack of reliable diagnostic tools to detect those infected in order to isolate them and monitor their progress of recovery. One such tool for detection is the body temperature check because the virus was proposed to cause elevated body temperature in infected patients. This technique was not reliable because an increase in body temperature could be a result of other underlying medical conditions or environmental temperature. At that time, the only viable option was to seek ways to reduce the incessant deaths by breaking the chain of SARS-CoV-2 transmission through robust government policies to restrict large gatherings and movement of people. By this measure, countries and interstate land boarders were locked including the shutdown of international airports, seaports, markets and public organizations, churches and mosques, educational institutions, and so on. During the period, many people on international trips were stranded. Some passenger ships and crew with suspected cases of COVID-19 were not allowed to

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dock, leaving them stranded in the sea for weeks. The world economy crumbled with nothing working.

Note: *This special note was written on July 29, 2020, prior to the submission of this book to the press. This note was necessary to serve as a caution in the use of hydroxychloroquine. Details of hydroxychloroquine were discussed fully in this chapter.*

Still within the period of the aforementioned date, the world began experiencing another spike in cases of COVID-19, suggesting another need for worldwide lockdown just a few weeks after a brief relapse which enabled selective reopening of borders, government institutions, markets, and the world football leagues, among others, under strict health preventive measures such as social distancing and compulsory wearing of face masks and hand washing, as recommended by the World Health Organization (WHO). The period of the pandemic also coincided with the US-China trade war which led the US President, Donald J. Trump among other reasons to refer to the virus as "China virus." His tactics in confronting the virus by initially downplaying its severity left gaps in the healthcare system. Not only Trump many world leaders downplayed the virulent nature of SARS-CoV-2, partly because only little was known about the virus. One such outspoken figure is the President of Brazil, Jair Bolsonaro who called the virus "little flu." Bolsonaro boasted about the use of HCQ to treat COVID-19 just like Trump earlier suggested due to an in vitro preliminary result that found that CQ and HCQ inhibited the replication of SARS-CoV-2. Unfortunately for Bolsonaro, the "little flu" got hold of him while his country, Brazil, became the second worst-hit country behind the United States. Earlier before Bolsonaro, the Prime Minister of United Kingdom, Boris Johnson, had already contacted the virus and spent days in the intensive care unit of the hospital. Trump later got infected but recovered quickly. Eventually, they recovered but tens of thousands of others were not so lucky. At a later date after the ordeal by Johnson, he was quoted as saying that his government regretted downplaying the severity of the virus and should have handled it differently.

Again, the lack of information coming out from China about the real statistics of deaths from the onset and the approach of the WHO also affected the management of the disease. In the United States, the power tussle between the US Democrats and the Republicans about Donald Trump's impeachment in December 2019 (the same period that COVID-19 emerged) got attention diverted. Also, the mainstream media and the focus on the upcoming US presidential election (in November 2020) did not help the situation. All these factors including the Black Lives Matter movement (caused by the Police murder of George Floyd, a black man resident in Minneapolis, Minnesota) did not help the situation as attention got diverted to internal issues instead of everyone working jointly to stop the rampaging virus.

From the foregoing and the pressure surrounding the fact that people are dying in large numbers led to the first suggestion and the wide acceptance of HCQ as a therapeutic option for COVID-19. But what really matters is the question, "*Did it really work*?" Unfortunately, results from preclinical studies found negative results

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Letter from the editor—cont'd

with adverse health problems. This stance is still in dispute as many medical experts who treated patients with HCQ believed it worked. These two arguments call for the need to reexamine the potentiality of HCQ against SAR-CoV-2. On this background, I recommend new randomized, double-blind, placebo-controlled studies that should be free from any government sponsorship or big pharmaceutical industries so that there could be an authentic study that will bring closure on whether HCQ worked or not.

To potential users of this book, I recommend that you read this chapter in full to find existing information about the good and dark side of HCQ.

8.1 Introduction

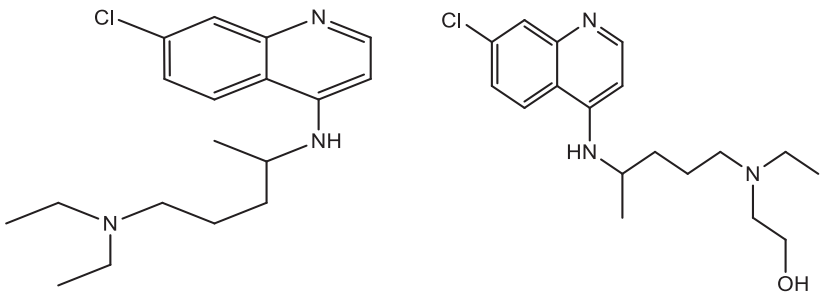
Towards the end of December 31, 2019, the people of China, Hubei Province, Wuhan city, were reported to be suffering from incomprehensible respiratory distress of an unknown etiology and were admitted to the hospital [1], by reason of which physicians and health officials regards as pneumonia. However, throat specimens were evaluated for the identification of the pathogen, and surprisingly genetic analysis of PCR reactions (real-time) and next-generation sequence ascertained an agent like coronavirus [2]. Later on January 7, 2020, a new human pathogenic coronavirus was discovered [2] and momentarily the WHO gave it the name "novel coronavirus 2019 (nCoV-19)" [3]. This name was later changed by the International Committee on Taxonomy of Viruses (ICTV) that is responsible for viral nomenclature to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) due to its similarity with SARS coronavirus at genomic level [4]. Initially, the disease of SARS-CoV-2 was thought to be viral pneumonia, but as a result of some exceptional clinical distinctiveness and unique nature, the WHO officially named it as coronavirus disease 2019 (COVID-19) [5]. COVID-19 is characterized by pyrexia, fatigue, and respiratory distress such as flu, sneezing, coughing, sputum production, and, in severe cases, diarrhea or death [6—9]. Also, comparing the symptoms seen in COVID-19 patients and those suffering from malaria, it was found that some similarities exist. These symptoms include headache, fever, and fatigue.

The incessant deaths arising from the ongoing COVID-19 pandemic has inspired the adoption of several therapeutic options and strategies against this newly emergent viral infection, yet without success. Early studies suggest that CQ and HCQ could be effective against COVID-19 with immunomodulatory properties [10,11]. CQ and HCQ are frequently used against malaria, skin diseases, and arthritis. On March 29, 2020, the US Food and Drug Administration (FDA) issued emergency authorization for the use of HCQ sulfate as a possible treatment option for COVID-19 or for use in clinical trials [12]. This

permission was necessary to allow the use by doctors who do not have any other therapeutic option for COVID-19 [13]. However, this raised hopes and prompted high market demand for both drugs because some countries had adopted them and began prescribing them as being effective against COVID-19 [13,14]. Unfortunately, various studies performed to investigate the clinical effects of both drugs against COVID-19 came with unsatisfactory results [14]. A thorough analysis of patients' data who were administered HCQ shows that there was no improvement of any sort [15]. Both drugs were eventually found to cause various disorders in COVID-19 patients including serious cardiovascular diseases like ventricular tachycardia, characterized by treacherously fast heart rate and drug-induced prolonged QT (QT refers to an interval seen in an electrocardiogram [EKG] test of heart function) [15,16]. Also, it was found that higher doses of HCQ when used in combination with other drugs, such as the antibiotic azithromycin, increased the risk of side effects [15,17–20].

8.2 Chloroquine and COVID-19

CQ is a medication that has been around for years. It was made in the year 1934 as an antimalarial drug. The analog of CQ called HCQ (Fig. 8.1) has been used for the treatment of autoimmune diseases, e.g., rheumatoid arthritis, systemic lupus erythematosus, etc. Compared to chloroquine, HCQ has less drug-drug interactions and less severe toxicities [21,22]. CQ is no longer allowed in some countries such as the United States and Uganda for the treatment of malaria due to the resistance built by the parasites that cause malaria. However, both CQ and its analog (HCQ) are routinely used in pediatrics for the treatment and prevention of rheumatologic conditions. HCQ has been approved by the US FDA as a medication for malaria, rheumatoid arthritis, and lupus erythematosus. HCQ is commercially available in the United States, but it is not approved for COVID-19 treatment. CQ is not commercially available in the United States [22,23].



Chloroquine Hydroxychloroquine

FIGURE 8.1 Chemical structures of chloroquine and hydroxychloroquine.

CQ and its analog HCQ were reported to be possible inhibitors to some coronavirus, especially SARS coronavirus (Fig. 8.2). Both drugs seem to prevent viruses from binding to the cells of humans and block their chance of having access to replicate in human cells. It appears to have stimulating effects on the immune system of humans [22]. However, there have been mixed reactions and reports regarding the effectiveness of HCQ for COVID-19 treatment. The WHO dropped the clinical trial of HCQ, as a drug candidate for

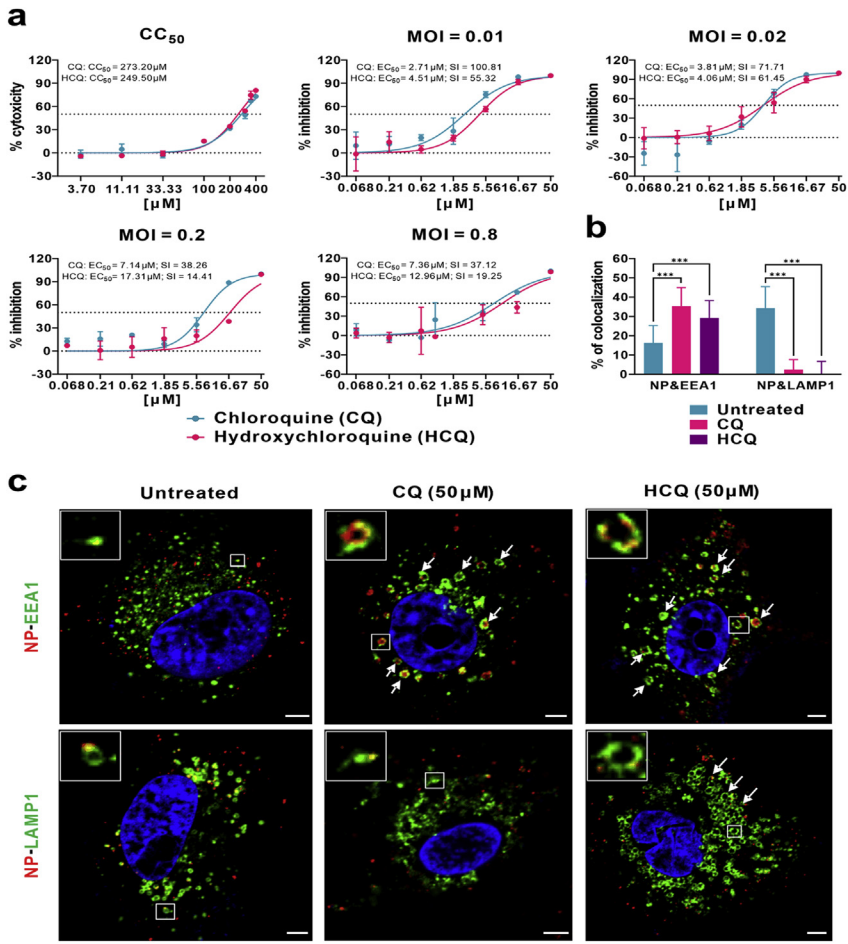


FIGURE 8.2 Comparative antiviral efficacy and mechanism of action of chloroquine (CQ) and hydroxychloroquine (HCQ) against SARS-CoV-2 infection in vitro. (A) Cytotoxicity and antiviral activities of CQ and HCQ. (B, C) Mechanism of CQ and HCQ in inhibiting virus entry. *Reproduced from Liu J, Cao R, Xu M, et al. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. Cell Discov 2020;6:16. https://doi.org/10.1038/s41421-020-0156-0. License: http://creativecommons.org/licenses/by/4.0/.*

COVID-19 treatment, stating their inefficacies against the virus. A study in China reported that CQ improved outcomes on COVID-19 patients and "might improve the success rate of treatment" and also "shorten hospital stay." Clinical data on the treatment of COVID-19 with HCQ mostly arise from their usage in COVID-19 patients with symptoms ranging from mild to moderate [22,23]. The data on severe COVID-19 patients are very limited. Similarly, the data on critical patients are rare.

On June 4, 2020, a major multinational analysis was retracted after clearly reporting no clinical benefits observed for administering chloroquine, or HCQ, only or in company with a macrolide. It reported that they did raise the risk of side effects, especially cardiac dysrhythmias. The FDA, on June 15, 2020, added updates to their fact sheets on remdesivir, warning that the antiviral activity of remdesivir may reduce if used with CQ or HCQ [23].

8.2.1 Chloroquine antiviral mechanisms of action

CQ has antiviral effects on certain viruses. It has several mechanisms of action which often differ accordingly. Overall, CQ increases the pH of late endosomes and lysosomes, causing impaired viral release [22]. The viral release from the endosome and/or lysosome requires low pH. Consequently, the virus cannot release genetic materials, making it impossible to replicate or even enter the cell [21,22]. CQ appears as a zinc ionophore which allows the extracellular zinc entrance into cells and inhibits RNA polymerase of viruses. In addition, the interaction between haem and CQ prevents in vivo ferriprotoporphyrin (FPIX) incorporation into haemozoin, resulting in toxic FPIX buildup that consequently overwhelms the parasite.

Both CQ and its analog increase pH of the endosome, blocking the fusion of SARS-CoV-2 and membranes of host cells [21]. CQ also prevents glycosylation of "cellular angiotensin-converting enzyme 2 receptor" that might interfere with the binding of the SARS coronavirus to cell receptors. CQ and HCQ might block SARS-CoV-2 transport from initial endosome to endolysosome, in vitro, which might be needed for releasing the genome of the virus.

CQ has been reported to impair the initial stage of the viral replication through interfering with the endosome-mediated entering of enveloped viruses, including the chikungunya virus or dengue virus, which is pH-dependent [21]. Owing to the endosomal alkalization, CQ was effective in vitro against chikungunya viruses when it was added to Vero cells before exposure to the virus [21]. The pH-dependent entry mechanism was reported for SARS-CoV-1 too. Chloroquine-mediated hepatitis A virus inhibition was connected with uncoating, therefore inhibiting its cycle of replication entirely.

CQ inhibits pre-entry stage of the virus cycle through meddling with the virus ability to bind to the cellular cells surface receptors. In addition, CQ was reported to prevent the action of quinone reductase 2, "a structural neighbor of UDP-*N*-acetylglucosamine 2-epimerases," which involves sialic acids

biosynthesis. Devaux et al. [21] defined sialic acids as "acidic monosaccharides found at the extremity of sugar chains present on cell transmembrane proteins and are critical components of ligand recognition." It is likely that CQ interference with the biosynthesis of sialic acid may explain the drug broad antiviral spectrum because viruses use moieties of sialic acid as receptors. In vitro, the anti-SARS coronavirus 1 effect of CQ was attributable to glycosylation deficit of the cell surface receptors of the virus [21].

8.2.2 Chloroquine bioavailability and toxicity

The average oral bioavailability of CQ is 90% [24]. CQ has a great apparent distribution volume as a result of its extensive tissue binding capacity. Its elimination rate from the body is very slow and has urine detectability for up to 12 months after administration. The terminal elimination half-life of CQ is 45−55 days and 59−67 days for desethylchloroquine, its main plasma metabolite [23]. The bioavailability of CQ oral solution often ranges from 52% to 102%, while oral tablets range from 67% to 114% [23]. Oral CQ has C_{max} of 65−128 μg/L with 0.5h T_{max} [23]. Intravenous CQ has C_{max} of 650−1300 μg/L [21−23]. Patients with an overdose of CQ may experience cardiovascular collapse, visual disturbances, nausea, headache, drowsiness, vomiting, shock, cardiac arrest, hypokalemia, convulsions, respiratory arrest, and coma [22]. The side effects of CQ may include weakness, dyspnea, nausea, vomiting, dysphagia, tremors, and convulsions. Itching is reported in blacks. Prolonged administration of CQ may lead to retinal toxicity, resulting in blindness.

8.3 Plaquenil (hydroxychloroquine sulfate)

HCQ is a common plant derivative of CQ which is well recognized for its different pharmacological activities. HCQ which was first synthesized by the United States in 1946 is obtained by adding hydroxyl group above CQ. It has been found that it is less harmful and toxic compared to CQ. From scientific entry, HCQ ($C_{18}H_{26}C_1N_3O$) is known as aminoquinolines because it has an amino group attached to the quinoline ring (Fig. 8.1). It was approved by the United States in 1955 for medicinal purposes. HCQ is one of the most essential medicines in the WHO list, which is safer and highly effective in the medical health system. HCQ is more soluble in comparison to the other quinolines due to the hydroxyl group. HCQ, a 4-aminoquinoline, is a frequently used antimalarial drug [25]. HCQ has been used for the treatment of different types of diseases (Table 8.1), which include malaria, HIV, Whipple's disease, fungal infection, rheumatoid arthritis, porphyria cutanea tarda, antiphospholipid antibody syndrome, systemic lupus erythematosus, Q-fever, and immunological diseases [26,27]. Also, HCQ is an important drug of neurological disease that easily crosses the blood-brain barrier. HCQ has a half-life of about

TABLE 8.1 Medical Uses of hydroxyquinine.

Diseases	Indication	References
SARS-CoV-2/COVID-19	400 mg dose of HCQ sulfate twice a day and 200 mg twice daily for 4 days have been found to be suitable for COVID-19 treatment	[34]
HIV	Inhibits the posttranslational modification process of glycoprotein 120 (gp 120)	[35]
Diabetes	Used in combination with insulin or glibenclamide for up to 6 months. Type 1 diabetes mellitus and glucose control	[36]
Lipid metabolism	Reduction in triglycerides	[37,38]
Q fever	A combination of HCQ and doxycycline has always been proposed and used for primary treatment for chronic Q-fever	[39]
Whipple's disease	Whipple's disease is treated using a combination of HCQ and doxycycline	[40]
Fungal infections	HCQ shows in vitro antifungal activity against intracellular fungi such as *Histoplasma capsulatum* and *neoformans*	[41]
Zika virus	Zika virus, a member of the Flaviviridae family that is spread in humans by mosquitoes and ticks. HCQ prevents these mosquitoes and ticks from spreading the infection	[42]
Sjogren's syndrome	Sjogren's syndrome is widely treated with HCQ	[43]
Chikungunya virus	Chikungunya virus is an alphavirus that is mainly transmitted by *Aedes aegypti* and *Aedes albopictus* mosquitoes. The combination of methotrexate and sulfasalazine with HCQ showed potent effects.	[44]
Rheumatic disease (lupus erythematosus)	HCQ is used in mainly cutaneous lupus patients	[45]
Rheumatoid arthritis	The triple-drug therapy including (methotrexate, sulfasalazine, and HCQ) is considered for treatment	[46]

Continued

TABLE 8.1 Medical Uses of hydroxyquinine.—cont'd

Diseases	Indication	References
Porphyria cutanea tarda (PCT)	Repeated phlebotomy or low-dose regimen of HCQ (100–200 mg twice weekly)	[47]
Chronic ulcerative stomatitis (CUSs)	HCQ is beneficial for the treatment of CUS	[48]
Polymorphic light eruption (PLE)	HCQ is effective and safe in the treatment of PLE	[49]
Cancer/neoplastic	Used to treat cancer with significant direct and indirect effects on the body	[50,51]

1–2 months [28]. HCQ is excreted unchanged in the urine. Drug and its metabolites are excreted slowly in urine; the unabsorbed drug is excreted in feces. The entire process is completed through the N-desethylation pathway, in which it is metabolized by some enzymes (CYP2D6, CYP2C8, CYP3A4, and CYP3A5) into N-desethylhydroxychloroquine. The relationship between blood N-desethylhydroxychloroquine level and efficacy is directly tied to the treatment of diseases through HCQ [29]. HCQ appears to be much more potent in vitro against COVID-19 causative agent [10,30–32] and also the in vitro antiviral activity of HCQ showed more potent activity in comparison to CQ [33]. It's used against malarial parasites and inhibits the developed erythrocytic stage of plasmodia. It produced irregular heart rhythms when used with azithromycin antibiotic.

8.3.1 Hydroxychloroquine sulfate properties

Plaquenil is a white crystalline powder that is soluble in water and insoluble in ethyl alcohol, chloroform, and petroleum ether. Plaquenil IUPAC name is "2-[[4-[(7-chloro-4-quinolyl) amino] pentyl] ethylamino] ethanol sulfate" (1:1). Its molecular weight is 433.95 and the molecular formula is $C_{18}H_{26}C_1N_3OH_2SO_4$. Its structure is flat, aromatic core, and weak base. It occurs in two different symmetry or enantiomer (R and S isomers) forms. HCQ with (R) − (−) is present at a much higher concentration than (S) − (+) HCQ [35].

8.3.2 Pharmacokinetics (A, D, M, and E)

HCQ is therapeutically used in sulfate salt form and is absorbed into the upper intestinal tract of the intestine. The lag time before oral absorption of HCQ sulfate 200 mg (taken as Plaquenil tablets) is measured in the blood as the diastereoisomer ranges from 0 to 0.85 h (mean 0.43 h) [52].

The half-life of HCQ is 40−60 days. It is distributed in aqueous cellular and intercellular compartments with (−1300 h) residence times. It exhibits pharmacokinetic properties similar to CQ with very rapid GI absorption and mass distribution and elimination by the kidney. HCQ is metabolized to N-desethylhydroxychloroquine by cytochrome P-450 "CYP-2D6, 2C8, 3A4, and 3A5" enzymes [53].

8.3.3 Cytokine (production and immune activation)

HCQ indirectly produces different types of cells and reduces the production of anti-inflammatory cytokine. It inhibits the production of "IL-1, IL-6, TNF, IFN-α, and IFN-γ."

8.3.4 Pharmacodynamics

HCQ is lipophilic and a weak base that can easily pass through the plasma membrane. In the cell, the pH value of lysosomes increases from 4 to 6 [54]. Changes in pH result in the inhibition of lysosomal acidic proteases, which lead to reduced proteolysis effects [55]. The intracellular processing effect also decreases as the lysosomes have a higher pH value, which is responsible for glycosylation and protein secretion in immunologic and nonimmunologic components [56].

8.3.5 Adverse effects

Side effects of HCQ are headache, dizziness, stomach cramps, vomiting, nausea, loss of appetite, and diarrhea [28,57]. Other side effects are itching, liver failure, hair loss, anemia, acne, blood disorders, convulsions, change on feeling and emotion, skin coloring, psoriasis, skin inflammation and scaling, rash, vertigo allergy, vision problems, heart problems, urinary problems, weight loss, nightmares, and bleaching of hair blisters [29]. Also, the following less frequent side effects are seen: erythroderma, urticaria, exfoliative dermatitis, morbilliform rashes, eczematous eruptions, photosensitivity, and erythema annulare centrifugum [27,58].

8.3.6 Drug interactions

Caution should be taken in the combination of the following drugs with HCQ or CQ: digoxin, insulin, chlorpropamide, glipizide, glimepiride, glyburide, repaglinide, mefloquine, antiepileptics, amiodarone, chlorpromazine, clarithromycin, phenytoin, carbamazepine, and cyclosporine. Importantly, HCQ gets easily transferred into mammal's breast milk [59], so it is not recommended for pregnant or nursing mothers.

8.3.7 Approval and disapproval of the use of HCQ

The approval for use of HCQ and CQ in the treatment of COVID-19 was suggested and permitted to off-label use by AIFA Scientific Technical Commission of Italian Medicines Agency, dated March 17, 2020 [60]. After that, the US FDA (EUA) also allowed to use HCQ sulfate and CQ phosphate in the treatment of COVID-19 [61,62]. Due to the anticipation of product shortage, the FDA circulated specific guidelines to all generic drug manufacturers to make sufficient production of HCQ sulfate and CQ phosphate [63]. At the end of April 2020, there has been not sufficient evidence to support the use of HCQ for the treatment of COVID-19 [64]. Based on this reason, on April 30, 2020, HCQ use as a COVID-19 drug was disapproved except for emergency situations [65].

8.4 Future projection

Due to the fact that HCQ and CQ earlier showed some signs of inhibiting the replication of SARS-CoV-2 in vitro and the fact that some medical practitioners are testifying of their usefulness against COVID-19, it is enough reason to conduct a new clinical trial in order to unravel the truth whether they work or not.

8.5 Conclusions

As the number of confirmed cases of COVID-19 is still on the increase and the fact that people are dying because of lack of drugs, the use of HCQ in such a scenario should not be outlawed but traded with caution as new clinical trial outcomes are expected.

List of abbreviations

COVID-19 Coronavirus disease 2019
CQ Chloroquine
FDA Food and Drug Administration
HCQ Hydroxychloroquine
HIV Human immunodeficiency virus
IL Interleukin
SARS-CoV-2 Severe acute respiratory syndrome coronavirus 2
TNF Tumor necrosis factor
WHO World Health Organization

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