Contents lists available at ScienceDirect

One Health

journal homepage: http://ees.elsevier.com

Editorial Commentary

Coalition: Advocacy for prospective clinical trials to test the post-exposure potential of hydroxychloroquine against COVID-19

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ARTICLE INFO

Keywords
COVID19
SARS-CoV2
Hydroxychloroquine
Chloroquine
Systemic lupus erythematosus
Immunomodulation, Coronavirus, malaria, antiviral

ABSTRACT

Our coalition of public health experts, doctors, and scientists worldwide want to draw attention to the need for high-quality evaluation protocols of the potential beneficial effect of hydroxychloroquine (HCQ) as a post-exposure drug for exposed people, meaning people with close contact with positive tested patients, including home and medical caregivers. We have reviewed the mechanisms of antiviral effect of HCQ, the risk-benefit ratio taking into consideration the PK/PD of HCQ and the thresholds of efficacy. We have studied its use as an antimalarial, an antiviral, and an immunomodulating drug and concluded that the use of HCQ at doses matching that of the standard treatment of Systemic Lupus erythematous, which has proven safety and efficacy in terms of HCQ blood and tissue concentration adapted to bodyweight (2,3), at 6 mg/kg/day 1 (loading dose) followed by 5 mg/kg/day, with a maximum limit of 600 mg/day in all cases should swiftly be clinically evaluated as a post-exposure drug for exposed people.

1. Introduction

The world is facing significant challenges because of COVID-19. Briefly, these include [1] how to prevent the disease, [2] how to treat severe cases, [3] how to reduce the medical, social, and economic impact of the illness, and [4] how to end the pandemic. Social distancing measures were rapidly implemented, albeit not uniformly, and other known public health measures such as contact tracing are also variably implemented. Clinical trials are underway using repurposed drugs, new drugs, and new technologically developed antibody drugs. Review of the recently shared preliminary results reveals that most of the data, while valuable, fail to provide definitive evidence of effective lead compounds. Mainly this is because most of these initial studies are observational and not controlled studies. Thus, documented treatment is still lacking. In spite of the paucity of clinical evidences of an unequivocal beneficial effect of chloroquine on COVID-19, the absence of an effective treatment so far, the untimely publicity given to the potential effect of chloroquine and the consequent social and political pressure raised the demand for urgent clinical trials and even resulted in the simultaneous release of the drug for its compassionate use in the treatment of severe cases.

Meanwhile, the development of a safe and effective vaccine is likely to take many months or years.

A crucial issue that has not yet been adequately addressed is the pharmacological control of virus replication in contact cases before individuals show symptoms. Use of drugs has the potential to both reduce the risk of disease manifestation and to decrease the presymptomatic spread of SARS-CoV2.

Considering the incredible amount of conflicting medical, political and social debates, not always scientifically based, about the use of drugs for COVID-19 treatment, it is time to implement prospective clinical trials to answer the question: can prophylactic doses of hy-

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https://doi.org/10.1016/j.onehlt.2020.100131

Available online xxx
2352-7714/

droxychloroquine decrease the risk of clinical infection in documented exposed people? Considering the ongoing world tragedy, no option should be discarded even if more robust scientific evidences are still lacking.

We want to draw attention to the need for high-quality evaluation protocols of the potential beneficial effect of hydroxychloroquine (HCQ) as post-exposure drug for exposed people, meaning people with close contact with positive tested patients, including home and medical caregivers.

Here we provide information that justifies a clinical trial of hydroxychloroquine [1] as a post-exposure drug together with the background needed to safely and properly design such a clinical trial, taking into consideration the PK/PD of hydroxychloroquine, its action against virus including *Coronaviridae*, its potential toxicity in humans and the impact of repurposing for patients with inflammatory diseases.

2. Hydroxychloroquine post-COVID-19 exposure: for whom, when, how, why?

2.1. For whom

Millions of people are currently exposed to a high risk of contamination. Among them, adults taking care of family members who tested positive for SARS-CoV-2 at home, and medical and paramedical staffs treating hospitalized patients with symptomatic COVID-19, are highly susceptible to infection and may represent a second wave of extreme importance in the next few weeks. If those people get sick, we'll face another significant problem. Those highly exposed people should be protected. In that case, social distancing measures do not apply. In the absence of a vaccine, post-exposure pharmacological protection is the only way to prevent caregivers from becoming symptomatic.

We do not promote the general use of HCQ as prophylaxis in the general population for four main reasons: (1) There is evidence that HCQ may kill the virus *in vitro*, but there is as yet, no data regarding the use of HCQ as a post-exposure for asymptomatic people.

(2) Such recommendation will favor uncontrolled use of HCQ leading to risks of inappropriate use that could cause serious side effect, inefficacy, supply shortage and non-authorized speculation.

(3) Designing prospective clinical trials to test general use would be difficult because of the challenge of establishing a control population of unexposed persons, leading to difficulties in data analysis and lack of evidence.

(4) The risk of side-effects required close follow-up and clinical monitoring.

2.2. When

We recommend the post-exposure regimen of HCQ for asymptomatic people, whether or not they have been tested for SARS-CoV-2, in close contact with symptomatic patients positive for SARS-CoV-2 and to start the regimen as soon as possible. For HCQ blood concentration to reach a steady-state takes time (approximately six days), while the incubation period of COVID-19 before symptoms is also approximately six days; thus, the regimen should be started on the first day of exposure to the risk.

2.3. How

We promote the use of the HCQ to match that of the standard treatment of Systemic Lupus erythematous which has proven safety and efficacy in terms of HCQ blood and tissue concentration adapted to bodyweight [2,3], at 6 mg/kg/day 1 (loading dose) followed by 5 mg/kg/day, with a maximum limit of 600 mg/day in all cases. The duration of the post-exposure regimen should last as long as the contact with a positive patient last or in case of repeated exposure, with a minimum of 10 days to reach a blood concentration at steady state. The terminal elimination half-life is approximately 50 days [4] leading to a long term efficacy.

Considering the highly documented safety of orally administered HCQ for a short time, we consider that the highest possible safe dose should be used, under the control of competent medical staff, in order to reach the minimum HCQ tissue level required to inactivate a clinically significant proportion of the virus.

2.4. Why

Hydroxychloroquine is a more soluble hydroxy-analogue of chloroquine (CQ), which was first synthesized by Hans Andersag in 1934, and proven by military testing during World War II as a safe antimalarial used successfully during the 20th century to prevent and treat malaria in endemic areas [5]. In the 1990s studies revealed that hydroxychloroquine (HCQ), has immunomodulatory properties; leading to its use in the treatment of autoimmune diseases such as Lupus and rheumatoid arthritis [5,6].

As early as the 1990s, researchers noted the antiviral effect of hydroxychloroquine [7]. Currently, there are over 123 references on PubMed obtained using the keywords: “virus, hydroxychloroquine” similarly, web of science reveals a high interest in hydroxychloroquine and its role in viral diseases since the early 1990s.

Hydroxychloroquine and chloroquine have demonstrated *in vitro* antiviral effectiveness against Herpes simplex virus type 1 [8], Zika [9,10], HIV [11], MERS [12], SARS-CoV [12], HCoV-OC43 [13], Chikungunya [14], Hepatitis C [15], and several other viruses [11,16]. For coronavirus, some studies suggested, at least *in vitro*, some efficacy of chloroquine on the SARS-CoV virus [12,13] or MERS-CoV [17].

Using Vero E6 cells infected with nCoV-2019BetaCoV/Wuhan/WIV04/2019, Wang et al. [18] conducted standard assays to determine the potency (half-maximal effective concentration or EC_{50}) and the cytotoxicity at 50% (the half-maximal cytotoxic concentration or CC_{50}) of Chloroquine. Wang's study showed CQ has potency against SARS-CoV-2 at 1.13 μM (EC_{50} of 1.13 μM) and great safety at therapeutic doses since CQ did not show significant toxicity until the concentration exceeded 100 μM (CC_{50} greater than 100 μM). A previous study showed that CQ had an IC_{50} of 2.5 ± 0.7 μM with a CC_{50} of 31.5 ± 14.8 [19]. More recently, Yao et al. showed that Hydroxychloroquine (HCQ) was more potent than chloroquine (EC_{50} = 0.72 and EC_{50} = 5.47 μM respectively) at 48 h [20].

Hydroxychloroquine shows a high partitioning in tissue, including lung and brain. This chemical property offers a key clinical advantage in the case of COVID-19.

HCQ has a ten-fold concentration ratio in the lungs [21]. A recent review described a series of 85 case reports of children presenting interstitial lung diseases and treated with HCQ or CQ at doses ranging from 3.5 to 10 mg/kg body weight/day with a maximum of 600 mg/day. HCQ was well-tolerated in most cases with relatively few side effect. Of the 16 patients who were treated exclusively with HCQ or CQ, the symptoms improved in 14 cases [21].

Signs of anosmia and hyposmia are common in coronaviruses, and currently, loss of smell is noted in as many as 30% of patients with COVID-19 [22], even those who are otherwise asymptomatic (www.entuk.org/sites/default/files/files/LossofsenseofsmellasmarkerofCOVID). These signs likely arise as a consequence of the SARS-CoV2 passing through the olfactory epithelium to the olfactory areas of the brain, a concept supported by studies of other coronaviruses [23,24]. Previous work with SARS-CoV1 indicated that it could cross the cribriform plate of the ethmoid bone which can produce cerebral involvement [25]. A study of the neurological manifestations of 214 hospitalized patients with COVID19 revealed neurologic symptoms in 36.4% which fell into three categories [1] central ner-

vous system (CNS) symptoms or diseases (headache, dizziness, impaired consciousness, ataxia, acute cerebrovascular disease, and epilepsy), [2] peripheral nervous system (PNS) symptoms (hypogeusia, hyposmia, and neuralgia), and [3] skeletal muscular changes (Mao L, et al. Neurological Manifestations of Hospitalized Patients with COVID-19 in Wuhan, China: a retrospective case series study: pre-print, medRxiv not yet peer-reviewed] 25 Feb, 2020).

Hydroxychloroquine penetrates the central nervous system. Patients with glioblastoma were safely treated with HCQ (600 mg/day) used in conjunction with radiation and adjuvants [26]. The correlation between brain and plasma concentrations showed a 4 to 30-fold difference for HCQ, demonstrating its ability to diffuse in the brain [27]. Based on this observation, hydroxychloroquine may reach antiviral concentrations in the brain, leading to an expected preventive effect on early symptoms such as anosmia, which may persist after recovery from COVID-19.

3. Benefits/risks of hydroxychloroquine against the virus

3.1. Benefits

Hydroxychloroquine has a wide range of indications, including rheumatoid arthritis, systemic lupus erythematosus, and polymorphous light eruption (Physicians' Desk Reference. Hydroxychloroquine sulfate - Drug Summary. https://www.pdr.net/drug-summary/Plaquenil-hydroxychloroquine-sulfate-1911 (accessed 29 March 2020)). HCQ is administered orally in doses ranging from 100 to 600 mg daily. HCQ has also been tested for other indications such as cancers [28], multiple sclerosis, and diabetes mellitus [29]. In the current context of this extreme worldwide emergency, it is reasonable to propose that even if we could only reduce viral replication by 10 to 30% there would likely be a significantly reduced transmission and severity of COVID19, and improved clinical outcome. By using EC50, we are describing the proposed thresholds of efficacy at values that exceed those values, specifically, we are describing that these 4-aminoquinoline drugs could decrease virus replication or viral survival by 50%. Based on that proposal, lower plasma concentrations of HCQ, which we can easily obtain from a standard dosage regimen, is likely to be of significant clinically and public health impact.

3.2. Risks

The antiviral activity of HCQ is thus, demonstrably higher than its cytotoxic side effects, which permits a high selectivity index. Currently, CQ and HCQ are denigrated by some because of their potential side effects. But toxicity is described as a feature of transiently high and dangerous peak concentrations that may develop during parenteral not appropriate oral, administration [30].

The risk of retinopathy associated with hydroxychloroquine treatment has been well documented for decades. It was recently shown that the prevalence of retinopathy ranged from 5.2 to 7.5% in patients who were treated for >5 years [31]. There is no need to use HCQ for such extended periods for as a post-exposure medication for COVID-19.

The risk of cardiomyopathy, including cardiac conduction disorders, is reduced with this drug regimen. However, we recommend ECG before initiation of treatment in case of cardiac antecedents; but this should not delay the start of the post-exposure regimen.

There is evidence for the lack of significant risk of retinal toxicity after exposure to HCQ *in utero* [32], but considering the lack of evidence for safety of post-exposure hydroxychloroquine during pregnancy, we consider that pregnant women should be excluded from the future clinical trials.

4. Mechanisms of antiviral effect of chloroquine/ hydroxychloroquine

The exact mechanism of action of chloroquine and hydroxychloroquine against the virus has not been clearly depicted; however, laboratory data show that 4-aminoquinoline compounds (Chloroquine and hydroxychloroquine) have four mechanisms by which they act against diverse RNA viruses including SARS-CoV1 and reduce the cytokine storm that these viruses can generate.

1. **Inhibition of viral entry**: Chloroquine interferes with terminal glycosylation of angiotensin-converting enzyme 2 which serves as the cellular receptor for SARS-CoV-1 and SARS-CoV-2. In cell culture chloroquine effectively prevents the spread of SARS CoV and works as a prophylactic [12].
2. **Inhibition of viral release into the host cell**: HCQ is a weak base which rapidly diffuses across membranes of cells and organelles to acidic cytoplasmic vesicles such as endosomes, lysosomes, or Golgi vesicles causing an increase in pH of the organelles. Unlike other enveloped viruses, Coronaviruses bud and assemble at the endoplasmic reticulum (ER)-Golgi intermediate compartment (ERGIC). 4-aminoquinoline compounds become highly concentrated in organelles causing dysfunction of enzymes including enzymes needed for proteolytic processing and post-translational modification of viral proteins [33]. Experimental data from the Wuhan Institute of Virology demonstrated that chloroquine inhibits the replication of the SARS-CoV-2, in part because of its ability to alkalinize endosomal organelles [18]. Hu et al. [34] have proposed that CQ suppresses phosphatidylinositol binding clathrin assembly protein (PICALM) and thereby prevents endocytosis-mediated uptake of SARS-CoV-2. There is also data that chloroquine interferes with organelle acidification, which may lead to hindering fusion of viral particles, when chloroquine treatment was used for different emerging or non-emerging virus over the previous five decades: Mouse hepatitis virus (MHV-3) [35], Feline infectious peritonitis virus (FIPV) [36], or H5N1 strain of Influenza A [37].
3. **Reduction of viral infectivity**: Chloroquine inhibits viral particle glycosylation [38]. The envelopes of coronavirus contain two major glycoproteins the Spike (S) [39] and the Membrane (M) proteins. Lack of proper glycosylation damages the S protein [40], needed for receptor binding.
4. **Immunomodulation**: At the cellular level, chloroquine and hydroxychloroquine inhibit immune activation by reducing signaling by Pattern Recognition Receptors (Toll-like receptor signaling) and cytokine production [1]. Hydroxychloroquine also inhibits the activity of the nucleic acid sensor cyclic GMP-AMP (cGAMP) synthase (cGAS) by interfering with its binding to cytosolic DNA. By preventing TLR signaling and cGAS–stimulator of interferon genes (STING) signaling, hydroxychloroquine can reduce the production of pro-inflammatory cytokines, including type I interferons [1]. These drugs also reduce the expression of CD154 (CD40L) on helper T-cells which is essential for a successful antibody response and class switching [41]. These immunomodulatory actions could help prevent the transition from mild or moderate disease to the dreadful acute respiratory distress syndrome (ARDS) by reducing the cytokine storm [42] .

5. Conclusion

Non-pharmaceutical measures such as social distancing, school closure and teleworking (Di Domenico et al. Expected impact of school closure and telework to mitigate COVID-19 epidemic in France. Report #8, 14 March 2020 Epicx-lab.com, https://www.epicx-lab.com/uploads/9/6/9/4/9694133/inserm_covid-19-school-closure-french-

regions_20200313.pdf) are expected to delay and reduce the peak incidence and to achieve a reduction of the final attack rate of 15% (Additional Epicx-lab Reports www.epicx-lab.com/covid-19.html). Reasonable interventions that can lead to a significant reduction in the impact of the epidemic profile and should be considered and evaluated without any delay.

As we observe the logarithmic increase in the number of cases and death, as well as the social and economic impact of COVID-19, measures for prevention and means to control the outbreak become urgent. The use of hydroxychloroquine as a post-exposure means to reduce sickness and transmission of COVID-19 demands immediate attention and should be taken into consideration.

It is of utmost importance to promote the design of prospective clinical trials to test the hypothesis: 'Does a post-exposure non-toxic dose of hydroxychloroquine significantly alter SARS-CoV-2 replication in people exposed to a documented infective contact; and does it reduce the severity of subsequent disease? These futures clinical trials should document the benefit/risk ratio of this strategy rapidly.

This strategy for prevention is clearly achievable considering the safety of hydroxychloroquine for a short period of time, its demonstrated antiviral effect and its low cost and accessibility. In the context of the COVID-19 epidemic, if clinical evidence from prospective controlled clinical trials confirms the positive impact, its implementation will be urgently needed. Supply shortage of hydroxychloroquine, which remains needed for standard indications such as Lupus or rheumatoid arthritis should be prevented by a significant effort of pharmaceutical companies, already ongoing, for increasing the production of hydroxychloroquine specifically for COVID-19. Other initiative such as the "Defense Production Act" in the US may be activated.

Using post-exposure HCQ is in line with WHO's strategic objectives to limit human-to-human transmission. If we do not seriously consider using this easy and safe option, we are taking the risk of allowing the pandemic to sore further out of control. As recently stated, the urgency of the epidemic necessitates choices about which interventions to employ. Early HCQ administration to all people at risk of infection from close contact with a positive patient is one of the most reasonable choices. Moreover, it is a choice that could potentially have a considerable impact on the early termination of the COVID-19 pandemic. However, its administration should be done under medical control to avoid potential side effects and to prevent an uncontrolled use leading to supply shortages.

Declaration of Competing Interest

The authors declare no conflict of interest.

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