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Narrative Review

Pharmacological aspects and clues for the rational use of Chloroquine/Hydroxychloroquine facing the therapeutic challenges of COVID-19 pandemic

François Noël[a, b, c], **Jaderson Lima**[d].

[a]Laboratory of Biochemical and Molecular Pharmacology, Institute of Biomedical Sciences, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil; SIGfarmaco, Brazil; Post-graduation Program in Pharmacology and Medicinal Chemistry, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil, [b]SIGfarmaco, Brazil, [c]Post-graduation Program in a Pharmacology and Medicinal Chemistry, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil, [d]Brazilian Alliance of Clinical Research.

Corresponding Author: François Noël, Av. Carlos Chagas Filho, 373 - 21941-902, Rio de Janeiro, Brazil. Tel: (21)3938-6732; e-mail: **fnoel@pharma.ufrj.br**

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ABSTRACT

Since there is an urgent need for COVID-19 treatment, the pandemic disease caused by SARS-CoV-2, the repurposing of available drugs is a quick and cheap option, with chloroquine (CQ) and hydroxychloroquine (HCQ) being the most quoted drugs in this context. As a rigorous evaluation of the available data is needed to help to decide on the eventual use of these drugs, the first objective of this work is to critically review the available in vitro assay, clinical studies and putative mechanism(s) of action of CQ/HCQ concerning COVID-19, either alone or in association with azithromycin (AZM). The second objective is to discuss the drug alternatives to treat COVID-19, with emphasis on Brazil, Latin America, and countries where malaria is endemic. Finally, we describe some of the on-going international clinical trials and their therapeutic schemes. We conclude that: 1) there is a good rationale for HCQ use, at least within a compassionate approach, for COVID-19 treatment, possibly at not to severe stage of the disease; 2) the risk/benefit ratio of HCQ use alone or in combination with other drugs such as AZM has yet to be established with the available level of evidence, according to the evidence-based medicine principles.

Keywords: COVID-19, SARS CoV-2, chloroquine, hydroxychloroquine, azithromycin

RESUMEN

Ante la urgente necesidad de un tratamiento para COVID-19, pandemia causada por SARS-CoV-2, se han adaptado fármacos desarrollados para otras indicaciones, pero que ya se encuentren disponibles. Esto constituye una opción rápida y económica. Cloroquina (CQ) e hidroxicloroquina (HCQ) han sido los fármacos más citados en este contexto. Dado que es necesaria una evaluación rigurosa de la información disponible para poder tomar decisiones acerca del uso de estos fármacos, el primer objetivo de este trabajo es revisar, de modo crítico, los ensayos ***in vitro***, los estudios clínicos y el(los) mecanismo(s) de acción putativo(s) ralacionados con la actividad contra COVID-19 de CQ/HCQ, ya sea solos o en combinación con azitromicina (AZM). El segundo objetivo es discutir las alternativas farmacológicas para tratar COVID-19, especialmente en Brasil, Latinoamérica y en países donde la malaria es endémica. Concluimos que: 1) existe una buena justificación para usar HCQ para el tratamiento de COVID-19, al menos desde un abordaje compasivo y posiblemente no en etapas muy graves de la enfermedad; 2) la tasa de riesgo/beneficio del uso de HCQ, solo o en combinación con otros fármacos como AZM, debe aún establecerse con base en el nivel de evidencia disponible y de acuerdo con los principios de medicina basada en evidencia.

Palabras clave: COVID-19, SARS CoV-2, cloroquina, hidroxicloroquina, azitromicina

INTRODUCTION

COVID-19, the pandemic disease caused by SARSCoV-2, started in Wuhan, China, and rapidly spread worldwide with 205 countries/territories/area having reported at least one case (WHO, situation report - 73, on 2 April 2020). Epidemiologic data report high levels of transmission (April 6th, 2020, 1,289,380 laboratory-confirmed COVID-19 cases and 70,590 deaths). Since there is no treatment available, there is an urgent need for discovering some effective drugs to face this overwhelming unmet medical need. Thus, one quick op tion would be repurposing already approved drugs due to economic and urgency reasons. Indeed, repurposing is broadly

used as a strategy to cost-effective drug development for compounds with known safety profiles and has already yielded several successes.[1] Chloroquine (CQ), and its derivative hydroxychloroquine (HCQ), is perhaps the most quoted drug in this context. However, since there are a lot of controversies and biased information in the social networks and public media, the scientific community needs rigorous evaluation of the data available to help to decide on the eventual use of this drug for COVID-19 treatment. For these reasons, the first objective of this review is to report the available in vitro data, clinical results and putative mechanism(s) of action of CQ/HCQ concerning COVID-19, with or without azithromycin (AZM). The second objective is to discuss the drug alternatives, with emphasis on Brazil and Latin America, as well as to describe some of the on-going international clinical trials.

A rational basis for CQ/HCQ use as COVID-19 treatment

I. 1. In vitro and in vivo studies

In a review published 13 years ago, the Didier Raoult's group in Marseille, France, proposed that CQ and HCQ could be used for different intracellular bacteria and virus infections.[2] The idea of repurposing these antimalarial drugs was based on a great number of in vitro studies showing that CQ and HCQ were able to inhibit diverse bacteria, fungi, and viruses, including HIV and SARS-CoV-1.

Similar results have now been reported with the new coronavirus, SARS-CoV-2, at least initially by two different groups in China, where the COVID-19 pandemic started. The first report, available online on February 4th showed that CQ potently blocked virus infection at low-micromolar concentrations.[3] Furthermore, the authors showed that CQ functioned at both, entry and post-entry stages of the SARS-CoV-2 infection in Vero E6 cells. Using a similar approach for the 48-h treatment of infected Vero cells and quantification of the virus by qRT-PCR in the culture supernatant, the second paper, available online on March 9th, reported that HCQ (EC_{50} = 0.72 µM) was more potent than CQ (EC_{50} = 5.47 µM).[4] Interestingly, these authors used a physiologically-based pharmacokinetic model (PBPK) for proposing a therapeutic scheme, very similar to what is now used in clinical trials (see later, Table 3). A few days after (March 18th), the Wang group confirmed the efficacy of HCQ and CQ "pre-treatment" of infected Vero cells.[5] These authors also make some translational considerations based on the fact that safe HCQ dosage can generate serum levels around 1 µM in humans and that the drug is highly distributed to tissues such as lungs where its level is estimated to be 200-700 times higher than in serum.

As far as clinical data are concerned, the first published paper in English was available on February 19th, when Gao et al.[6] reported in a short letter that "results from more than 100 patients have demonstrated that chloroquine phosphate is superior to the control treatment in inhibiting the exacerbation of pneumonia, improving lung imaging findings, promoting a virus-negative conversion, and shortening the disease course according to the news briefing. Severe adverse reactions to chloroquine phosphate were not noted in the aforementioned patients."

Such clinical data were of fundamental importance for the decision of Chinese authorities (National Health Commission) to include CQ treatment as one of the drugs considered in their guidelines for COVID-19 treatment (version 6, February 19th, 2020), as reported by Dong et al.[7] On March 20th, the already strongly-commented paper of Didier Raoult group was finally available online.[8] In this paper, the authors reported an impressive decline in the percentage of patients with RT-PCR-positive nasopharyngeal samples in COVID-19 patients: at day 6 post-inclusion, the six (100 %) patients treated with HCQ and azithromycin combination were virologically cured compared to 8 of 14 (57.1 %) patients treated with HCQ only, and 2 of 14 (12.5 %) in the control group.

This study has been criticized due to its several methodological limitations. Indeed, it is an open (uncontrolled) study, not randomized, with a small sample of patients, recruited from different centers. There are also concerns related to the controls used, and the fact that there was no consideration about the drop-out of six HCQ treated patients. Moreover, absence of long-term outcome follow-up and the clinical value of the end-point used (presence of the virus in the nasopharyngeal swab, as measured by qPCR, an indirect, surrogate, measure of efficacy for clinical improvement) are also sources of controversy. Albeit, we can easily agree with the authors when they concluded that "However, in the current context, we believe that our results should be shared with the scientific community".

In a very recent report, not yet published[9], the French authors reported an additional observational study with 80 COVID-19 patients (53.8 % with computerized tomography compatible with pneumonia). All the patients were treated with HCQ/AZM. The authors

concluded that the treatment was effective, based on the following clinical results: 81.3 % had a favorable outcome and were discharged from Infectious Disease Unit; 15 % required oxygen therapy; 3.8 % needed to be transferred to Intensive Care Unit and 1.2 % died. On the other hand, a very small descriptive Chinese study (30 patients divided into two arms) reported no benefit of HCQ.[10] However, the fact that only the abstract was in English makes it difficult to critically analyze the methodology and results. The more recent clinical study available at the time this review is being finished (April 6th, 2020) is a preprint of a paper intended to be published that should be more properly considered as a small (64 COVI-19 patients with pneumonia) descriptive study and not a randomized clinical trial as claimed by the authors.[11] Whatever the limitations, the authors concluded that HCQ could significantly shorten the time to clinical recovery, the body temperature recovery time and promote the absorption of pneumonia. Interestingly to note, the four patients who progressed to severe illness belonged to the control group.

I. 2. Putative mechanisms of action

Among the most popular proposed mechanisms of action for the CQ/HCQ effect against COVID-19 we can cite are the following (see details and didactic scheme of Figure 2, published by Zhou et al.[12]):

- Interference with glycosylation of angiotensin-converting enzyme 2 (ACE2) (↓ infection);
- ↑ pH of lysosomes (infection) and endosomes (↓ replication);
- Disruption of RNA interaction with Toll-like receptors (TLRs) and nucleic acid sensor cyclic GMP-AMP (cGMP) synthase (cGAS) (↓ cytokine production);
- Repression of major histocompatibility complex (MHC) class II-mediated autoantigen presentation, in antigen-presenting cells (APCs) and thus inhibition of T cell activation (↓ cytokine production).

Besides the above-mentioned mechanisms, two other putative effects of CQ/HCQ could be of some relevance for their effect against COVID-19: CQ has been demonstrated to be a zinc ionophore in A2780 cells, targeting zinc to the lysosomes.[13] As zinc has anti-viral properties and was shown in a laboratory study to inhibit the replication of coronaviruses in cells[14], this ionophore property of CQ/HCQ could be clinically relevant and supports the rationale for the addition of zinc to the pharmacological treatment of COVID-19 patients. Indeed, supplementing people with zinc deficiency, such as elderly people and vegetarians, with zinc (e.g. 20 mg per day) may improve the immune function, increase resistance to pathogens, and decrease the incidence and duration of pneumonia.[15] On the other hand, HCQ could have vascular protective effects and prevent the development of thrombotic complications. This effect could be most relevant in the presence of systemic inflammation and secondary coagulopathy.[16] This putative effect deserves investigation since pulmonary embolism may complicate pneumonia in patients with COVID-19.[17,18]

II. A rational basis for the use of azithromycin (AZM) as an add-on of CQ/HCQ treatment

A priori, the role of AZM, as other antibiotics, would be to avoid a secondary bacterial infection that could develop in patients with viral pneumonia. AZM is a macrolide antibiotic already used for the treatment of community-acquired pneumonia caused by designated, susceptible bacteria, and for the treatment of other bacterial infections (www.drugs). However, AZM has also antiviral and anti-inflammatory activity and may work synergistically with other antiviral treatments. Indeed, as reviewed by Ikemoto et al.[19], AZM exerts not only anti-bacterial activity but also anti-inflammatory effects, which are related to the NF-κB pathway, inhibition of quorum sensing, and anti-virulence effects. This results in decreased production of pro-inflammatory cytokines in the acute phase of respiratory diseases[20] so that macrolides, as a whole, can suppress the “cytokine storm” of inflammation and confer an additional clinical benefit through their immunomodulatory properties.[21]

II.Drugs alternatives for COVID-19 treatment in Latin America

Many clinical trials related to COVID-19 have been registered and are available on classical platforms such as the USA https://clinicaltrials.gov and the WHO International Clinical Trials Registry Platform (https://www.who. int/ictrp/en/). Among these, several involve the use of drugs, highlighting the antimalarial drugs CQ or HCQ, the adenosine analogue remdesivir, the fixed-dose combination of antiretroviral protease inhibitors lopinavir/ritonavir, and the antiviral

favipiravir. Thus, what should be considered as feasible options in Brazil and Latin-America? As shown in Table 1, only CQ, HCQ and lopinavir/ ritonavir combination are registered in Brazil and most countries; then it could be used immediately.

Table 1. Potential drugs for treatment and or prophylaxis of COVID-19 infection already registered (Yes) or not (No) for other indications

DRUG	WORLD	BRAZIL
Chloroquine (phosphate)	Yes	Yes
Hydroxychloroquine (sulfate)	Yes	Yes
Remdesivir	No	No
Lopinavir/Ritonavir	Yes	Yes
Favipiravir	No (only Japan)	No

Besides the rationale for their use, CQ and HCQ merit special attention because they are available in most countries where malaria is endemic and are much cheaper than the combination of lopinavir/ritonavir (around 23 times based on the factory price in Brazil, considering the number of tablets for one treatment). CQ, originally developed in 1934 and used in World War II to prevent malaria, has been used for decades for the prophylaxis and treatment of malaria and is one of the most prescribed drugs worldwide. HCQ, approved by the FDA in 1955, has a similar pharmacokinetic and pharmacodynamic profile as CQ but is safer (see below safety assessment). Furthermore, a recent clinical trial with 199 hospitalized adult patients with severe COVID-19 concluded that no benefit was observed with lopinavir-ritonavir treatment beyond standard care.[22]

IV. CQ/HCQ: adverse effects and safety concerns

The most common adverse effects of CQ/HCQ are gastrointestinal, including nausea, vomiting, diarrhea, and abdominal discomfort. However, these drugs can also induce cardiotoxic effects, including rhythm disorders (such as a prolonged QT interval) and the development of cardiomyopathy in patients with rheumatic diseases.[16] Note that HCQ is 2-3 times less toxic than CQ, as reported in animal studies.[23]

The most severe complication attributed to antimalarial treatment with these drugs is the development of retinopathy which occurs only after long-term treatment. Note that retinopathy is also more commonly associated with CQ than with HCQ, which can be used in high doses for long periods with very good tolerability. Likewise, HCQ is widely used at 400 mg daily for months or even years for the treatment of Lupus Erythematosus and rheumatoid arthritis.[24]

Drug-Drug Interaction (DDI)

When one considers the complexity of the pharmacokinetic and pharmacodynamic properties of both, CQ and HCQ, the potential DDIs must be considered, as described in the literature (www.apsf.org; www.drugs.com).

Regarding the pharmacokinetics, CQ is metabolized through CYP2C8, CYP3A4, CYP2D6, and CYP1A1 so that the concomitant administration of a CYP inhibitor should be contra-indicated to avoid the increase of CQ/ HCQ plasma concentration leading risk of QT prolongation.[16] As ritonavir is a strong CYP3A4 and weak CYP2D6 inhibitor[25,26], the association of lopinavir-ritonavir with CQ/HCQ should be avoided.

On the other hand, pharmacodynamic interaction can also occur particularly when these drugs are co-administered with AZM which is also described as an agent interfering with the myocardial electrical transmission (iKr inhibition). As a result, caution is imposed when co-administering these two drugs, even considering that in vivo data has shown that AZM/HCQ combination does not increase monophasic action potential duration in guinea pigs.[27] On the other hand, due to putative adverse event probabilities when used in the clinical setting (www.webmd.com), close patient monitoring in clinical trials as well as during compassionate use is mandatory. Clear pre-enrolment, enrolment and ongoing monitoring rules are required.

V. On-going clinical trials and therapeutic schemes involving HCQ or CQ

In Table 2 we report some examples of on-going large clinical trials involving HCQ and that were registered at the WHO platform. We also included a Brazilian multicenter trial (Alliance COVID-19 Brasil I) evaluating the effect of HCQ and AZM administration in light-to-moderate cases. This is an interesting fact since there is some rationale for the beneficial effect to avoid the cytokine storm that is probably responsible for the rapid aggravation observed before the patients need intubation.

Table 2. On-going registered large clinical trials (WHO platform) with HCQ: some examples

Nickname	Sponsor Country (Registry)	Type	Target size	Inclusion criteria	Treatment
COVID-19 PEP	Minnesota University USA (March 11)	Blind Randomized	3000	Prophylaxis: asymptomatic Therapy: symptomatic	Hydroxychloroqu
DisCoVeRy	INSERM France 8 countries (March 13)	Open-label Randomized Adaptive design	3100	Defined COVID-19	-HCQ - Remdesivir - Lopinavir-Ritona - Lopinavir-Ritona + Interferon-bet
Solidarity	WHO 13 countries (March 25)	Open-label Randomized Adaptive design	10,000	Defined COVID-19	- CQ or HCQ - Remdesivir - Lopinavir-Ritona - Lopinavir-Ritona + Interferon-bet
	Brazil* (March 30)	Open-label Randomized	630	Light/moderate cases	-HCQ -HCQ + AZM

Alliance COVID-19 Brasil I & II

*Albert Einstein, HCor & Sírio-Libanês hospitals + BRICNet and EMS pharmaceutical industry.

Concerning approval of CQ/HCQ for COVID-19 use by regulatory agencies, the situation in the USA, is of use within an expanded approach (compassionate use), since the FDA did not carry out fast-tracked approval of these drugs for COVID-19. The compassionate use is an FDA regulatory pathway that allows the use of investigational treatments if there are no other approved options available in life-threatening circumstances. In Brazil, on March 27th, the Ministry of Health issued an information note to regulate the use of CQ (or HCQ) as an adjunct therapy in the treatment of severe forms of COVID-19 (Nota informativa Nº 5/2020-DAF/SCTIE/MS).

Finally, we present some therapeutic schemes used in different studies with HCQ (with or without AZM) for prophylaxis or treatment of COVID-19 (Table 3). It is noteworthy that the University of Minnesota will test the putative prophylactic effect of HCQ since this possibility has been claimed based on in vitro studies.

Table 3. Therapeutic schemes used in different studies with HCQ and AZM for prophylaxis or treatment

Loading dose	Daily maintenance dose		Study/Group
	HCQ	AZM	
	3 x 200 mg (10 days)	500 mg (D1) + 250 mg (4 days)	Raoult group IHU-Marseille[9]
2 × 400 mg (2 days)	400 mg (3 days)	-	MGH Massachusetts[29]
400 mg + 400 mg (after 6-8 h)	400 mg - 1 or 2/week (up to 12 weeks)	-	Minnesota university (Prophylaxis) [29]
800 mg + 600 mg (after 6-8 h)	600 mg (4 days)	-	Minnesota university (Treatment)[29]
-	2 x 400 mg (7 days)	500 mg (7 days)	COVID-19[29] Brazil
2×400 mg	400 mg (9 days)	-	DisCoVeRy[29] INSERM-France

CONCLUSIONS

Concerning the clinical use of these drugs (CQ/HCQ), one has to take into account the systematic approach of evidence-based medicine principles and rules30, which implies the best level of scientific evidence, together with clinical judgment and patient values as the foundation of the decision-

making process. With this in mind, there would be two scenarios in which these drugs are to be considered in the clinical setting, including the clinical trials and compassionate use already authorized in many countries. Concerning clinical trials, many ongoing, as well as some not yet recruiting trials, are displayed in the databases. It is worth considering that with the available level of evidence, the risk/benefit ratio of CQ/HCQ use alone or in combination with other drugs has not yet been established, albeit preliminary data and rationale for their use lead us to hope for benefit. Compassionate use must follow legal and regulatory rules in each country where available. On the other hand, controlled clinical trials should be planned and executed by following ethical/scientific principles to avoid harm to patients.30 The objective of this paper is to streamline up to date options for including these drugs in the clinical scenarios in which the drugs are to be experienced, that is to say, clinical trials and compassionate use. With this in mind and aiming to have the best evidence from clinical trials, it would be better to have the best evidence possible with controlled clinical trials with less biased possible methodology, whatever it takes. No contribution would be seen if a posteriori bias would be detected facing this serious public health problem.

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