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SUMÁRIO

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SUMÁRIO

Capítulo 21

Hydroxychloroquine in fighting COVID-19: What led WHO to suspend clinical trial of drug?

Thyago José Arruda Pacheco
Danielle Galdino de Souza
Raquel Santos Faria
Laise Rodrigues de Andrade

Abstract: ***Purpose:*** On March 11, 2020 the pandemic status of COVID-19 (Coronavirus Disease 2019) was declared. The milestone of thousands of daily deaths from Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) was reached worldwide. So far, there is still no proven effective treatment against this disease. This study summarizes the main clinical findings on the use of hydroxychloroquine (HCQ) to treat COVID-19. The goal is to gather the evidence that led WHO to suspend the HCQ arm of its Solidarity Trial, contributing to the understanding of its denouement. ***Methods****:* LitCovid platform was searched for the term "hydroxychloroquine" in the "treatment" field. All clinical studies published in the period from January 1st to June 17th were included in the review. ***Results****:* We included ten articles on HCQ in COVID-19 positive patients (eight non-randomized and two randomized clinical studies). Most studies did not report a benefit in the use of HCQ. There is no evidence of decreased risk of intubation or death, and in some cases adverse effects have been reported, such as abnormal liver function, transient blurred vision, diarrhea. ***Conclusions***: The overview of the available data on HCQ in COVID-19 patients can guide future studies, still needed to support public policies and health authorities in fighting COVID-19.

Keywords: hydroxychloroquine, clinical trials, COVID-19, SARS-CoV-2

1. INTRODUCTION

In late December 2019, a novel coronavirus called Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), began a global spread from China [1] , leading the World Health Organization (WHO) to declare the pandemic status of Coronavirus Disease 2019 (COVID-19) on March 11, 2020 [2]. This is the third serious coronavirus outbreak in less than 20 years, but SARS-CoV-2 has led to more deaths. Up to 30th July 2020, 17,130,295 cases had been confirmed worldwide with 669,160 deaths, while 919 deaths by SARS-CoV and 858 by Middle East Respiratory Syndrome Coronavirus (MERS-CoV) were recorded in the same period [3, 4].

The overall case-fatality rate is about 2.3%, but reaches 14.8% in elderly patients (≥80 years) who develop severe symptoms, such as shortness of breath, chest pain, loss of speech or movement [5]. It is difficult to measure the actual mortality rate due to underreporting of cases. For example, in Santa Clara, California, the number of cases can be 50-85x greater than the reported cases, as it was found that 1.5% of the population in that region has antibodies against SARS-CoV-2. The mortality rate in the region is estimated to be 0.12-0.2% [6]. The cause for disparities in mortality rates is still not well understood. Some hypotheses have been proposed, including the circulation of different strains of the virus, idiosyncrasies in COVID-19 testing strategies, policies in countries, quality of and access to health care, demographic factors, as well as the prevalence of elderly people in a given population and socioeconomic factors [7, 8].

There is currently no proven effective treatment against COVID-19. The drug repositioning approach is a potential strategy in fighting the disease, because information about the safety profile, side effects, dosage and drug interactions is well described in the literature [9]. Chloroquine (CQ) and hydroxychloroquine (HCQ) are widely used in the treatment of malaria and rheumatic diseases, and have been suggested as COVID-19 treatments due to their anti-inflammatory and antiviral activities [10, 11]

Both CQ and HCQ can interfere with the glycosylation of cell surface angiotensin-converting enzyme 2 (ACE2) and reduce the binding efficiency between ACE2 and the SARS-Cov-2 spike protein, blocking virus fusion with the host cell. These drugs - weak bases - increase pH intracellular compartments, especially endosomes and lysosomes, which also seems to be crucial to blocking the entry and replication of the virus [12–15]. In particular, once HQC enters antigen-presenting cells (APCs) and raises its lysosomal pH, it prevents antigen processing and major histocompatibility complex (MHC) class II-mediated autoantigen presentation to T cells [16, 17]. As a result, the activation of T cells and expression of CD154 and other cytokines, like interleukin-6 (IL-6), are repressed, attenuating a possible exacerbated inflammatory response [14, 16, 17].

The literature reports a higher toxicity associated with CQ than HCQ [13]. Conventionally, the maximum tolerable dose for CQ and HCQ is 500 mg and 1200 mg, respectively, but the antiviral effect achieved in 1200 mg of HCQ is equivalent to the use of 750 mg of CQ [18]. In more recent times, it has been shown that HCQ is more effective than CQ in inhibiting the SARS-CoV-2 infection in Vero cells (HCQ EC50=0.72 μM, CQ EC50=5.47 μM) [19]. Moreover, high mortality rates have been recorded in clinical trials with COVID-19 patients treated with CQ [20]. Although HCQ appears to outperform CQ, on June 17, WHO suspended the HCQ of its international clinical trial, called Solidarity Trial [21] . This study provides a narrative summary of the main clinical findings on the use of HCQ to treat COVID-19, contributing to the understanding of its denouement. Thus, we hope to offer support for the design of future studies and for health professionals' decision-making towards fighting COVID-19.

2. METHODS

Electronic searches were performed at LitCovid [22] for the term "hydroxychloroquine" in the "treatment" field. This review included all clinical trials published from January 1st to June 17th, the date on which the WHO announced the suspension of HCQ treatment in COVID-19 Solidarity Trial. The tracking of ongoing clinical tests was also carried out in the same period through Clinical Trial Tracker [23] and presented in terms of numbers (%).

3. RESULTS

On the LitCovid platform, HCQ or CQ appear as the most investigated drugs for COVID-19 treatment. Ten clinical studies regarding HCQ in COVID-19 patients were found (eight non-randomized and two randomized clinical studies) and are summarized in order of publication in Table 1. According to the Clinical Trial Tracker, by June 17th, 1932 clinical tests were in progress worldwide; 303 (15.68%) of these tests were with HCQ or CQ.

Table 1. Clinical studies on the use of hydroxychloroquine (HCQ) in COVID-19 patients

Reference	Study type (n=patients)	Country	Gender (n/N)	Average Age	Clinical condition (n/N)	ICU patients (n/N)
Gautret et al. [26]	Open-label, non-randomized study (n=36)	France	*F (21/36) **M (15/36)	45,1 years	Asymptomatic (6/36) Pneumonia (30/36) - Infection of the upper (22/36) and lower (8/36) respiratory tract	0/36
Gautret et al. [27]	Observational, non-randomized study (n=80)	France	†NR	52 years	NR	3/80
Million et al. [28]	Retrospective non-randomized study (n=1.061)	France	F (569/1.061) M (492/1.061)	43,6 years	NR	10/1.061
Molina et al. [29]	Observational, non-randomized study (n=11)	France	F (4/11) M (7/11)	58,7 years	Severe ‡COVID-19 (11/11) Obesity (2/11) Solid cancer (3/11) Hematological cancer (2/11) §HIV (1/11)	2/11
Yu, Wang and Li, [30]	Retrospective non-randomized study (n=568)	China	NR	68 years	Severe acute respiratory distress syndrome (n=568)	NR
Geleris et al. [31]	Observational, non-randomized study (n=1.376)	United States	NR	60-79 years	Moderate to severe respiratory illness (n=1.376)	246/1.376
Rosenberg et al. [32]	Observational, non-randomized study (n=1.438)	USA	F (580/1.438) M (858/1.438)	63 years	NR	NR
Chen et al. [35]	Randomized study (n=30)	China	NR	NR	NR	NR
Tang et al. [34]	Randomized study (n=150)	China	F (68/150) M (82/150)	46 years	Mild to moderate COVID-19 (148/150) Severe COVID-19 (2/150)	NR
Mahévas et al. [33]	Observational non-randomized study (n=181)	France	F (181/51) M (181/130)	60 years	NR	41/181

Table 1. (continued)

Table 1. Clinical studies on the use of hydroxychloroquine (HCQ) in COVID-19 patients

Reference	Treatment Protocol	Control group (n=patients)	Adverse effects	Mortality (n/N)	Main Findings
Gautret et al. [26]	£HCQ (200 mg, 3x/day, for 10 days) alone (n=20) or combined with €AZM (500 mg on day 1 and 250 mg on day 2-5) (n=6)	Yes (n=16) Without treatment	NR	0/36	HCQ group: 57% negative ¥PCR test on day HCQ+AZM group: 100% negative PCR on day 6
Gautret et al. [27]	HCQ (200 mg/day, 3x/day for 10 days) and AZM (500 mg on day 1 and 250 mg on day 2-5) (n=80)	No	NR	1/80	83% and 93% negative PCR test on days 7 and 8, respectively. 97.5% negative virus culture on day 5.
Million et al. [28]	HCQ (600 mg/day for 10 days) and AZM (500 mg on day 1 and 250 mg on day 2-4) (n=1.061)	No	24/1.061 Adverse effects: - Gastrointestinal; - Skin symptoms; - Headache; - Insomnia; - Transient blurred vision.	8/1.061	Virological cure in 91.7% patients within 10 days. 4.4% patients with prolonged viral carriage: negative viral culture at day 10. 0.75% patients died (respiratory failure) and 4.3% showed poor clinical outcome.
Molina et al. [29]	HCQ (600 mg/day for 10 days) and AZM (500 mg on day 1 and 250 mg on day 2-5) (n=11)	No	10/11 Adverse effect: - Fever	1/11	80% positive PCR test on day 5-6.
Yu, Wang and Li [30]	HCQ (200 mg, 2x/day, for 7-10 days) (n=48)	Yes (n=520) Antiviral drugs Immunoglobulin Immunoenhancer Antibiotics Interferon	NR	247/268 -HCQ group (9/48) -Control group (238/520)	HCQ group: significant reduction in the µIL-6 level from 2,2 (8.3-118,9) to 5,2 (3,0-23,4) pg/ml. Control group: no difference in the IL-6 level
Geleris et al. [31]	HCQ (600 mg 2x/day on day 1.400 mg on day 2-5) (n=811)	Yes (n=565) NR treatment	NR	578/1.376 -Without intubation (166/578) -With intubation (246/578)	Without significant association with increased or decreased risk of intubation or death (risk rate of 1.04; 95% CI, 0.82 to 1.32).

Table 1. (continued)

Table 1. Clinical studies on the use of hydroxychloroquine (HCQ) in COVID-19 patients

Reference	Treatment Protocol	Control group (n=patients)	Adverse effects	Mortality (n/N)	Main Findings
Rosenberg et al. [32]	HCQ (n=271) AZM (n=211) HCQ+AZM (n=735) 21 days of treatment / dosage not informed	Yes (n=221) Without treatment	NR	292/1.438 - HCQ group (54/271) -AZM group (21/211) -HCQ+AZM group (189/735) -Control group (28/221)	Treatments were not significantly associated with differences in hospital mortality.
Chen et al. [35]	HCQ (400 mg/day for 5 days) (n=15)	Yes (n=15) Conventional treatment	7/30 - HCQ (4/15) - Control group (3/15) Adverse effects: - Diarrhea; - Abnormal liver function.	0/30	HCQ group: 86% negative viral ΣRNA on day 7; and 33.3% negative chest ΩCT for pneumonia. Control group: 93.3% negative viral RNA on day 7; and 46.7% negative chest CT for pneumonia.
Tang et al. [34]	HCQ (1.200 mg/day for 3 days + 800 mg/day on day 4-14 or -4-21) (n=70) and Standard of care (antiviral agents, antibiotics and systemic glucocorticoid therapy) (n=80)	Yes (n=80) -Antiviral agents -Antibiotics -Systemic glucocorticoid therapy	7/150 -HCQ (7/70) Adverse effects: -Diarrhea	0/150	Administration of HCQ did not result in a significantly higher probability of negative conversion than standard of care alone in patients admitted to hospital with mainly persistent mild to moderate COVID-19.
Mahévas et al. [33]	HCQ (600 mg/day) (n=84 HCQ within 48 hours of admission; n=8 HCQ more than 48 hours after admission) and control group (n=89)	Yes (n=89) -Tocilizumab; -Lopinavir; -Ritonavir; -Remdesivir.	NR	17/181 -HCQ within 48 hours of admission (9/84); -HCQ more than 48 hours after admission (0/8); -Control group (8/89).	HCQ treatment did not have any effect on survival without acute respiratory distress syndrome at day 21 after hospital admission. These results do not support the use of hydroxychloroquine in these patients.

Legend: (*) Female; (**) Male; (†) Not registered; (‡) Corona Virus Disease 2019; (§) Human Immunodeficiency Virus; (£) Hydroxychloroquine; (€) Azithromycin; (¥) Polymerase Chain Reaction; (μ) Interleukine-6; (∑) Ribonucleic acid; (Ω) Computed tomography.

4. DISCUSSION

Four months after the detection of SARS-CoV-2 in Wuhan, China, the novel virus has already spread to 188 countries/regions and threatened to be the greatest pandemic of modern times, with more than four million infected and the number of deaths growing at an alarming rate [24]. The drug repositioning approach is a possible alternative strategy for COVID-19 treatment and there seems to be a preference for HCQ over CQ due to previous evidence of less toxicity [9, 15]. In this study, we compiled recent clinical trials with HCQ for COVID-19 treatment. Relevant factors such as type of study, sample size, age of patients, clinical conditions and dosing regimens were considered for analysis.

Although there is a similar number of confirmed cases of COVID-19 between the sexes, men die more than women, 1.7% and 2.8 %, respectively [25]. No work has registered a significant difference in therapeutic intervention comparing men and women. According to Gautret et al. [26], Gautret et al. [27] and Million et

al. [28] there was a virological cure in over 80% of HCQ-azithromycin-treated patient, whereas Molina et al. [29] btained the opposite results, and 8 out of 11 patients (about 70%) remained SARS-CoV-2-infected after receiving the same dosing regimens as Gautret et al. and reported adverse effects [26, 27]. These discrepant results may be a consequence, at least in part, of the different patients' health conditions in each study. The result of study by Yu, Wang and Li [30] agree that HCQ increases patient survival. However, the testing protocols were different (such as patient's clinical conditions, dosage and duration of treatment), which can lead to inaccurate interpretations. Other studies found no significant association between the use of HCQ and the evolution of the patient's clinical condition [31–33], in one, performed by Rosenberg et al. [32] the HCQ dosage was not even reported. All of the above observations are the result of non-randomized clinical trials. In this type of design, it is not possible to eliminate other factors that may have occurred concurrently with the implanted intervention, and that may have contributed to the change in the outcome.

The randomized clinical trial presented here evaluated high HCQ dosing regimens in mild or moderate COVID-19 cases [34]. In this work, the HCQ treatment showed no benefits in antiviral activity. In addition, 30% of patients presented adverse effects, gastrointestinal problems, a value approximately 3 times higher than in patients who did not receive HCQ. Also although Chen et al. has had 86% negative viral RNA on day 7, some patients have had adverse effects such as diarrhea and abnormal liver function [35].

There is evidence that HCQ can cause irreversible damage to the retina and disturbed heart rhythm (changes in the QT interval) [36, 37]. On 17 June 2020, WHO stopped the use of HCQ on COVID-19 patients in Trial Solidarity, an international clinical trial decision based on evidence from the Solidarity trial, UK's Recovery trial and a Cochrane review of other evidence on based on evidence that treatment with HCQ does not result in the reduction of mortality when compared to standard of care [21]. Despite this, some world leaders continue to systematically promote CQ or HCQ against COVID-19 without proven safety and efficacy. The US and Brazilian governments support the use of HCQ as a prophylactic measure against the new virus [38] and despite recognizing the risk of clinical decline, a new Brazilian protocol expands the use of CQ and HCQ, including for mild cases of the disease [39].

Given this scenario, it is important to note that the risks can outweigh the unproven benefits in some COVID-19 patients; therefore, prescriptions should be made with caution on a case-by-case basis. Moreover, the indiscriminate use of HCQ can cause a shortage on the market, harming patients who depend on the drug for the prevention and treatment of malaria and also for the treatment of some rheumatic diseases such as rheumatoid arthritis and lúpus [39]. In addition, recent randomized studies published after the suspension of testing by WHO, showed that hydroxychloroquine have no statistically significant benefit to treat COVID-19, and have also shown side effects in patients who were part of the hydroxychloroquine-treated group, corroborating the evidence that HCQ lacks proven efficacy and safety in COVID-19 [40, 41].

5. CONCLUSIONS

There is still not enough evidence of the effectiveness and safety of HCQ against SARS-CoV-2. WHO stopped the use of HCQ on COVID-19 patients based on evidence from the Solidarity trial and other studies detailed here. In most of the studies referenced here, there was no benefit in the use of HCQ. In addition to not promoting a reduction in hospitalizations or in mortality due to COVID-19, the drug caused adverse effects in some cases. The overview of the available data, as presented here, can guide future studies. More information about this drug is needed to support public policies and health authorities in fighting COVID-19.

5.1. CONFLICTS OF INTEREST

The authors declare that they have no conflict of interest.

5.2. ROLE OF THE FUNDING SOURCE

No funding was received.

5.3. ETHICAL APPROVAL

All analyses were based on previous published studies; thus, no ethical approval is required.

5.4. INFORMED CONSENT

All analyses were based on previous published studies; thus, no informed consent is required.

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