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Research Article

The Role of Chloroquine, Hydroxychloroquine and Azithromycin in the Treatment of COVID19 Patients: A Review of the Information Available to Date

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Abstract

Importance: Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) emerged in Wuhan, China, in December 2019. This virus spread around the world in a short period of time. On March 11, 2020, the World Health Organization (WHO) named this infection as Coronavirus Disease 2019 (COVID-19) and declared a pandemic. During this time, a wide variety of treatments have been proposed. For instance, Chloroquine (CQ) and its derivative, Hydroxychloroquine (HCQ) were suggested as promising drugs because of their proved *in vitro* activity against SARS-CoV-2. Moreover, the addition of Azithromycin (AZH) to HCQ potentiated its effect of reducing viral load in a few small studies. After these findings, a large number of articles has been published on the benefits and risks of these three medications.

Observations: We present a review of the information available to date about the use of these drugs in the COVID-19 pandemic, as well as a list of the biggest ongoing clinical trials on this topic. While the effectiveness of these drugs as therapies for COVID19 is still on question, their adverse effects are well known and include QTc prolongation and Torsades de Pointes.

Conclusion and Relevance: In conclusion, there is insufficient data to determine that HCQ, CQ and AZH alone or in combination have a role in the treatment for SARS-CoV-2 infection. At the moment we are still waiting for the results of larger randomized clinical trials listed in this review.

Keywords: COVID-19; SARS-COV-2; SARS; Chloroquine; Hydroxychloroquine; Azithromycin

Introduction

SARS-CoV-2 emerged in December 2019, in Wuhan, Hubei Province - China. On March 11, 2020, the WHO named this disease COVID-19, and declared a pandemic [1]. It represents the greatest global public health crisis since the pandemic influenza outbreak of 1918 [2] and implies one of the biggest concerns in the population worldwide. As a new virus, SARS-CoV-2 has revolutionized the world of science, making every researcher work untiringly to

understand this infection. To date, there are 885 COVID-19 related clinical trials listed on the NIH website [3].

Because of the large number of people infected and the severity of this illness in some populations, effective therapies are urgently needed.

Five months after the onset of this outbreak, different treatments have been proposed, however, there is no certainty of the most useful and less harmful therapy.

The aim of this review is to summarize the available information on the role of two of the most popular drugs used in the treatment of COVID-19: CQ and HCQ; and the combination of HCQ with AZH. We describe the most relevant findings related to the efficacy and adverse effects of these medications in more than 245 000 patients.

Methods

We searched on PubMed database for the most relevant articles published in English until May 16th, 2020. We used the following terms: (COVID19 OR SARS-Cov-2 OR Novel Coronavirus OR Wuhan Coronavirus OR Coronavirus Disease 19 OR Severe Acute Respiratory Syndrome Coronavirus 2 OR 2019-nCoV infection OR ("severe acute respiratory syndrome coronavirus 2" [Supplementary Concept]) OR ("COVID-19" [Supplementary Concept])) AND (Hydroxychloroquine OR chloroquine OR azithromycin OR ("Hydroxychloroquine"[Mesh]) OR ("Hydroxychloroquine/adverse effects"[Mesh]) OR ("Chloroquine"[Mesh]) OR ("Azithromycin"[Mesh])). We found 382 results and summarize the most relevant information ahead, including the biggest and most transcendental studies available to date.

Moreover, ongoing clinical trials on these three medications were searched on the National Institutes of Health (NIH) website, using the following terms: Hydroxychloroquine OR chloroquine OR azithromycin AND COVID19, Recruiting, Not yet recruiting, Active, not recruiting, Enrolling by invitation Studies, Interventional Studies. We found 197 ongoing clinical trials on this topic to date and list the studies with the biggest populations.

Results and Discussion

After the emergence of Severe Acute Respiratory Syndrome (SARS), Keyaerts., *et al*. and Vincent., *et al*. demonstrated that CQ is a potent Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) inhibitor *in vitro*, using Vero E6 cells [4]. Similar work was done after the onset of the Middle East Respiratory Syndrome Coronavirus (MERS-CoV), which showed that CQ had anti-MERS-CoV activity in immortalized cell lines [4]. Since COVID-19 resembles phylogenetically and symptomatically the Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS), *in vitro* studies were developed and demonstrated that CQ had potent *in vitro* activity against SARS- CoV-2 [1,4]. As a derivative of CQ, HCQ has similar effects [2].

Furthermore, Gautret., *et al*. reported that the addition of AZH to HCQ as treatment for COVID-19 in 20 patients, potentiated its effect of reducing viral load. After the results obtained from this study, the use of this combination has been contemplated, despite the small sample size of this study [5].

Mechanisms of action

Chloroquine and hydroxychloroquine

Their antiviral effect is related to the capacity of HCQ and CQ to interfere with the disease cycle, either decreasing the viral replication *in vitro* when used early in the course of the disease or reducing the number of infected cells when used later in the course of infection; furthermore, they alter the viral fusion and dissemination by increasing the Ph in endosomes, lysosomes and Golgi apparatus in the antigen presenting cells. They also affect the intracellular transport of the virus and the glycosylation of ACE-2, thus preventing the adhesion of the virus to the host cells [4,6,7].

Moreover, their immunomodulatory effect is related to the fact that they reduce the affinity for TLR-7/9 (which interferes in the recognition of SARS-Cov-2 and induces cytokines production). They reduce the activation and differentiation of T cells and thus the production of T-CD4+ and proinflammatory cytokines like IL-6 and TNFα. In addition, they inhibit the activity of AMP-GMP synthase in host cells and thus prevent the production of IFNβ (which is activated by SARS-Cov-2). These drugs reduce the function of cytotoxic NK lymphocytes and limit degranulation in T-CD8+ which impairs their cytotoxic function [4]. Finally, CQ and HCQ reduce the entry of iron into cells decreasing viral replication and production of inflammatory cytokines [7].

Azithromycin

As an antibacterial agent, it binds to the 50S subunit of ribosomes and blocks translocation thus inhibiting protein synthesis;

however, it also has potential anti-inflammatory and immunomodulatory effect in some viral respiratory infections [8]. There is insufficient data about its effect on viral clearance. SARS-Cov-2 possesses a domain in protein "S" which binds to GM1 gangliosides in the membrane of host cells and it seems that AZH has a structure similar to this domain, binding to the virus thus preventing it from adhering to the cell [9].

Pharmacology and security

Chloroquine and hydroxychloroquine

They have a high absorption capacity and their concentration peak is 2 to 3.5 hours after administration. Their half-life is 22 to 45 days. They reach a serum concentration of 1.5 µm with a dose of 6.5 mg/kg/day. Their hepatic, renal, splenic and especially pulmonary accumulation have been demonstrated in animal models. Recent studies also suggest ocular and skin accumulation [4]. In China the recommended dose of CQ diphosphate is 500 mg twice a day for 10 days [10]; on the other hand, the first non-randomized clinical study of HCQ in humans conducted in France mentions that the optimal dose is 600 mg three times a day for 6 days to produce viral clearance [6]. There is no clear evidence about the use of HCQ/CQ at high or low doses and survival in COVID-19 patients; however, higher mortality has been seen in those with high doses (especially in older patients, who have greater predisposition to cardiac disorders [10]. *In case of administering these medications, it is recommended to constantly monitor patients, evaluate QTc and modify doses if necessary*.

RCTs are required to establish clear recommendations regarding the use of these drugs in patients with COVID-19. It should be mentioned that until now their use has not been associated with immunosuppression or an increased risk of infection [4].

Regarding the use of HCQ + AZH, HCQ alone, AZH alone or no drug, there are no differences related to the mortality of patients but to adverse effects [11] (Refer to adverse effects).

Azithromycin

It reaches its maximum plasma concentration 2 to 3 hours after its administration. It has a wide distribution and its half-life is 68 - 72 hours [12]. The recommended dose is 500 mg the first day and 250 mg/day from the 2nd to the 5th day or 500 mg once a day for 5 days [8,10].

There is evidence to support its effectiveness *in vitro* in studies for ebola and zika viruses.

Are these treatments effective for COVID-19?

Despite the popularity of HCQ, CQ and AZH as potential treatments for COVID-19, we observed that most of the published literature revealed indeterminate results about the effectiveness of these drugs. Cartegiani., *et al*. [13] in their Systematic Review of 21 randomised clinical trials and 6 other articles demonstrated only *in vitro* effectiveness. To date, the available *in vivo* studies have inconclusive and questionable results because of observational study designs and methodological errors. The potential hazards from the use of these drugs alone or in combination need to be assessed with more accuracy. Borba., *et al*. [10] reported a double blind, randomised clinical trial with 81 adult patients who were hospitalised with severe COVID-19 at a tertiary care facility in Brazil. This study suggested that a higher dose of CQ was associated with more toxicity and lethality (prolonged QTc Interval), especially when taken concurrently with AZH. In another pharmacovigilance cohort study, Sarayani., *et al*. [15] found that HCQ and CQ were not associated with safety signals in FAERS (FDA Adverse Events Reporting System) analysis and recommended that AZH alone must be used with caution due to its QTc prolongation events.

The most relevant findings of the reviewed studies are synthetized on table 1.

Adverse effects in the context of COVID-19

Most of the studies published to date haven't considered the possible adverse effects associated with the use of HCQ, CQ, AZH, or any combination between these drugs [11]. We describe ahead the most important findings regarding adverse effects reported in patients with COVID-19.

Borba., *et al*. compared the administration of high dose CQ (600 mg BID for 10 days) vs low dose CQ (450 BID × 1 day then 450 mg daily × 4 days) in a total of 81 patients, who also received ceftriaxone and azithromycin. They demonstrated that more than 25% of patients in the high dose arm developed a prolonged QTc > 500 ms. The high dose group had an increased mortality rate of 17% vs 13.5%. There was no evidence for the rapid clearance of viral load on their testing. Because of concerns about safety and no clear benefit to the higher dose of CQ, the study was stopped [10].

Author	Type of Study	Sample	Findings	Notes
Cortegiani., *et al*. [13]	Systematic Review 21 RCTs, 6 Studies (1 Narrative review, 1 letter to the Editor, 1 *In vitro* Study, 1 Expert Review, 2 National guidelines)	3090 patients	CQ effectiveness only *In vitro*. *In vivo* Results are inconclusive.	Despite the good sample size analyzed in this review, the clinical trials are still ongoing and the other articles are low quality evidence.
Zhong., *et al*. [14]	Meta-analysis and Systematic Review 18 Studies: 5 RCTs, 13 cohorts (4 for HCQ, 5 lopinavir/ ritonavir, 9 Ribavirin, 5 for Interferon, 2 for Arbidol)	4941 patients	The relevant findings in terms of mortality, viral clearance, radiographic improvement, ARDS prevalence, intubation, and mechanical ventilation were inconclusive.	Imprecise results were obtained, making it difficult to give a recommendation.
Borba., *et al*. [10]	Double-blind RCT	81 patients	High CQ doses (600 mg CQ twice daily for 10 days) or low CQ doses (450 mg twice daily on day 1 and once daily for the next 4 days).	High dose CQ caused more toxicity and lethality (prolonged QTc Interval). The limited sample size did not allow the study to demonstrate any benefit regarding treatment efficacy.
Rosenberg., *et al*. [11]	Multicentric Cohorts	1438 Patients	The probability of death for patients receiving: HCQ + AZH was: 25.7% [CI 95%, 22.3% -28.9%] HCQ only: 19.9% [CI 95%, 15.2% -24.7%] AZH only: 10.0% [CI 95%, 5.9% -14.0%] No drugs: 12.7% [CI 95%, 8.3% -17.1%].	The interpretation of these results may be limited by the observational design.
Sarayani., *et al*. [15]	Cohorts	237 350 Patients	HCQ/CQ and AZH + HCQ / CQ did not show safety signs for QT prolongation or death. PRRs for QT prolongation are 1.43 for HCQ/CQ (95% CI 1.29-2.59), and 3.77 for AZH + HCQ/CQ (95% CI 1.80-7.87)	It is a pre-proof study, with valid statistical analysis of pharmacovigilance.
Tang., *et al*. [16]	RCT	150 patients (75 HCQ + Standard treatment vs 75 Standard treatment)	The administration of HCQ did not contribute to the negative seroconversion of the patients.	This is an “Open Label” study

Table 1: Studies about the effectiveness of treatment with HCQ, CQ and AZH for COVID-19. RCT: Randomized Control Trial; HCQ: Hydroxychloroquine; CQ: Chloroquine; AZH: Azithromycin; ARDS: Acute Respiratory Distress Syndrome; CI: Confidence Interval; PRR: Proportional Reporting Ratios.

Furthermore, Rosenberg., *et al*. concluded that HCQ (400 mg BID) in combination with AZH (500 mg QD) increased the risk of cardiac arrest after the third-day dose: OR 2.13 [95% CI: 1.12 - 4.05]. Similarly, HCQ alone increased the risk of cardiac arrest: OR, 2.97 [95% CI, 1.56 - 5.64] compared with AZH alone [11].

Finally, Sarayani., *et al*. described that HCQ and CQ were not associated with safety signals related to QTc prolongation and Torsades de Pointes while AZH alone did show an association with QTc prolongation events according to FDA Adverse Event Reporting System (FAERS) data. Thus, its use is recommended with caution [15].

Ongoing studies

197 ongoing clinical trials on the use of AZH, HCQ and CQ in patients with COVID-19 are listed to date on the National Institutes of Health (NIH) website [17].

On table 2 we quote the trials with the largest number of patients.

NCT	Intervention	Results	Population	Country
NCT04341207	HCQ + AZH in cancer patients	3 months mortality	1 000	Germany
NCT04340544	HCQ vs PLB	Symptoms resolution	2 700	Germany
NCT04334967	HCQ vs Vit C	Hospital vs no hospital	1 250	USA
NCT04334382	HCQ vs AZH for outpatients	Hospitalization	1 550	USA
NCT04334148	HCQ vs PLB	Viral load	15 000	USA
NCT04333732	Low dose/Standard dose/No CQ	Viral load	55 000	Multinational
NCT0432961	HCQ vs PLB to prevent severe disease	Intubation or death	2 660	Canada
NCT04325893	HCQ vs PLB	Death or ventilation	1 300	France
NCT04321993	HCQ vs Lopinavir vs Baricitinib vs Sarilumab	Clinical status on outcome scale	1 000	Canada
NCT04308668	HCQ vs PLB in severe disease	Mortality	3 000	USA

Table 2: Main characteristics of clinical trials with the largest populations to evaluate the efficacy of HCQ and CQ. NCT-NIH number of reference, HCQ-HCQ, CQ-CQ, PLB-Placebo, AZH-AZH. Information of the figure obtained in [2].

Conclusion

In conclusion, there is insufficient data to determine that HCQ, CQ and AZH alone or in combination have a role in the treatment for SARS-CoV-2 infection. At the moment we are still waiting for the results of larger randomized clinical trials, as we exposed previously on table 2.

It is important to mention that the IDSA (Infectious Diseases Society of America), approved the use of CQ and HCQ only if they are given in the setting of a clinical trial, based on the limited information available and the adverse effects known [11].

Patients receiving these drugs should be carefully monitored for their known and significant side effects [10,11,15].

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Conflict of Interest

Authors state no conflict of interest.

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