Hydroxychloroquine for treatment of SARS-CoV-2 infection
An exploratory review

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DO: https://doi.org/10.36104/amc.2020.1880

Abstract

Introduction: hydroxychloroquine has been recommended in this pandemic as a possible effective treatment for COVID-19. This is because Chinese experts have demonstrated its ability to inhibit viral replication through various mechanisms. At this juncture, it is vitally important to understand the latest research and clinical trials regarding an effective treatment regimen which would help improve the treatment of patients with SARS-CoV-2 infection.

Objective: to present the available information regarding the use of hydroxychloroquine as a treatment option for patients infected with SARS-CoV-2.

Material and methods: a review was carried out following the methodological framework proposed by Arksey and O’Malley. The data bases used were: PubMed, MedLine, Lilacs, Scopus, Clinical Trials, Cochrane and CNKI. Only texts in Spanish and English were included. Finally, the pertinent studies for this review were described and summarized.

Results: a total of 87 academic articles were included in the review, including experimental and non-experimental studies, all containing evidence regarding the use of hydroxychloroquine in COVID-19.

Conclusions: To date, there is no available substantiating scientific data with enough evidence to support the use of hydroxychloroquine as a pharmacological treatment for the current pandemic. Two randomized clinical trials contradict each other regarding the efficacy of hydroxychloroquine. However, they both share methodological errors and have small sample sizes. A single nonrandomized trial with the same errors shows efficacy of hydroxychloroquine. As far as the safety profile, there is data showing a lower rate of adverse effects for hydroxychloroquine compared with chloroquine, so its use would be preferred if it were to be proven effective against COVID-19. There are several randomized clinical trials underway which, it is hoped, will answer the questions raised by the literature review. (Acta Med Colomb 2020; 45. DOI: https://doi.org/10.36104/amc.2020.1880).

Key words: hydroxychloroquine, treatment, COVID-19, coronavirus, SARS-CoV-2

Introduction

In December 2019, an outbreak of an emergent disease caused by a novel coronavirus (SARS-CoV-2) began in Wuhan, China, which rapidly spread throughout all the continents, and was declared a pandemic on March 12, 2020 (1).

Chinese statistics and the disease’s behavior indicate that it has a clinical presentation spectrum ranging from a mild to a serious form (around 80% of those infected having the mild form), with an approximate lethality rate of 2.3%, reaching its highest percentage (14.8%) in those over 80 years old (2, 3).

As of July 2020, SARS-CoV-2 infection has affected more than 11 million people worldwide (4, 5). Given this significant number of cases at a global level, and considering that this is an emergent virus for which we have no knowledge of effective treatment measures, there is a need for research to find effective options to decrease mortality, the need for ventilatory support, hospital stay, or at least the length of viral excretion which may limit its transmission and expansion (3).

Through clinical trials, Chinese experts proposed chloroquine, an antimalarial already known to be a pharmacological option for treating the disease, finding good results with regard to viral elimination compared to control groups. Its use in this disease is based on the fact that this medication has broad-spectrum antiviral activity through increasing
the endosomal pH necessary for viral fusion to the cell, and interferes with glycosylation of the SARS-CoV cell receptors. The first in vitro studies report that chloroquine blocks SARS-CoV-2 infection at a low micromolar concentration, a maximum effective concentration of 1.13 μM and a semicytotoxic concentration greater than 100 μM (6).

The results of more than 100 patients have shown that chloroquine phosphate (CQ) is superior to the control treatment in inhibiting the progression of pneumonia, improving lung imaging findings, negativating the virus and shortening the disease course, according to the little available evidence. It is important to note that, to date, no serious adverse reactions to chloroquine phosphate have been reported in the previously mentioned patients (6). Hydroxychloroquine (HCQ), a chloroquine analog, has proven to have a higher clinical safety profile, which suggests that it could be a better treatment option (3).

It is important to point out that new data emerge daily on the clinical characteristics and treatment options of COVID-19. However, the objective of this exploratory review is to present the information available to date on the use of hydroxychloroquine as a treatment option for patients infected with SARS-CoV-2.

**Materials and methods**

**Study design**

A review was carried out following the methodological framework proposed by Arksey and O’Malley. The following five steps were followed for this exploratory review: a) identification of a clear research objective and search strategy, b) identification of published and unpublished articles, c) selection of articles, d) data extraction and mapping, and e) summary, discussion, analysis and reporting of the results. The review answered the question: What is the available evidence on the use of hydroxychloroquine as treatment for SARS-CoV-2 infection in the general population?

**Inclusion and exclusion criteria**

The following inclusion criteria were considered for this article: publications on the use of hydroxychloroquine as monotherapy or in combination for treatment of SARS-CoV-2 infection; articles with their own data, either in vitro o in vivo, or theoretical articles (narrative reviews or letters to the editor); published in English or Spanish, and published between December 1, 2019 and July 2, 2020. In the case of clinical trials, completed and ongoing studies were included.

Articles were excluded if the complete text was not available and if they only spoke of using hydroxychloroquine as prophylaxis in the management of COVID-19.

**Literature search strategies**

The literature for this review was identified through a search of the following online databases: PubMed, MedLine, Lilacs, Scopus, Clinical Trials, Cochrane and CNKI. The search terms were “hydroxychloroquine” AND “treatment” AND “COVID-19” OR “Coronavirus” OR “SARS-CoV-2”.

**Study selection and data extraction**

Articles were selected after reviewing their abstracts and determining that they contained the information of interest. At the same time, articles that did not meet the search criteria and duplicate articles were eliminated. In the end, 87 articles were included in this analysis. Figure 1 presents a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram showing the search process and selection of study articles.

After selecting the articles, the data were extracted and recorded on an Excel spreadsheet in which two formats were created, one for recording clinical trials and the other for the remaining documents. The extracted data included date of publication, language of publication, title of the article, country and affiliation of the authors, objectives of the study, the research domain and the key findings. For clinical trials, the recruitment status, study design, sample size, control and beginning or registration date were also recorded.

**Summary of findings**

Based on the primary objective of the study, the articles were classified as completed and ongoing clinical trials, meta-analyses, systematic reviews, observational studies, reviews and letters to the editor which include studies on hydroxychloroquine as COVID-19 treatment. The dates of publication, journal language, author affiliation, objectives of the study, methodological characteristics, where applicable, and results were analyzed.

**Results and discussion**

**Characteristics of the published studies**

Eighty-seven academic articles were selected, including two randomized clinical trials, one nonrandomized clinical trial, one in vitro experimental study, 52 ongoing clinical trials, one meta-analysis, six systematic reviews (one with only a preliminary report), two observational studies, 20 review articles and two letters to the editor, all of which seek to collect or create evidence on the use of hydroxychloroquine in COVID-19. All the research studies included in this review are organized in Tables 1 and 2, separating the completed experimental and nonexperimental studies from the ongoing clinical trials, and detailing the main author, objective(s), year, country in which it was carried out, type of publication, language and phase of the study, for experimental studies.

All the articles were published in 2020, since the pandemic began during the last days of 2019. The countries where the articles were most often conducted and/or where the most clinical trials are ongoing were United States, India and Brazil, making up almost 46% of the reviewed articles, highlighting the United States with almost 30%. Other countries with publications were China and France,
with 7% each; Italy with 4.5%; Saudi Arabia with a little more than 3%; Chile, Taiwan, Thailand, Spain, Mexico, Pakistan, England and Egypt with 2.2%; and Iran, Morocco, Canada, Israel, Czech Republic, Germany, Tunisia, Turkey, Australia, Senegal, Bahrain and Switzerland with only 1.1% of the reviewed articles. All the articles were in English, except for one which was in Spanish. Most of the articles were published in infectology journals along with internal medicine, molecular biology, chemistry, emergency medicine and bioscience, among others, showing the interest of various areas in researching this topic.

With regard to the four experimental studies reviewed, these draw attention to the lack of available evidence regarding the use of HCQ as a treatment for COVID-19, which is understandable in the context of an emergent disease.

We only had two randomized clinical trials, one published by Chen Z, et al. (7), with final results available, which evaluates the effectiveness of hydroxychloroquine treatment. This study, despite results suggesting a favorable result of hydroxychloroquine use, has low evidence in this regard due to some biases such as measurement (as there is no clear information on the randomization process) and concept bias (due to a short follow up time), along with a shaky statistical analysis in which some of the possible confounding variables are not mentioned, considering the inclusion and exclusion criteria used. The other randomized clinical trial is the one published by Tan W, et al. (8) with a sample of 150 patients, which is greater than that used by Chen Z, and the results are less encouraging than those of the other study, since this one could not show a greater probability of negativizing the SARS-CoV-2 test with hydroxychloroquine, and there was a greater number of adverse events in the group receiving the antimalarial.

A preliminary report of a nonrandomized clinical trial published by Gautret P, et al. (3) was found in the literature, which has several methodological flaws inherent in this type of study, as well as a very small sample size. Thus, it does not contribute results with sufficient validity.

Another experimental study included in the review was that of Yao, et al. (9). This was an in vitro study which supports the role of hydroxychloroquine in SARS-CoV-2 infection, opening the debate on its effectiveness; however, these findings must be confirmed with clinical studies.

Of the 31 non-experimental studies reviewed, we highlight one meta-analysis, six systematic reviews and two observational studies. The meta-analysis concludes that treatment with hydroxychloroquine may be beneficial in terms of radiological progression, with a safety profile comparable to the control treatment. In addition, it mentions the possible benefits with regard to temperature normalization and the resolution of symptoms such as cough. However, no significant differences were found in terms of virological cure, death or worsening disease; it must be taken into account that the number of clinical studies analyzed was small, with a small number of participants (10). With regard to the systematic reviews, most coincide in the lack of available evidence on the use of hydroxychloroquine and highlight the multiple limitations of the clinical trials published to date. However, they propose its use in the context of the pandemic, in the absence of any other valid treatment option, considering its risk-benefit (11-14). One of these reviews also highlights the need to monitor the risk (in patients who receive it) of adverse effects, keeping in mind aspects such as prior use of the medication, risk of retinopathy, and cardiovascular diseases, among others (14). The systematic reviews by Patel T, et al. and Das S, et al. (15, 16) do not recommend the use of hydroxychloroquine in COVID-19 patients. The first concludes that hydroxychloroquine does not improve mortality and, if given along with azithromycin, increases the risk of mortality compared to those who do not receive either of these medications. The second argues that the results of this medication are unsatisfactory, although the methodological flaws of the studies must be taken into account. One observational study by Gautret, et al. (18) studied a cohort of 80 patients treated with combined hydroxychloroquine and azithromycin for a minimum of three days. All the patients improved clinically, and a decreased nasopharyngeal viral load was demonstrated on days seven and eight; however, the sample size, short follow-up time and an apparent selection bias with patients having a lower NEWS scale, limit the validity of the study. On the other hand, the observational study published most recently by Geleris, et al. (17) is one of the studies with one of the largest samples (n=1,446). In its conclusions, no association was found between the use of hydroxychloroquine and the outcomes of intubation or death, although, being an observational study, confounding factors and biases were not measured. Both observational studies coincide in the need

Figure 1. PRISMA flow diagram for systematic reviews.
Table 1. General characteristics of completed experimental and non-experimental studies (N = 35).*

| Author             | Objective(s)                                                                 | Country | Type of publication | Language | Status of the study (where applicable) |
|--------------------|------------------------------------------------------------------------------|---------|---------------------|----------|----------------------------------------|
| Tang W, et al (8). | To evaluate the efficacy and safety of HCQ in adult COVID-19 patients.       | China   | Randomized clinical trial | English  | Completed                              |
| Chen Z, et al (7). | To evaluate the efficacy of HCQ in the treatment of COVID-19 patients.       | China   | Randomized clinical trial | English  | Completed                              |
| Gaunet P, et al (3). | To describe the first results of a clinical trial, focusing on the virological data in patients who receive hydroxychloroquine compared to a control group. | France  | Non-randomized clinical trial | English  | Preliminary report                     |
| Yao, et al (9).    | To investigate the antiviral and prophylactic activity of hydroxychloroquine *in vitro*. To construct a physiologically-based pharmacokinetic model for chloroquine and hydroxychloroquine using data from the literature. To predict the concentrations of the medications under different dosing regimens using the physiologically-based pharmacokinetic (PBPK) models developed. | China   | In vitro experimental study | English  | Completed                              |
| Sarma P, et al (10). | To evaluate the efficacy and safety of HCQ in clinical environments.       | India   | Meta-analysis        | English  | Completed                              |
| Singh AK, et al (13). | To collect all the available evidence which has emerged so far on the efficacy of chloroquine and hydroxychloroquine in the treatment of COVID-19 patients with or without diabetes and present a perspective on both compounds. | India   | Systematic review    | English  | Completed                              |
| Chowdhury MS, et al (12). | To review the currently available literature on the clinical use of chloroquine and hydroxychloroquine as treatment for COVID-19 patients in an effort to catalogue their recommendations and evaluate the medication’s efficacy. | United States | Systematic review    | English  | Completed                              |
| Patel TK, et al (15). | To discover the mortality tendencies of COVID-19 patients treated with hydroxychloroquine, based on the published literature. | India   | Systematic review    | English  | Completed                              |
| Das S, et al (16). | To systematically review the literature and produce evidence of the therapeutic role of hydroxychloroquine in patients diagnosed with COVID-19. | India   | Systematic review    | English  | Completed                              |
| Patil VM, et al (14). | To systematically review the mechanism of action, efficacy and safety of CQ and HCQ as therapeutic measures for curing COVID-19. | India   | Systematic review    | English  | Completed                              |
| Fundación Epistemonikos (11). | To summarize the most important available evidence of hydroxychloroquine as treatment for COVID-19 and guide towards better decision-making. | Chile   | Preliminary report of a systematic review | Spanish  | Preliminary report                     |
| Geleris J, et al (17). | To examine the association between the use of hydroxychloroquine and respiratory failure at a large medical center caring for a considerable number of COVID-19 patients in the city of New York. | United States | Observational        | English  | N/A                                    |
| Gaunet P, et al (18). | To describe the results of an uncontrolled, non-comparative observational study in a cohort of patients with relatively mild infection treated with HCQ together with azithromycin for at least three days, mainly assessing clinical outcome, contagion and length of stay. | France   | Observational        | English  | N/A                                    |
| Colson P, et al (21). | To present evidence on the use of chloroquine and hydroxychloroquine as an option for combating COVID-19. | France | Review             | English  | N/A                                    |
| Zahra SP, et al (22). | To analyze the role of some aminosulphonates which have shown activity against COVID-19. | Iran | Review             | English  | N/A                                    |
| Yazdany J, et al (24). | To provide guidance with regard to clinical decision-making for COVID-19 patients and those with autoimmune disease, and establish strategies to mitigate harm to these patients. | United States | Review             | English  | N/A                                    |
| Kim AHJ, et al (19). | To expose the methodological errors affecting the validity of the findings of the clinical trials published to date. | United States | Review             | English  | N/A                                    |
| Zhou D, et al (20). | To review the available information on hydroxychloroquine and chloroquine as COVID-19 treatment, suggesting the preferential use of one of the two medications. | China   | Review             | English  | N/A                                    |

* All the articles were published in 2020.
Continuation... Table 1. General characteristics of completed experimental and non-experimental studies (N = 35).* 

| Author | Objective(s)                                                                 | Country     | Type of publication | Language | Status of the study (where applicable) |
|--------|------------------------------------------------------------------------------|-------------|---------------------|----------|----------------------------------------|
| Sinha N, et al (23). | To review the history and mechanism of action of hydroxychloroquine and chloroquine, and their potential use in the current COVID-19 pandemic. | United States | Review | English | N/A |
| Choudhary R, et al (27). | To provide a comprehensive view of the knowledge available regarding the combination of hydroxychloroquine, ivermectin and azithromycin in the context of the current worldwide health emergency. | India | Review | English | N/A |
| Sargane S, et al (28). | To review the global epidemiological situation and the effectiveness of the use of chloroquine and hydroxychloroquine in COVID-19 treatment. | Morocco | Review | English | N/A |
| Meyerowitz EA et al (29). | To review the known effects of hydroxychloroquine on viral replication and the immune system and present the evidence to date and evident considerations regarding treatment with hydroxychloroquine in COVID-19 patients. | United States | Review | English | N/A |
| Shukla AM (30). | To present the available in vitro and in vivo evidence on the role of chloroquine/ hydroxychloroquine in COVID-19 with due concern for applying the known facts to large populations increasingly affected by COVID-19. | United States | Review | English | N/A |
| Kapoor A, et al (31). | To present a brief review of the cardiovascular effects of hydroxychloroquine in regard to its predisposition to cause a prolonged QT interval and potentially fatal cardiac arrhythmia. To discuss the identification of the high-risk population and monitoring to prevent sudden cardiac death. | India | Review | English | N/A |
| Barbosa Pereira B, et al (32). | To present and discuss relevant aspects for preventing toxicological effects during and after COVID-19 treatment. | Brazil | Review | English | N/A |
| Pastick KA, et al (33). | To discuss the strengths and weaknesses | United States | Review | English | N/A |
| Lu CC, et al (34). | To summarize the current evidence on potential therapeutic agents which have been reported to have experience in treating SARS-CoV-2 infections, such as lopinavir/ritonavir, remdesivir, favipiravir, chloroquine, hydroxychloroquine, interferon, ribavirin, tocilizumab and sarilumab. | Taiwan | Review | English | N/A |
| Balabaskaran Nina P, et al (35). | To review the available evidence for and against the use of hydroxychloroquine as COVID-19 prophylaxis or treatment, mainly in the Indian context. | India | Review | English | N/A |
| Ibáñez S, et al (36) | To review and discuss the possible role of hydroxychloroquine and chloroquine in the treatment of COVID-19. | Chile | Review | English | N/A |
| Quiros Roldán E, et al (37). | To review current knowledge of the mechanism of action of CQ and HCQ as antiviral, anti-inflammatory and antithrombotic drugs, and discuss the current experimental evidence of the potential mechanisms of action in SARS-CoV-2. To propose a different perspective of the effects of CQ and HCQ, suggesting a potential role in iron homeostasis in COVID-19. To briefly review and discuss current knowledge regarding the efficacy of these medications in the treatment of COVID-19 patients. | Italy | Review | English | N/A |
| Hashem AM, et al (38). | To explore the evidence supporting the use of CQ or HCQ in COVID-19 patients through an exhaustive review of the previous studies in which they were used as antiviral treatment. | Saudi Arabia | Review | English | N/A |
| Olushola Shittu M, et al (39). | To review the interaction between chloroquine, hydroxychloroquine and zinc and the possibility of their synergistic administration to mitigate COVID-19 exacerbation. | United States | Review | English | N/A |
| Alexander PE, et al (40). | To discuss the COVID-19 research methodologies and the published reports on CQ and HCQ, combined with azithromycin. | Canada | Review | English | N/A |
| Liu J, et al (25). | To perform an analysis of the results of a study which analyzes the effect of CQ and HCQ inhibiting SARS-CoV-2 infection in vitro. | China | Letter to the editor | English | N/A |
| Guastalegname M, et al (26). | To issue an analysis regarding the studies published on hydroxychloroquine as SARS-CoV-2 treatment. | Italy | Letter to the editor | English | N/A |

* All the articles were published in 2020.
Table 2. General characteristics of the ongoing clinical trials (ClinicalTrials) (N = 52).*

| Author | Objective(s) | Country | Type of publication | Language | Phase (Where applicable) |
|-------|--------------|---------|---------------------|----------|--------------------------|
| Kongsaengdao S, et al (41). | To compare various combinations of protease inhibitors, oseltamivir, favipiravir and hydroxychloroquine for treating COVID-19. | Thailand | Randomized clinical trial | English | Phase 3 |
| Mitja O, et al (42). | To evaluate the efficacy of the “test and treat” strategy in infected patients, and prophylactic treatment with chloroquine for all contacts. | Spain | Randomized clinical trial | English | Phase 3 |
| Domingo P, et al (43). | To evaluate the use of tocilizumab combined with hydroxychloroquine and azithromycin for treating hospitalized adults with COVID-19. | Spain | Randomized clinical trial | English | Phase 2 |
| Hongzhou L, et al (44). | To evaluate the efficacy and safety of HCQ in the treatment of COVID-19 pneumonia. | China | Randomized clinical trial | English | Phase 3 |
| Dubee V, et al (45). | To evaluate the response to treatment with hydroxychloroquine in COVID-19 patients in terms of prognosis, mortality and use of IMV. | France | Randomized clinical trial | English | Phase 3 |
| Zampieri F, et al (46). | To compare HCQ + azithromycin and HCQ monotherapy for treating hospitalized patients with COVID-19. | Brazil | Randomized clinical trial | English | Phase 3 |
| Amaravadi R, et al (47). | To evaluate, through three different cohorts, the use of high-dose HCQ as treatment for COVID-19 patients at home, different doses of HCQ in hospitalized patients, and low-dose HCQ as prevention in healthcare workers. | United States | Randomized clinical trial | English | Phase 3 |
| Brown S, et al (48). | To compare hydroxychloroquine and azithromycin to determine which is better for treating hospitalized patients with suspected or confirmed COVID-19. | United States | Randomized clinical trial | English | Phase 2 |
| Hernandez C, et al (49). | To evaluate the safety and efficacy of hydroxychloroquine as treatment for severe COVID-19 respiratory disease. | Mexico | Randomized clinical trial | English | Phase 3 |
| Farooq U, et al (50). | To find the effectiveness of hydroxychloroquine as monotherapy and combined with azithromycin in patients with mild to severe COVID-19 pneumonia at Ayub Teaching Hospital, Pakistan. | Pakistan | Randomized clinical trial | English | Phase 3 |
| Berwanger O, et al (51). | To evaluate the efficacy and safety of hydroxychloroquine combined with azithromycin, compared to hydroxychloroquine monotherapy, in patients hospitalized with SARS-CoV-2 pneumonia in Brazil. | Brazil | Randomized clinical trial | English | Phase 3 |
| Rambam P, et al (52). | To evaluate the efficacy of HCQ in COVID-19 patients with a recent diagnosis who have mild to moderate disease or a risk for complications. | Israel | Randomized clinical trial | English | Phase 1 |
| Ferrara L, et al (53). | To evaluate the efficacy of HCQ and azithromycin as treatment for moderate to severe COVID-19 pneumonia. | Brazil | Non-randomized clinical trial | English | Phase 1 |
| Martinelli G, et al (54). | To evaluate the role of hydroxychloroquine versus observation alone in the prevention of COVID-19 infection or the treatment of patients with early-stage COVID-19. | Italy | Randomized clinical trial | English | Phase 2 |
| Novartis Pharmaceuticals (55). | To determine if monotherapy with oral hydroxychloroquine, or in combination with azithromycin, produces a clinical benefit in hospitalized patients with COVID-19 pneumonia. | United States | Randomized clinical trial | English | Phase 3 |
| Nori P, et al | To evaluate the efficacy of hydroxychloroquine in healthcare workers in the Montefiore Healthcare System (United States) who are at greater risk for severe COVID-19 disease. | United States | Non-randomized clinical trial | English | Phase 2 |

* All the articles were published in 2020.
Continuation...  **Table 2. General characteristics of the ongoing clinical trials (ClinicalTrials) (N = 52).**

| Author          | Objective(s)                                                                                                                                                                                                 | Country            | Type of publication                  | Language | Phase (Where applicable) |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|--------------------------------------|----------|--------------------------|
| Duska F, et al  | To test the hypothesis that early administration of combination therapy (hydroxychloroquine and azithromycin) slows disease progression and improves survival without the need for mechanical ventilation. | Czech Republic     | Randomized clinical trial            | English  | Phase 3                  |
| Curlin M, et al | To evaluate the efficacy and safety of hydroxychloroquine as treatment for patients with lower respiratory tract infections due to SARS-CoV-2.                                                             | United States      | Randomized clinical trial            | English  | Phase 4                  |
| Spivak A, et al | To evaluate the efficacy and safety of hydroxychloroquine in reducing viral load and viral elimination in adult ambulatory COVID-19 patients.                                                              | United States      | Randomized clinical trial            | English  | Phase 2                  |
| Richards WO, et al | To see if hydroxychloroquine decreases the viral load (through PCR), seven days after beginning treatment, compared to control patients who receive a placebo.                                    | United States      | Randomized clinical trial            | English  | Phase 2 and 3            |
| Mordmüller B, et al | To identify the effect of hydroxychloroquine on *in vivo* viral clearance.                                                                                                                                   | Germany            | Randomized clinical trial            | English  | Phase 3                  |
| Conigliaro J, et al | To evaluate and compare the clinical efficacy of treatment with hydroxychloroquine or combined with high-dose intravenous famotidine, in hospitalized COVID-19 patients.                               | United States      | Randomized clinical trial            | English  | Phase 3                  |
| Papanicolaou G, et al | To test the efficacy of hydroxychloroquine as treatment for COVID-19 patients.                                                                                                                             | United States      | Randomized clinical trial            | English  | Phase 2                  |
| Sanofi (63).    | To evaluate the effect of hydroxychloroquine on the nasopharyngeal viral load of ambulatory SARS-CoV-2 patients.                                                                                           | United States      | Randomized clinical trial            | English  | Phase 1                  |
| Shah P, et al   | To evaluate the efficacy of combination therapy with azithromycin, hydroxychloroquine and zinc or favipiravir in patients with suspected or confirmed COVID-19 infection.                                        | United States      | Randomized clinical trial            | English  | Phase 3                  |
| Servolo de Medeiros E, et al | To evaluate the safety and efficacy of hydroxychloroquine in patients with symptomatic SARS-CoV-2.                                                                                                         | United States      | Randomized clinical trial            | English  | Phase 3                  |
| Thakore A, et al | To evaluate the safety and efficacy of hydroxychloroquine and zinc combined with azithromycin or doxycycline in a high-risk COVID-19-positive ambulatory population.                                           | United States      | Randomized clinical trial            | English  | Phase 4                  |
| Reynes J, et al | To evaluate the efficacy and safety of hydroxychloroquine combined with azithromycin compared to hydroxychloroquine monotherapy in hospitalized patients with confirmed COVID-19 pneumonia.                     | France             | Randomized clinical trial            | English  | Phase 2 and 3            |
| Vojta D, et al  | To prove that high-dose hydroxychloroquine for two weeks may be an effective medication for both ambulatory patient treatment as well as prophylaxis/treatment for healthcare workers.                     | United States      | Randomized clinical trial            | English  | Phase 2                  |
| O’Halloran J, et al | To test the efficacy and recovery time of non-critical (not requiring mechanical ventilation) hospitalized patients with COVID-19 who will receive hydroxychloroquine or chloroquine with or without azithromycin. | United States      | Randomized clinical trial            | English  | Phase 3                  |
| Akram J, et al  | To evaluate the efficacy of hydroxychloroquine in eliminating the virus and improving the course of the disease, compared to other interventions: oseltamivir and azithromycin alone and combined with hydroxychloroquine.              | Pakistan           | Randomized clinical trial            | English  | Phase 3                  |

* All the articles were published in 2020.
## Table 2. General characteristics of the ongoing clinical trials (ClinicalTrials) (N = 52)*

| Author                         | Objective(s)                                                                 | Country      | Type of publication        | Language | Phase (Where applicable) |
|--------------------------------|------------------------------------------------------------------------------|--------------|---------------------------|----------|--------------------------|
| Thompson B, et al (71).        | To evaluate the efficacy of hydroxychloroquine for treating hospitalized adults with COVID-19. | United States | Randomized clinical trial  | English  | Phase 3                  |
| Abd-Elsalamb S, et al (72).    | To research if zinc supplementation improves the clinical efficacy of chloroquine in COVID-19 treatment. | Egypt        | Randomized clinical trial  | English  | Phase 3                  |
| Esmat G, et al (73).           | To evaluate the safety and efficacy of adding anti-hepatitis C (HCV) treatment to the standard regimen for treating patients who are candidates for hydroxychloroquine according to the Egyptian MOHP protocol. | Egypt        | Randomized clinical trial  | English  | Phase 2 and 3            |
| Suputtamongkol Y, et al (74).  | To evaluate oral ivermectin versus hydroxychloroquine plus darunavir/ritonavir in adult asymptomatic SARS-CoV-2 carriers in the Thai population. | Thailand     | Randomized clinical trial  | English  | Phase 4                  |
| WellStar Health System (75).   | To evaluate the impact of hydroxychloroquine on hospitalized patients with COVID-19 and risk factors for critical/severe disease. | United States | Randomized clinical trial  | English  | Phase 4                  |
| Rea-Neto A, et al (76).        | To test if chloroquine or hydroxychloroquine are effective in treating COVID-19 and improving a primary ordinal outcome composed of a nine-level scale recommended by WHO. | Brazil       | Randomized clinical trial  | English  | Phase 3                  |
| Letaief A, et al (77).         | To investigate the efficacy and tolerance of a five-day regimen of hydroxychloroquine or hydroxychloroquine azithromycin in COVID-19 patients. | Tunisia      | Randomized clinical trial  | English  | Phase 3                  |
| Kara A, et al (78).            | To evaluate the efficacy and safety of hydroxychloroquine and favipiravir in the treatment of patients with possible or confirmed COVID-19. | Turkey       | Randomized clinical trial  | English  | Phase 3                  |
| Reis G, et al (79).            | To evaluate the use of hydroxychloroquine and lopinavir/ritonavir alone or combined in COVID-19 patients. | Brazil       | Randomized clinical trial  | English  | Phase 3                  |
| Ried K, et al (80).            | To evaluate the efficacy and safety of azithromycin, hydroxychloroquine, zinc, vitamin D3/B12 and vitamin C treatment compared to azithromycin, hydroxychloroquine, zinc, and vitamin D3/B12 in participants with COVID-19. | Australia    | Randomized clinical trial  | English  | Phase 2                  |
| Bosaeed M, et al (81).         | To evaluate the efficacy of the combination of favipiravir and hydroxychloroquine as a potential treatment for moderate to severe COVID-19 cases. | Saudi Arabia | Randomized clinical trial  | English  | N/A                      |
| Sartori V, et al (82).         | To evaluate the efficacy of a combination of hydroxychloroquine and azithromycin in the fall in viral load at day five in patients with COVID-19 and hematologic malignancies. | France       | Randomized clinical trial  | English  | Phase 2                  |
| Arreola Guerra JM, et al (83). | To evaluate the safety and efficacy of treatment with hydroxychloroquine and ivermectin for serious COVID-19 infections in non-critical hospitalized patients. | Mexico       | Randomized clinical trial  | English  | Phase 3                  |
| Lutfy S. et al (84).           | To investigate the possible beneficial effects of hydroxychloroquine in the treatment of COVID-19 patients. | Saudi Arabia | Randomized clinical trial  | English  | Phase 2                  |
| Gabrielli A, et al (85).       | To evaluate if the addition of tofacitinib to the standard hydroxychloroquine treatment in the early phase of COVID-19 pneumonitis can prevent the development of severe respiratory failure requiring mechanical ventilation. | Italy        | Randomized clinical trial  | English  | Phase 2                  |
| Taieb F, et al (86).           | To evaluate and compare viral clearance between the different therapeutic interventions: hydroxychloroquine and the combination of hydroxychloroquine and azithromycin. | Senegal      | Randomized clinical trial  | English  | Phase 3                  |

* All the articles were published in 2020.
to create clinical trials which will produce final results with regard to the use of the antimalarial as a COVID-19 treatment (17). These results coincide with what was published in the reviews by Kim AHJ, et al. and Zhou D, et al. (19, 20)

Some of the review articles analyzed mention that hydroxychloroquine causes a similar effect on the viruses as chloroquine, since they share the same mechanism of action, and that hydroxychloroquine may be a better option for treating SARS-CoV-2 since it has fewer adverse effects, making it safer to use (20-23).

Yazdany J, et al. mentioned the public health crisis which could occur in hydroxychloroquine-dependent autoimmune patients due to scarcity of the medication caused by an exaggeration of the available data. They recommend avoiding the misuse of hydroxychloroquine until solid scientific evidence becomes available (24).

Finally, two letters to the editor were reviewed. The one by Liu J, et al. (25) suggested that hydroxychloroquine shows its in vitro effect due to its antiviral and anti-inflammatory action, diminishing the production of cytokines and proinflammatory factors. According to Guastalegname M, et al. (26), the effect of hydroxychloroquine in humans or in vivo SARS-CoV models has not been proven, and thus it may not be useful in COVID-19 patients, and may even cause damaging effects such as those produced in patients with chikungunya infection who received this medication; it must be used with caution.

Limitations

As this review was carried out in a short period of time, seeking to obtain results in a hurry, the literature search was performed by the authors and was not guided by a librarian. Only clinical trials registered on the Clinical Trials platform were included; however, this platform has the highest number of records on this topic. Studies published in languages other than English or Spanish were also not included, which may have left some articles out, but it must be noted that most of the articles available in the literature are in English, which ensures having achieved the greatest collection of articles on this topic.

The findings are subject to the scant information available on the topic and the design of the reviewed literature.

Conclusions

The current global situation due to the novel coronavirus SARS-CoV-2 pandemic, its rapid expansion, its exponential growth of infected individuals and the resulting healthcare systems’ crisis necessitates the rapid identification of a cost-effective treatment.

Antimalarials have been proposed as a possible treatment for COVID-19 (especially hydroxychloroquine, due to its lower rate of adverse effects compared to chloroquine [20]) because of their known antiviral effect due to their mechanisms of action.

After conducting an exploratory review of the available information to date on this topic, we found that there are two randomized studies with methodological flaws and mutual contradictions. The available clinical trials are mostly nonrandomized, which limits their validity. There are 52 randomized trials currently underway and projected to have results in an average of one year. These intend to test hydroxychloroquine as monotherapy or associated with other antivirals, from which results are expected to be extrapolatable to the global population and to instate
hydroxychloroquine as an effective treatment for SARS-CoV-2 infection.

The foregoing concludes that there is no scientific information available to date that supports and provides enough evidence that hydroxychloroquine may be used to manage the current pandemic. On the contrary, its misuse may result in greater adverse effects for those who take it without an indication, as well as for the health of patients who are dependent on this medication for their survival, as a result of diminished available reserves (24).

For now, we should continue to wait for the results of the ongoing clinical trials in order to determine with enough certainty that this antimalarial should be used, or, on the contrary, rule it out. Overestimation of the information available to date should be avoided and, given the uncertainty regarding its usefulness and potential toxicity, its use in patients should be restricted to clinical studies only.

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