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Review Article

Safety and Efficacy of Hydroxychloroquine and Chloroquine in Treatment of COVID-19: A Rapid Review of Evidence

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Abstract

Context: The coronavirus (named COVID-19) 2019 pandemic has caused significant morbidity and mortality around the world and has created serious challenges for health systems. To date, no medical treatment is developed for COVID-19 with proven effectiveness. This study is a rapid review aimed to identify and summarize evidence on the efficacy and safety of Hydroxychloroquine (HCQ) and Chloroquine (CQ) for COVID-19 infection.

Methods: This study is a rapid review that systematically searched electronic databases, including PubMed, EMBASE, ClinicalTrials.gov, and Cochrane Library, until May 22, 2020. Peer-reviewed randomized clinical trials, reviews, and observational studies on the efficacy and safety of HCQ and CQ for the prevention and treatment of COVID-19 infection were included.

Results: There were seven review articles, five clinical trial studies, and eight observational studies focusing on CQ or HCQ to treat COVID-19 patients. Of five clinical trials, three reported favorable outcomes among patients who received CQ or HCQ. Of eight observational studies, four reported no difference between the use of HCQ alone or combined administration of HCQ and Azithromycin with other medications. Three studies showed that the combined administration of HCQ and Azithromycin or HCQ alone is associated with improved clinical outcomes.

Conclusions: The included studies reported conflicting results on the efficacy and safety of HCQ and CQ in treating COVID-19. Therefore, it seems that there is not sufficient evidence about the effectiveness and safety of HCQ and CQ to treat patients with COVID-19 and more studies, which also report long-term follow up results, are needed.

Keywords: Hydroxychloroquine; Chloroquine; COVID-19; Safety; Efficacy

1. Context

In December 2019, an emerging disease named COVID-19 originated from a new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) with symptoms of acute respiratory syndrome in the city of Wuhan (China) and rapidly spread to the other countries worldwide. Since the virus was spread quickly, countries were suddenly faced with large numbers of infected people. According to the preliminary studies, about 40-65% of acute respiratory failures cases caused by COVID-19, who need mechanical ventilation, were died, which is significantly higher than the reported mortality rate for the acute respiratory syndrome caused by other viruses (1). Interventions should not only be focused on correcting hypoxia and providing adequate support to the body's organs but also should reduce the viral load and severity of the disease (2). To treat COVID-19, a wide range of antiviral, such as Favipiravir, chloroquine, and Remedsivir, is recommended. Chloroquine is commonly used to treat malaria, except in drug-resistant cases. Moreover, due to their anti-inflammatory properties, Chloroquine (CQ) and Hydroxychloroquine (HCQ) also are recommended to treat rheumatic disorders, such as Lupus Erythematosus and Rheumatoid Arthritis. These medicines are known as anti-rheumatic drugs and change the course of the disease. Unlike non-steroidal anti-inflammatory drugs and steroids, CQ and HCQ not only remove the symptoms of the disease but also affect its prognosis (3). It is more than 70 years that CQ is used all around the world and is on the World Health Organization's list of essential drugs (4).

Since its emergence, many efforts have been directed to develop specific antiviral treatment or vaccine against COVID-19 infection. CQ and its derivative, including HCQ , are among medicines that are used to treat COVID-19. The antiviral and anti-inflammatory properties of the CQ and HCQ led to special attention to these drugs to treat COVID-19 (2). Also, the results of primary in vitro studies indicate the effectiveness of CQ to treat infections caused by the new acute respiratory coronavirus

virus (5). These drugs modulate the interaction between the host and the virus, and it is shown that by inhibiting the production of inflammatory cytokines, particularly TNF-α, have therapeutic effects and can reduce or remove the viral load in patients with COVID-19 infection. According to lung CT scan findings, the administration of CQ for COVID-19 patients reduces the symptoms. Besides, fever and the recovery period of patients were significantly reduced following the administration of CQ, and it increased the rate of negative nucleic acid coronavirus tests (6, 7). On the other hand, the administration of CQ and HCQ may lead to adverse effects, including retinopathy-related toxicological outcomes, Neuromyopathy, and Cardiomyopathy. The efficacy and safety of these two drugs in patients with COVID-19 are not yet established, so they should not be self-used or be routinely used without prescription (3).

In Iran, according to the latest guideline for diagnosis and treatment of COVID-19 in outpatient and inpatient health centers, which is published by the Ministry of Health and Medical Education on May 10, 2020, CQ phosphate and HCQ are recommended as drugs that can be used to treat COVID-19 infection. Regarding that CQ and HCQ has been incorporated into the guidelines for the treatment of patients with COVID-19 in different countries, including Iran, this study aimed to collect and analyze available evidence on efficacy and safety of these two drugs in the treatment of patients with COVID-19 infection.

Methods .2

This study is a rapid review aimed to analyze current evidence to find the role of CQ and HCQ in the prevention and treatment of COVID-19. PubMed, EMBASE, ClinicalTrials.gov, and Cochrane Library were searched till 22 May 2020 using various combinations of the following keywords: “chloroquine”, “Hydroxychloroquine”, “Anthraquinone”, “CQ”, “HCQ”, “coronavirus”, “coronavirus disease”, “coronavirus disease-19”, “COVID-19”, “severe acute respiratory syndrome”, “SARS-CoV-2”, “efficacy” and “safety”. The search was expended using the snowballing method applied to the references of retrieved papers.

Inclusion criteria were as follow peer-reviewed papers written in English that investigated the safety and efficacy of HCQ and CQ in patients with COVID-19 in comparison with other routine treatments (such as administration of other medicine) or placebo. Since the current study aimed to review current evidence, the following study designs were considered and included: systematic or rapid reviews, randomized clinical trials, non-randomized clinical trials, and observational studies (cohort studies and case-control studies). Other types of studies, including case reports, physician’s opinions, commentaries, and letters to editors, were excluded. Preprint papers that were not peer-reviewed also excluded. After reviewing the literature, six reviews, five clinical trials, and eight observational studies were identified (Table 1).

Table 1. Summary of the Characteristics of the Identified Studies

	Title	Authors	Some Characteristic of the Study	Details
1	**Breakthrough: Chloroquine phosphate has shown apparent efficacy in the treatment of COVID-19 associated pneumonia in clinical studies**	Gao et al.	Study type: Letter (Report of a clinical trial results)	This study, which is published as a letter, concluded that the administration of CQ in a group of 100 patients in China was 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. It should be noted that the details of this trial have not yet been published. The authors recommended the introduction of CQ to the national guideline of China for COVID-19 treatment (6).
2	**Hydroxychloroquine and Azithromycin as a treatment for COVID-19: results of an open-label non-randomized clinical trial**	Gautret et al.	Study design: open-label non-randomized clinical trial; Study period: 10 days; Investigated outcome: the viral load of the nasopharyngeal swab.	In this study, which is conducted in France, the effect of using HCQ alone or combined with Azithromycin on the viral load of 26 patients with COVID-19 is investigated. Depending on the clinical symptoms, Azithromycin was also added to the medication (for 6 patients). The control group was patients hospitalized in another healthcare center (n=16), and the viral load in Nasopharyngeal swabs on the sixth day was defined as the outcome of the intervention. Authors concluded that although the sample was small, they have provided evidence of a beneficial effect of co-administration of HCQ with Azithromycin in the treatment of COVID-19 and its potential effectiveness in the early reduction of contagiousness. No adverse effect is mentioned for HCQ in this study (7).

3	**Chloroquine and Hydroxychloroquine in the treatment of COVID-19 patients with or without diabetes: A systematic search and a narrative review with a special reference to India and other developing countries**	Singh et al.	Study type: a systematic and narrative review (included studies = 2 clinical trials	Although evidence regarding the effectiveness of CQ and HCQ is limited, considering the minimal risk of administration, their long-term use in the treatment of other diseases, cost-effectiveness, and availability in India, the authors concluded that these drugs worth a fast track clinical trial for the treatment of COVID-19 patients. Given that HCQ is approved for diabetic patients in India, the authors mentioned the need for further examination of its effect on the treatment of diabetic and COVID-19, since patients with diabetes are at increased risk of dying due to COVID-19 (8).
4	**Clinical and microbiological effect of a combination of Hydroxychloroquine and azithromycin in 80 COVID-19 patients with at least a six-day follow up: an observational study**	Gautret et al.	Study type: observational study; study duration: 10 days; Investigated outcomes: viral load of nasopharyngeal swab, and hospitalization period.	In this study, which is conducted in Marseille France, the effect of combined administration of HCQ and azithromycin on 80 relatively mildly infected inpatients is investigated. The administered medication was the same as their previous study (7). On the seventh day, 83% of nasopharyngeal viral load was negative, which increased to 93% on the eighth day. Virus cultures from patient respiratory samples were negative in 97.5% of patients on Day 5. The authors concluded co-administration of HCQ with Azithromycin has potential benefits in the treatment of COVID-19, and it is potentially effective in the early reduction of contagiousness (9).
5	**Treating COVID-19 with Chloroquine**	Huang et al.	Study type: randomized clinical trial; Study duration: 14 days; Investigated outcomes: the viral load of nasopharyngeal swab, CT imaging	This clinical trial was conducted from January 27, 2020, to February 15 in China to assess the efficacy and safety of CQ in hospitalized COVID-19 patients. The control group received Lopinavir/Ritonavir. Twenty-two positive COVID-19 patients who were diagnosed with RT-PCR were included in the study. Ten patients were treated with CQ 500, and 12 received Lopinavir/Ritonavir 400/100 mg twice a day for 10 days. Preliminary results showed that one patient became negative after receiving CQ , and after 13 days, all patients who were treated with CQ became negative. These results suggest that patients treated with CQ appear to be recovered better and regained their pulmonary function quicker than those treated with Lopinavir/Ritonavir. The authors concluded that CQ can be an effective and inexpensive choice compared to other treatment options such as Lopinavir/Ritonavir (10).
6	**Should Chloroquine and Hydroxychloroquine be used to treat COVID-19? A rapid review**	Gbinigie and Frie	Study type: rapid review; (number of investigated studies = three clinical trials)	This review study concluded that there is not sufficient evidence to decide whether CQ and HCQ are safe and effective for the treatment of patients with COVID-19. High quality, adequately powered randomized clinical trials in primary and secondary care settings are urgently required to guide policymakers and clinicians. These studies should report medium- and long- term follow- up results, and safety data (11).
7	**A systematic review of the prophylactic role of Chloroquine and Hydroxychloroquine in Coronavirus Disease-19 (Covid-19)**	Shah et al.	Study type: systematic review (no original article were found and included)	This study aimed to investigate the evidence on the role of CQ and HCQ in the prevention of COVID-19. The authors concluded that the results of pre-clinical studies on the therapeutic effects of these two drugs are promising; however, there is a dearth of evidence to support the efficacy of CQ and HCQ in preventing COVID-19. Therefore, considering potential safety issues and the possibility of inducing a false sense of their safety, administration of prophylaxis with CQ and HCQ against COVID-19 should be evaluated thoroughly using high-quality randomized clinical trials (12).

8	**Review: Hydroxychloroquine and Chloroquine for treatment of SARS-CoV-2 (COVID-19)**	Pastick et al.	Study type: rapid narrative review (included studies = 4, including 2 clinical trials, one report of clinical trials, and one cohort study)	While reviewing related studies, the authors evaluated the strengths, weaknesses, and limitations of the included studies. They also reported that regarding their adverse effects, including cardiac arrhythmias and QT prolongation, more studies should be conducted on the effectiveness and safety of HCQ and CQ in the prevention and treatment of COVID-19. Besides, due to the weaknesses of the current evidence, larger, higher-quality randomized controlled trials are needed before the widespread incorporation of HCQ and CQ into the national and international treatment guidelines (13).
9	**Effect of High vs. Low Doses of Chloroquine Diphosphate as Adjunctive Therapy for Patients Hospitalized with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection**	Borba et al.	Study type: randomized clinical trial; Study duration: 28 days; Investigated outcomes: viral load, adverse drug reactions	In this double-blinded clinical trial, which is conducted in Brazil and published in the JAMA journal, the effectiveness and safety of CQ phosphate are evaluated in 81 critically ill patients. 41 of these patients received high doses of the drug (600 mg tablets twice a day for 10 days) and 40 patients received low doses (two 450 mg tablets for the first day and one tablet for other days, for 4 days). The results of this study showed that mortality in the group that received higher doses of CQ was higher than the other group (39% rather than 15%), and these patients had a longer QT interval. The authors concluded that high doses of CQ (especially combined with other drugs such as Azithromycin and Oselatamivir) were not recommended for older patients, particularly in patients with cardiovascular disease, because of risks associated with drug safety. This study suggested further investigation of the effect of CQ on patients with mild to moderate symptoms of COVID-19 and the prophylactic effect of this drug in the prevention of COVID-19. It should be noted that the sample size of the study was 440, which was stopped after observing the preliminary results (14).
10	**No Evidence of Rapid Antiviral Clearance or Clinical Benefit with the Combination of Hydroxychloroquine and Azithromycin in Patients with Severe COVID-19 Infection**	Molina et al.	Study type: prospective cohort; Study duration: 10 days; Investigated outcome: nasopharyngeal viral load	In this study, which is conducted in France with a sample size of 11, the effect of administration of HCQ and Azithromycin on 11 patients (which 8 of them had co-morbidity) is investigated. 10 (out of 11) participants received oxygen. Examination of patients on the fifth day indicated the persistence of the virus in the Nasopharyngeal swab of 8 (out of 10) treated patients. As well, one patient died during the study period, and two were transferred to the ICU. The authors conclude that despite a reported antiviral activity of CQ against COVID-19 in-vitro, there is no evidence of a strong antiviral activity or clinical benefit of the combination of HCQ and azithromycin for the treatment of the hospitalized patients with severe COVID-19 infection and ongoing clinical trials should provide clear responses about effectiveness and safety of these combinations (13).
11	**A Rapid Systematic Review of Clinical Trials Utilizing Chloroquine and Hydroxychloroquine as a Treatment for COVID-19**	Chowdhury et al.	Study type: rapid systematic review 7 completed clinical trials and 29 registered trails	This systematic review is performed on available studies on HCQ and CQ as a treatment for COVID-19. The results of the study show that 7 completed and 29 registered clinical trials are focused on the treatment of COVID-19 with HCQ and CQ. Of these clinical trials, 7 are completed, 5 studies had reported favorable outcomes for patients using HCQ and CQ, while the other two studies did not mention to differences between the two groups. All 7 completed clinical trials performed had some degree of error and poor study design. There is not sufficient evidence to support the routine administration of HCQ and CQ for the treatment of COVID-19 (15).

12	**QT Interval Prolongation and Torsade De Pointes in Patients with COVID-19 treated with Hydroxychloroquine/ Azithromycin.**	Chorin et al.	Study type: retrospective cohort; Investigated outcomes: QT interval and arrhythmic events	In this multicenter retrospective cohort study on 251 COVID-19 patients who were treated with HCQ and Azithromycin in the US the authors intended to determine the progression of QT as well as incidence and mortality of arrhythmia among patients with COVID-19 who were treated with HCQ and Azithromycin. The combination of HCQ and Azithromycin significantly increased the QT interval, which is a threat to cardiac arrhythmia. Since the efficacy of this drug is not proved, risk/benefit considerations should be carefully and individually evaluated, and preventive measures should be applied when using this regime (16).
13	**Early treatment of COVID-19 patients with Hydroxychloroquine and azithromycin: A retrospective analysis of 1061 cases in Marseille, France**	Million et al.	Study type: retrospective cohort; Investigated outcomes: death, transfer to ICU and hospitalization, and viral shedding persistence	This retrospective study reported 1,061 patients with COVID-19 who had been treated with HCQ and azithromycin for at least three days in France. Defined outcomes were death, clinical worsening (transfer to ICU, and >10-day hospitalization), and viral shedding persistence. According to the results, good clinical outcomes and viral treatment were achieved in 973 patients over 10 days. A prolonged viral infection was observed in 47 patients. All patients, except one, had a negative PCR after 15 days. All eight deaths were due to respiratory failure and heart attack. Finally, prescribing a combination of HCQ with azithromycin before the onset of the complexity of COVID-19 is safe and is associated with a low mortality rate (17).
14	**Observational Study of Hydroxychloroquine in Hospitalized Patients with COVID-19**	Geleris et al.	Study type: observational; Study duration: 22.5 days; Investigated outcomes: intubation or death	In this retrospective cohort study that is conducted in the United States with a sample size of 1,376 COVID-19 patients, the association between HCQ administration and intubation or death is investigated. The authors concluded that the risk of intubation or death in patients who were receiving HCQ was not significantly higher or lower than others. Due to the observational nature of this study and its relatively open confidence interval, the authors believed that the results of the study cannot form a basis for making decisions about HCQ administration in COVID-19 patients. However, the authors believed that results do not support the use of HQC until its efficacy is confirmed by clinical trials (18).
15	**Association of Treatment with Hydroxychloroquine or Azithromycin with In-Hospital Mortality in Patients with COVID-19 in New York State**	Rosenberg et al.	Study type: observational; Study duration:13 days; Investigated outcomes: hospital mortality, cardiac arrest, and abnormal electrocardiogram findings	This retrospective cohort study is conducted in 25 hospitals in the New York State hospitals with a sample size of 1,438 patients. The authors examined the clinical status of patients in four groups: (1) HCQ with Azithromycin, (2) HCQ without Azithromycin (HCQ alone), (3) Azithromycin alone, and (4) neither drug. They concluded that treatment with HCQ , Azithromycin, or both, compared with neither treatment, was not significantly associated with differences in in-hospital mortality. However, the interpretation of these findings may be limited by the observational design (19).
16	**Clinical efficacy of Hydroxychloroquine in patients with COVID-19 pneumonia who require oxygen: an observational comparative study using routine care data**	Mahévas et al.	Study type: observational; Investigated outcomes: survival without transfer to ICU, overall survival 21 days	This is an observational study on 181 patients with COVID-19 in four French tertiary care centers. HCQ 600 mg was administered daily over 48 hours in the treatment group, and in the control group, the standard treatment was given without HCQ. In patients admitted to hospital with COVID-19 pneumonia who require oxygen, HCQ seemed to have no effect on reducing admissions to intensive care or deaths at day 21 after hospital admission. HCQ treatment did not have any effect on survival in patients without acute respiratory distress syndrome on day 21 after hospital admission. The results of this study do not support the use of HCQ in these patients (20).

17	**Low dose of Hydroxychloroquine reduces fatality of critically ill patients with COVID-19**	Yu et al.	Study type: observational; Investigated outcomes: fatality of patients, and inflammatory cytokine levels	In this retrospective study, 550 critically ill COVID-19 patients who need mechanical ventilation and were hospitalized in Tongji Hospital (Wuhan) from February 1, 2020, to April 4 are investigated. All 550 patients received comparable basic treatments, including antiviral drugs and antibiotics, and 48 of them were treated with oral HCQ treatment (200 mg twice a day for 7-10 days) in addition to the basic treatments. The measured outcomes were mortality and inflammatory cytokine levels between two groups. The results showed that mortality in the HCQ group was 18.8%, which was significantly less than 47.4% in the control group. The hospitalization period in patients before death was 15 days for the HCQ group and 8 days for the control group. There was no difference between the two groups concerning the decreased levels of inflammatory cytokines. The authors stated that HCQ is very effective in reducing mortality as an outcome for critically ill COVID-19 patients (21).
18	**A pilot study of Hydroxychloroquine in treatment of patients with common coronavirus disease-19 (COVID-19)**	Chen et al.	Study type: open label randomized clinical trial; Study duration: 7 days; Investigated outcomes: respiratory pharyngeal swab	The study, which was conducted in Shanghai (China), investigated the effectiveness and safety of HCQ on a sample of 30 patients with COVID-19. Patients were randomly divided into intervention and control groups. On the seventh day, no significant difference was observed between the two groups concerning the nasopharyngeal viral load. Also, no significant difference was observed for other clinical outcomes, including the duration of fever and CT scan of the lungs. After two weeks, the viral load test was negative for both groups. Based on the results, the prognosis of COVID-19 moderate patients is good. It is necessary to conduct studies with larger sample sizes to investigate the effects of HCQ in the treatment of COVID-19. Subsequent research should be performed to determine better endpoint and fully consider the feasibility of experiments such as sample size (22).
19	**Hydroxychloroquine and Chloroquine for COVID-19 infection. Rapid systematic review**	Pacheco and Riera	Study type: systematic Review (included studies: one open-label randomized trial, one open-label non-randomized trial and 28 ongoing studies)	Based on the results of this review, there is still insufficient evidence to evaluate the effectiveness and safety of HCQ and CQ to treat patients with COVID-19. Therefore, till providing sufficient information through ongoing trials, routine administration of HCQ and CQ is not recommended (23).
20	**A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19**	Cortegiani et al. (Article in press)	Study type: systematic review (Included studies: n = 6. One narrative letter, one in-vitro study, one letter to the editor, one expert consensus, and two national guidelines).	The study concluded that pre-clinical rationale for the effectiveness of CQ in the treatment of COVID-19 and the evidence for the safety of long-term use of it for other diseases can justify further research for its administration in COVID-19 patients. However, the authors argued that the importance of ethical review of research proposals of clinical trials related to CQ is higher than before. Although according to the available evidence, administration of CQ may be helpful in the treatment of COVID-19, due to its adverse effects, clinical use should either adhere to the Monitored Emergency Use of Unregistered Interventions (MEURI) framework or be ethically approved as a trial, as stated by the World Health Organization. Safety data and data from high-quality clinical trials are urgently needed (4).

3. Results

3.1. Clinical Trials and Observational Studies

The current study reviewed five clinical trials and eight observational studies. In terms of chronology, the first study on the administration of CQ/HCQ to treat COVID-19 patients is conducted in China, in which Chen and colleagues (24) in a randomized clinical trial compared the effect of HCQ with standard care. The researchers found no significant difference between the nasopharyngeal viral loads of the two groups. Moreover, no significant difference was observed concerning other clinical outcomes, including the duration of disease course and lung images (22). In another study, Gao and colleagues (6) noted that the administration of CQ improved COVID-19 patients, but no further explanation is provided about trial design or any further information about the study results. Another study performed in France has concluded (22) that HCQ was effective in treating patients with COVID-19 (7). However, it had several major limitations, including, the small size of the intervention group, so that only 20 patients received HCQ (six received azithromycin), and only 16 were included in the final analysis. The decisions, as who received Azithromycin, are not clear in the reporting. Also, the study period was only six days. There are also other issues such as lack of randomization, significant differences in basic characteristics of two groups, and not mentioning to effects of the medications on the clinical course of the disease (2). Moreover, the only reported consequence is viral load, while other important factors such as mechanical ventilation and mortality, which could be better outcomes to report, were not investigated. Clinical follow-up and occurrence of side-effects are not discussed in the paper (13).

Another clinical trial which is conducted in Brazil has investigated the effectiveness and safety of CQ phosphate among 81 critically ill patients. That 41 patients received high doses of medicine and 40 received low doses. Among those who received high doses of CQ, the mortality was higher than other groups and these patients had a longer QT interval. The authors concluded that high doses of CQ (especially with other drugs such as Azithromycin and Oselatamivir) are not suitable for older patients, especially those with cardiovascular disease, because of risks associated with drug safety. One of the advantages of this randomized clinical trial to other studies is considering the adverse effects of the CQ administration as an outcome. The study had limitations, including small sample size, having a single-center design, lack of a placebo control group, and the absence of exclusion criteria based on the QT interval at baseline (14).

Another clinical trial conducted in China has assessed the efficacy and safety of CQ in hospitalized COVID-19 patients. Twenty-two positive COVID-19 patients who had RT-PCR results were entered in the study. Ten patients were treated with CQ 500 and 12 received Lopinavir/Ritonavir for 10 days. Preliminary results indicated that one patient became negative after being treated with CQ and after 13 days, all patients who were treated with CQ became negative. These results suggested that patients treated with CQ appeared to be recovered better and regain their pulmonary function quicker than those treated with Lopinavir/Ritonavir. The authors concluded that CQ can be an effective and inexpensive choice compared to other treatment options, such as lopinavir/Ritonavir. Meanwhile ,the study has some flaws ,including a small sample size .Besides ,much of the results were statistically insignificant ,and there was a significant bias in randomization since the mean age of the CQ group) 53 years old (was higher than Lopinavir/Ritonavir group)41.5 years old) (10 .(Despite these shortcomings ,it was one of the pioneering studies introducing the possibility of multi-antiviral treatment of COVID-19 .Also ,it has monitored and reported adverse events related to the administration of CQ.

At present ,of five completed clinical trials evaluating CQ or HCQ safety and efficacy in the treatment of COVID-19 ,three reported improved clinical outcomes among patients received CQ or HCQ ;one reported no difference between their administration and supportive care .One of them concluded that because of risks associated with drug safety ,CQ ,especially if be administered with other drugs such as azithromycin and Oseltamivir ,should not be recommended for older patients.

In addition to the aforementioned trials ,8 observational studies were included in our review ,with sample sizes ranging from 11 to 1438 patients .Of eight observational studies ,4 concluded that treatment with HCQ or a combination of Azithromycin HCQ ,compared with other treatments ,was not significantly associated with improved outcomes .Three studies showed that the administration of a combination of HCQ and Azithromycin or HCQ alone is associated with improved clinical outcomes. One study investigated the side effects associated with the combined administration of HCQ and Azithromycin and concluded that a combination of HCQ and Azithromycin significantly prolongs the QT interval in patients with COVID-19. Therefore, Due to the unproven efficacy of this drug, Risk-benefit considerations should be carefully and individually evaluated, and preventive measures should be applied when using this regime.

Four studies concluded that treatment with HCQ or a combination of Azithromycin and HCQ was not significantly associated with improved outcomes compared to other treatments. In a prospective cohort study conducted in France, in response to Gautret et al.'s study (7), 11 patients received the medication that was used in Gautret et al.'s study (i.e., combined HCQ and Azithromycin). After five days, patients were examined. The results indicated continuity in the nasopharyngeal swab virus in 8 (out of 10) patients. In this small cohort, two patients were transferred to the intensive care unit, one died, and due to side effects caused by prolonged QT interval, one

patient was discontinued. In contrast to Gautret et al.'s study, patients with more severe illness were included (25). There were two large studies conducted in the U.S. with a sample size of more than 1000 patients that reported no difference between HCQ administration and other medications. However, they asserted that the interpretation of their findings may be limited by the observational design (18, 19). In a retrospective cohort study with a sample size of 1,376 COVID-19 patients, the authors concluded that the risk of intubation or death in patients received HCQ was not significantly higher or lower than others (18). In another retrospective cohort study conducted in 25 hospitals of New York State with a sample size of 1,438 patients, the authors examined the clinical status of patients in four groups: (1) HCQ with Azithromycin, (2) HCQ without Azithromycin (HCQ alone), (3) Azithromycin alone, and (4) neither drug. They concluded that treatment with HCQ, Azithromycin, or both, compared with neither treatment, was not significantly associated with differences in in-hospital mortality (19). A Comparative observational study on 181 patients with severe COVID-19 who required oxygen reported that HCQ seemed to have no effect on reducing admissions to intensive care or deaths on day 21 after hospital admission. HCQ treatment did not have any effect on survival in patients without acute respiratory distress syndrome on day 21 after hospital admission (20).

Three observational studies conducted in China and France reported that combined administration of HCQ and Azithromycin or HCQ alone is associated with improved clinical outcomes. An observational study conducted in France investigated the effect of combined use of HCQ and Azithromycin on 80 relatively mildly infected inpatients. The authors concluded that there are beneficial effects of co-administration of HCQ with Azithromycin in the treatment of COVID-19, and it is potentially effective in the early reduction of contagiousness (22). However, about 92% of patients had a low national early warning sign, which may indicate the mild severity of the disease. In this study, also, the only investigated outcome was viral load, and no other clinical consequences are reported. Another retrospective study reported 1,061 patients with COVID-19 who had been treated with HCQ and Azithromycin for at least three days in France. It concluded that the administration of a combination of HCQ with Azithromycin before the onset of the complexity of COVID-19 is safe and can reduce the mortality rate (17). In a study conducted in China, 550 critically ill COVID-19 patients who need mechanical ventilation received comparable basic treatments, including antiviral drugs and antibiotics, and 48 of them were treated with oral HCQ in addition to the basic treatments. The measured outcomes were mortality and inflammatory cytokine levels of the two groups. It concluded that HCQ is very effective in reducing mortality as an outcome for critically ill COVID-19 patients (21). In this study, HCQ and control groups were comparable for the age, gender, and severity of the disease. However, the authors did not specify the other treatment modalities in the study arms. Further, the authors did not specify the lag period for initiation of HCQ among included patients.

A multicenter retrospective cohort study on 251 COVID-19 patients who were treated with HCQ and Azithromycin in the US has investigated the progression of QT and incidence of arrhythmia and mortality among patients with COVID-19 treated with HCQ and Azithromycin. The combination of HCQ and Azithromycin significantly increases the QT interval, which is a threat to cardiac arrhythmia. Since the efficacy of this drug is not proved yet, its associated risks and benefits should be carefully and individually considered and preventive measures should be applied when administering this regime (16). The study did not include patients treated with each medication separately, and each patient served as self-control. Further, patients without a baseline or follow-up ECG were excluded from the analysis, which may have led to bias.

3.2. Reviews

In the current research, seven review studies were found which identified and reviewed some clinical trials based on their implementation date. Some of these studies reviewed other types of studies, such as the letter to editors or expert opinion. All of these reviews agreed that there is insufficient evidence to recommend routine medication with CQ and HCQ (2). However, it seems that the low cost and availability of these two drugs has resulted in recommending for treating COVID-19 patients, particularly in developing countries and countries with limited financial resources (8).

On the other hand, some studies emphasized that the effectiveness of these drugs in laboratory settings does not justify their administration for COVID-19 treatment, and regarding their side effects, the clinical use of these drugs in patients with COVID-19 should adhere to ethical codes (4). Since the number of clinical trial studies is not sufficient, some of them have low quality and high possibility of errors, and did not pay sufficient attention to the long-term consequences of use of these drugs; these reviews asserted that there is a need to conduct further high-quality clinical trials (4, 11-13, 15, 23).

4. Conclusions

Based on the results of this review, it seems that evidence about the effectiveness and safety of HCQ and CQ in the treatment of patients with COVID-19 are not sufficient. Moreover, the reviewed studies reported conflicting results on the efficacy and safety of HCQ and CQ in treating COVID-19 patients. In other words, the administration of CQ or HCQ for treatment or prevention of COVID-19 is mainly based on evidence provided by studies with small sample sizes or methodological shortcomings. It seems that to guide policymakers and healthcare providers

about incorporating these drugs into clinical practice guidelines, high-quality clinical trial studies are needed. Therefore, further studies should be conducted about the efficacy and safety of HCQ and CQ in the prevention and treatment of COVID-19 patients. Investigating current clinical trials showed that large-scale studies are currently conducting all around the world (and sometimes between several countries), which can provide significant evidence about the administration of CQ and HCQ in the prevention and treatment of COVID-19.

Administration of CQ and HCQ to treat patients with COVID-19 is expanding for reasons such as positive results of some clinical and laboratory studies on the effect of these drugs, low price, availability, and their use in the treatment of other diseases; However, if prescribed, the toxicological risks should be considered and necessary care for rational use of these drugs should be provided. When using CQ and HCQ to treat COVID-19 patients, necessary precautions should be taken so that adverse effects can be prevented as much as possible. Therefore, the main issue is to consider as many epidemiological and clinical aspects as possible before treating patients with CQ and HCQ.

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