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Chloroquine and Hydroxychloroquine in Treatment of Coronavirus Disease-19

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Abstract

At present, we are facing coronavirus disease (COVID)-19 pandemic caused by the severe acute respiratory syndrome coronavirus-2 with several treatment choices and reports of different treatment outcomes. Chloroquine and hydroxychloroquine use for the management of severely ill patients started as a quite enthusiastic treatment option, following several small clinical trials, case series reports, public authorities, and media affirmation. However, the evidence we have so far is conflicting and some national societies and professional institutions implicate that we should wait for definite treatment recommendations until there are solid data for or against the use of these drugs. Until we have more powerful evidence in our hands, we should be aware of safety issues of the old drugs for the new application in the emergency state we are facing today with the COVID-19 pandemic. We performed a concise review of strengths, limitations, and awareness for chloroquine and hydroxychloroquine use for COVID-19 infection treatment based on the evidence the science has today.

Introduction

Chloroquine and its analog hydroxychloroquine, drugs that had been used to treat malaria and systemic lupus erythematosus, rheumatoid arthritis, are recently promoted as a potential treatment for the coronavirus disease (COVID)-19. Initial results on the efficacy of chloroquine in severe acute respiratory syndrome caused by coronavirus-2 (SARS-CoV-2) are derived from in vitro studies [1]. The first results from patients with SARS-CoV-2-related pneumonia and chloroquine efficacy come form China [2].

Hydroxychloroquine as an analog of chloroquine with less gastric intolerance and less concerns for drug interactions was found *in vitro* to be more potent than chloroquine in inhibiting SARS-CoV-2 [3].

Food and drug administration (FDA) allowed the use of these drugs since April 2020 to certain hospitalized patients where health-care providers and patients are provided with information about the risks of these drugs [4]. However, after first enthusiasm, FDA has expressed caution against the use of these drugs for COVID-19 outside of the hospital settings or a clinical trial due to the risk of heart rhythm problems and close supervision was strongly recommended. Clinical trials are planned and some have been underway to determine efficacy and safety of these drugs in the treatment of COVID-19 infection. At the beginning of April 2020, World Health Organization has started a multi-arm, multi-country clinical trial for potential coronavirus therapies based on evidence from laboratory, animal, and clinical studies, among which chloroquine and hydroxychloroquine treatment is included in the study.

Rational to use chloroquine analog lays in the fact that this drug is found to be effective against a variety of viral infections by inhibiting acidification of endosomes during the replication of the virus and infection and by their immunomodulatory effects [5]. Therapeutic agents such as chloroquine analogs, acting with the prevention of activation of macrophages, and inhibition of the secretion of tumor necrosis factor α and interleukin 6 from various cells would express benefits in the treatment of viral infections [6], [7].

Materials and Methods

A literature review was performed using PubMed to identify relevant articles published through April 15, 2020. Used search terms were coronavirus, COVID-19, SARS-CoV-2, and chloroquine, hydroxychloroquine. This search resulted in 59 total articles. Additional

relevant articles were identified from the review of citations referenced. Case reports were also included.

The search terms COVID-19 or coronavirus or SARS-COV-2 and chloroquine or hydroxychloroquine on clinicaltrials.gov resulted in 14 active trials as of April 15, 2020. Ten of the trials are already recruiting patients, four still not recruiting patients. Seven of them are testing chloroquine or hydroxychloroquine alone, or controlled with placebo, three are testing low versus high dose hydroxychloroquine, and four are testing hydroxychloroquine versus hydroxychloroquine and azithromycin.

Discussion

Chloroquine, as an antimalarial drug, present at the pharmaceutical market more than 70 years has been tested regarding its safety profile multiple times. For many decades, people visiting malaria-endemic geographic areas received chloroquine prophylaxis and continued it for months after return in their homelands. In addition, some local residents in African countries took chloroquine continuously without any remarkable side effects. Hydroxychloroquine, on the other hand, has been used for a long time at much higher doses (up to 600 mg/day) for the treatment of certain autoimmune diseases. Regarding the longevity of clinical use and number of treated patients, nowadays, we can easily talk about good established safety profile of these drugs.

However, in the circumstances of acute viral infection with sometimes severe clinical presentation, attacking multiple systems, producing electrolyte, and metabolic changes, treatment with chloroquine/hydroxychloroquine may lead to dangerous adverse effects.

Results from clinical studies

After the initial modest positive results, the problem had appeared when many hospitals have simply been giving these drugs to all infected patients, without proven efficacy, concerning that treatment is relatively safe. The reports in literature from France, Brazil, China, US are conflicting; some do not include control groups, many have a small number of participants and have no power to draw conclusions, and conclusions are conflicting.

Published studies are summarized in Table 1.

The earliest published studies from China and France have been widely criticized because there was no control group to compare treated versus untreated patients. Some researchers even called this report anecdotal. In the open-label, non-randomized study, Gautret *et al*. reported 100% viral clearance in nasopharyngeal swabs in six patients after 5–6 days of treatment with hydroxychloroquine and azithromycin [8]. Such a rapid and full viral clearance was quite unexpected to other authors. A study from China in patients with COVID-19 infection did not found any difference in virologic clearance with, or without treatment with hydroxychloroquine, and even more no difference in the clinical course of the disease [9].

A small double-blind, randomized study in Brazil (81 patients) was discontinued early for safety reasons after patients on a higher dose of chloroquine showed increased mortality due to QTc interval prolongation on recorded standard 12 lead electrocardiogram and associated proarrhythmias [10].

Despite the again small size of the previous study, infectologists and drug safety experts express their opinion that the study provided further evidence that chloroquine and hydroxychloroquine can pose significant harm to some patients, specifically the risk of a fatal arrhythmia. Patients in Brazilian study were also given azithromycin, which also prolongs QTc interval. It seems that we need more data at every level.

Barbosa *et al*. decided to publish preliminary results, although their dataset is growly rapidly because of concerning safety signals [11]. They showed that hydroxychloroquine did not appear to have a beneficial effect on meaningful clinical outcome measures of mortality, lymphopenia reconstitution,

Table 1: Published studies about treatment with chloroquine or hydroxychloroquine for COVID-19 disease

Title	Drug	Type	Number of participants	Results
Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial [8]	Hydroxychloroquine 200 mg × 3 and azithromycin, versus placebo	Open-label non-randomized	36	Improved virologic clearance in treatment arm addition of azithromycin resulted in superior viral clearance
A pilot study of hydroxychloroquine in treatment of patients with common COVID-19 [9]	Hydroxychloroquine, 400 mg, daily for 5 days plus standard of care or standard care alone in a 1:1 fashion;	Open-label	30	No difference in virologic outcomes
Chloroquine diphosphate for the treatment of severe acute respiratory syndrome secondary to SARS-CoV2 (CloroCOVID19) NCT04323527 [10]	Low dose chloroquine diphosphate (450 mg), 5 days versus high dose (600 mg) 10 days	Double-blind, randomized adaptive clinical trial	440 ongoing data published for 81 pts.	Higher dose of chloroquine for 10 days was associated with more toxic effect and lethality, particularly affecting QTc prolongation
Clinical outcomes of hydroxychloroquine in hospitalized patients with COVID-19: A quasi-Randomized comparative study [11]	Hydroxychloroquine and supportive care versus supportive care alone initial loading dose of 400 mg b.i.d 1–2 days and 3–4 subsequent days 200 mg −400 mg o.d.	Quasi-randomized	63	Hydroxychloroquine was associated with an increased need for escalation of respiratory support. No benefits of hydroxychloroquine on mortality, lymphopenia, or neutrophil-to-lymphocyte ratio improvement
Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial ChiCTR2000029559 [12]	Hydroxychloroquine 400 mg/d (200 mg/bid) between days 1 and 5 versus standard treatment only.	Randomized parallel-group trial	62	Hydroxychloroquine use shortened time to clinical recovery

COVID-19: Coronavirus disease-19.

neutrophil-to-lymphocyte ratio, or risk for intubation. Patients in hydroxychloroquine arm appeared to have a worse clinical outcome in terms of need of respiratory support [11]. These results were in contrast to previously published results from Chen *et al*., showing shortened time to clinical recovery in hydroxychloroquine group in comparison with the control group (body temperature recovery time and cough remission time) [12].

The true answer to whether chloroquine or hydroxychloroquine has a beneficial effect for COVID-19 patients can only be obtained with a prospective randomized clinical study (Table 1).

Recommendations

According to the tendency of doctors and hospitals to give chloroquine or hydroxychloroquine, especially to severe ill patients, some associations, expert groups have published recommendations, and some refrain from making recommendations until the results of relevant clinical studies come out (Table 2).

Table 2: Available guidance about the treatment with chloroquine/hydroxychloroquine up to April 2020

Multicenter collaboration group of Department of Science and Technology of Guangdong Province and Health Commission of Guangdong Province for chloroquine in the treatment of novel coronavirus pneumonia. Expert consensus on chloroquine phosphate for the treatment of novel coronavirus pneumonia. Zhonghua Jie He He Hu Xi Za Zhi. 20 February 2020; 43 (0): E019.	The Panel recommends the use of the chloroquine at a dose of 500 mg BID for 10 days. Alternatively, you can use if it were not available chloroquine, hydroxychloroquine 200 mg BID.
Diagnosis and treatment protocol for novel coronavirus pneumonia (Trial Version 7) (Released by National Health Commission and State Administration of Traditional Chinese Medicine on March 3, 2020)	Chloroquine phosphate (500 mg bid for 7 days for adults aged 18–65 with body weight over 50 kg; 500 mg bid for Days 1 and 2 and 500 mg qd for Days 3–7 for adults with body weight <50 kg)
Handbook for the care of people with disease-COVI 19 Edition 2.0, March 13, 2020 SIMIT	Chloroquine/hydroxychloroquine in prophylaxis for COVID-19 is not recommended. At present, there is no evidence of efficacy of this drug in the prevention of disease COVID-19.
Italian Society of Infectious and Tropical Diseases SECTION Regione Lombardia	Chloroquine 500 mg twice daily for 20 days OR hydroxychloroquine 200 mg BID in patients with COVID-19 irrespective of the severity of symptoms
ESC guidance for the diagnosis and management of CV disease during the COVID-19 pandemic escardio.org/Education/ COVID-19-and-Cardiology/ ESC-COVID-19-Guidance	Results of ongoing clinical trials of chloroquine/hydroxychloroquine efficacy in the treatment of SARS-CoV2 should be awaited before definite recommendations are provided for or against the use of these drugs
Clinical management of severe acute respiratory infection when COVID-19 is suspected Interim guidance March 13, 2020, | World Health Organization	No recommendation
COVID-19 Interim Clinical Guidance for Management of Patients with confirmed COVID-19 CDC Center for Disease Control and Prevention	No recommendation

COVID-19: Coronavirus disease 2019.

Dose recommendations for chloroquine or hydroxychloroquine

After conducted clinical trials by Chinese teams, recommend a dose of chloroquine phosphate was 500 mg of twice a day in patients with mild, moderate, and severe forms of COVID-19 pneumonia [2].

With huge experience over the past 5 years in patients with long-term treatment (>1 year), for different indications, Lagier *et al*. recommended dosage for hydroxychloroquine of 600 mg/day with which concentration of 1 μg/mL is reached [13]. They also suggest administration of loading dose, followed by a maintenance dose and express their opinion that activity of hydroxychloroquine on viruses is probably the same as that of chloroquine, giving preference to hydroxychloroquine [13].

As a specific treatment for COVID-19 disease, Yao *et al*. recommended that the optimal dosing regimen for hydroxychloroquine should be a loading dose of 400 mg twice daily for 1 day followed by 200 mg twice daily [3]. However, similarly, as for Whipple disease, some authors make alternative recommendations of 600 mg total daily dose [14].

Effects on QT interval and recommendations

Chloroquine and hydroxychloroquine are listed as drugs that have known risk of polymorphic ventricular arrhythmia "Torsades de Pointes" (TdP), due to QT interval prolongation at crediblemeds.org. They have proarrhythmogenic effect through blocking I_{Kr} (rapid delayed rectifier potassium current) channels, causing a significant reduction in the amplitude of potassium tail currents [15] (Figure 1).

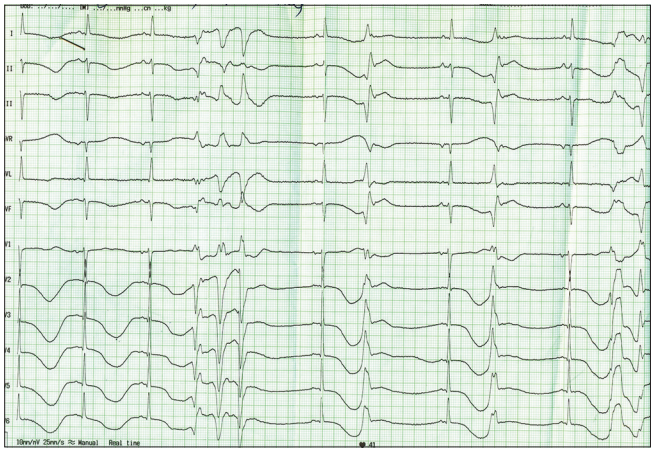

Figure 1: Hydroxychloroquine effect on electrocardiogram

The preliminary findings from the CloroCovid-19 trial suggest that a higher dosage of chloroquine should not be recommended for the treatment of severe COVID-19, especially in combination with azithromycin and/or oseltamivir, because of safety concerns [10]. Increased mortality was observed due to QTc interval prolongation and associated proarrhythmias [10] (Figure 1).

The most used formula for QTc interval calculation is the Bazett formula:

$$QTc = QT/\sqrt[2]{RR}$$

European Society of Cardiology has recently released "Guidance for the Diagnosis and Management

of CV disease during the COVID-19 pandemic" last updated on April 21, 2020 [16]. Before administration of chloroquine or hydroxychloroquine therapy, there are some suggestions:

- Drug-drug interactions including antiviral, antiarrhythmic, and anticoagulation drugs should be considered;
- In hemodynamically stable patients with atrial fibrillation or flutter, discontinuation of antiarrhythmic drugs and initiation of rate control therapy to allow safe use of hydroxychloroquine as antiviral medication is a reasonable therapeutic option.

When chloroquine or hydroxychloroquine therapy is started, the following interventions should be considered in order to reduce the risk of malignant arrhythmia and death [16], [17]:

- Withholding the drugs in patients with baseline QT prolongation (especially QTc ≥500 ms) or with known congenital long QT syndrome.
- On-treatment ECGs are recommended to monitor cardiac rhythm and rule out a significant prolongation of QTc (>500 ms, or by >60 ms vs. baseline)
- It is worth exploring alternative ECG monitoring methods (e.g., monitoring leads, smartphone-enabled mobile ECG, and handheld devices);
- Correction of hypokalemia to levels of >4 mEq/L targeting >4.5 mEq/L and hypomagnesemia to levels of >2 mg/dL.

The safety of QT-prolonging medications may be maximized by close monitoring and optimization of these factors. A risk score has been derived and validated by Tisdale *et al*., for the prediction of drug-associated QT prolongation among cardiac-care-unit-hospitalized patients [18]. Factors incorporated in this score are: Female gender, age ≥68 years, concomitant use of loop diuretics, antiarrhythmic drugs, and comorbidities such as acute myocardial infarction, heart failure, sepsis, hypokalemia, and admission QTc ≥450 ms. According to present additional factors, Tisdale score predicts low, medium, or high risk of drug-associated QT prolongation. The goal of QTc screening in this setting is not to identify patients whom are not candidates for therapy but to identify those who are at increased risk for TdP so aggressive countermeasures may be implemented [19].

Conclusion

There is a lack of evidence regarding the efficacy and risk of different treatment strategies in patients with COVID-19 disease. In this circumstance, facing deadly disease, many hospitals have simply been giving hydroxychloroquine to patients, reasoning that it might help and probably will not hurt because it is relatively safe.

To stay on a safe side, before we get relevant results from ongoing clinical studies in all patients undergoing antiviral treatment, including chloroquine or hydroxychloroquine, it is necessary to correct modifiable predisposing factors to QTc prolongation: Electrolyte imbalances, concomitant unnecessary drugs, and bradycardia.

Not to forget, while the patient is on chloroquine or hydroxychloroquine treatment ECG should be monitored also for conduction disturbances, despite these are rare and referred only during long-term treatment.

Definite recommendations will emerge once the results of ongoing clinical trials of chloroquine/ hydroxychloroquine efficacy in the treatment of SARS-CoV2 will be published.

Until than cautiously use is wise, with an awareness of side effects.

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