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MINIREVIEWS

Ethical review of off-label drugs during the COVID-19 pandemic

Qiu-Yu Li, Ye Lv, Zhuo-Yu An, Ni-Ni Dai, Xue Hong, Yu Zhang, Li-Jun Liang

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Abstract

High-quality scientific research is very important in attempting to effectively control the coronavirus disease 2019 (COVID-19) pandemic and ensure people's health and safety. Chloroquine (CQ) and hydroxychloroquine (HCQ) have received much attention. This article comprehensively investigates the ethical review of off-label CQ and HCQ research during the COVID-19 pandemic with regard to strictly abiding by review standards, improving review efficiency, ensuring the rights and interests of subjects and that ethics committees conduct independent reviews, and achieving full ethics supervision of research conducted during an emergency. Research must be both rigorous and prudent to ensure the best outcome, with the maximization of benefits as the core principle. Standardization of the application, implementation and ethical review processes are needed to prevent unnecessary risk.

Key Words: COVID-19; Off-label; Chloroquine; Hydroxychloroquine

Core Tip: High-quality scientific research is very important in the attempt to effectively control the coronavirus disease 2019 epidemic and ensure people's life health and safety. Chloroquine and hydroxychloroquine have received much attention.

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INTRODUCTION

High-quality scientific research is very important in attempting to effectively control the coronavirus disease 2019 (COVID-19) pandemic and ensure people's health and safety. Chloroquine (CQ) and hydroxychloroquine (HCQ) have received much attention. This article comprehensively investigates the ethical review of off-label CQ and HCQ research during the COVID-19 pandemic with regard to strictly abiding by review standards, improving review efficiency, ensuring the rights and interests of subjects and that ethics committees conduct independent reviews, and achieving full ethics supervision of research conducted during an emergency.

OFF-LABEL DRUG USE FOR COVID-19

Off-label studies investigate the use of drugs for purposes other than those that are already approved. These studies involve indications, treated populations, usages and dosages that are not included in the label approved by the drug regulatory authority[1]. Although the efficacy of the off-label use of a medication is unconfirmed, such uses may serve as life-saving treatments for patients with rare diseases or new infectious diseases for which there is no cure. In addition, due to the complexity of revising drug labels, such revision usually lags behind clinical practice; therefore, a drug label does not always reflect the cutting-edge use of the medicine in question[2]. At the same time, drug labels also have certain limitations, such as the specified dose. Randomized controlled trials (RCTs) and the consequent label content do not always reflect clinical practice. Off-label medication use is a form of medical exploration that largely meets some clinical needs. At present, foreign academic circles refer to this kind of expanded research as "drug reuse or relocation". There have been a large number of successful cases of drug reuse or relocation based on knowledge of the mechanisms of action of existing drugs. However, the use of medication beyond the scope of the instructions cannot be regarded as safe simply because the on-label use was deemed safe. The investigation of off-label medication use must be rigorous and prudent, with the maximization of patients' interests as the core principle. It is important to standardize the application, implementation and ethical review processes to prevent causing problems. Given that SARS-CoV-2 is a new pathogen, there is not yet a specific drug that can be used to treat COVID-19. The drugs recommended in diagnosis and treatment plans include interferon, lopinavir/ritonavir, ribavirin, and phosphoric acid. The treatment of COVID-19 with CQ and arbidol is considered off-label use; therefore, clinical trials need to be carried out to provide clinical evidence of their efficacy. Research has focused on the use of HCQ/CQ.

POTENTIAL EFFECTIVENESS OF HCQ/CQ FOR COVID-19

On February 4, 2020, an article published in "Cell Research" mentioned that remdesivir and CQ showed good inhibitory effects on SARS-CoV-2 in vitro, and the half maximal effective concentration (EC50) of remdesivir was 0.77 μmol/L, while that of CQ was 1.13 μmmol/L[3]. Although the effects of CQ are slightly weaker than those of remdesivir based on this index, its advantages are still obvious because it is a well-known drug that has been used for decades. Subsequently, HCQ, which is a CQ derivative, has also attracted attention. On March 20, 2020, French scientist Didier Raoult published an article suggesting that the combination of HCQ and azithromycin is effective for the treatment of COVID-19. The open clinical trial included a total of 20 patients. The article pointed out that the use of HCQ was related to a decrease in or the disappearance of the viral load, and the addition of azithromycin enhanced the therapeutic effect[4]. Although the sample of this trial was small and it was not a randomized double-blind trial, this result still stimulated research on HCQ. Although there is no systematic clinical evidence that HCQ and CQ are effective, it is undoubtedly very tempting to believe that established drugs have good treatment effects. On March 28, 2020, the United States FDA authorized the use of CQ and HCQ for the treatment of COVID-19. On April 3, 2020, the COVID-19 international working group comprising 80 clinical experts from 20 countries jointly issued interim guidance for the treatment of COVID-19, and HCQ/CQ was the only drug recommended by the group. On June 1, 2020, ClinicalTrials.gov had 203 registered COVID-19 trials related to HCQ, 60 of which focused on prevention. This article pertains to the currently ongoing clinical trials for CQ and HCQ (Table 1).

Table 1 Clinical trials of chloroquine and hydroxychloroquine use for coronavirus disease 2019

NCT Number	Population's age	Intervention	Control	Outcome measures
NCT04362332	18-110 yr	CQ or HCQ	Standard supportive care	Composite endpoint with disease progression defined as a NEWS2 score within 14 d or resulting in admission to the Intensive/Medium Care unit or resulting in death within 14 d | Side effects
NCT04303507	16 yr and older	CQ or HCQ	Placebo	Number of symptomatic COVID-19 infections | COVID-19 symptom severity | Number of asymptomatic cases of COVID-19 | Number of symptomatic acute respiratory illnesses | Severity of symptomatic acute respiratory illnesses
NCT04360759	18 yr and older	CQ or HCQ	Placebo	Event-free survival at 28 d postrandomization between the experimental group and standard of care group | Incidence of serious adverse events | Incidence of adverse events of special interest related to the investigational product at time of hospitalization | Premature discontinuation of treatment | Time from treatment initiation to death, ARDS (PF/SF ratio < 300), or mechanical ventilation | Proportion with moderate and severe ARDS | Duration of hospitalization and ICU stay for survivors | Incidence of COVID-19 in household contacts
NCT04420247	18 yr and older	CQ or HCQ	Standard care	World Health Organization (WHO) 9-levels scale (from 0-8) | WHO 9-levels scale (from 0-8) | Mortality | Ventilation-free days | Duration of mechanical ventilation | National Early Warning Score (NEWS) | ICU Length of Stay | Hospital Length of Stay | Acute Kidney Disease incidence | Percentage of patients needing dialysis | Mean C Reactive Protein Levels | Mean Leucocytes Levels | Mean Lymphocyte Levels
NCT04351191	20-50 yr	HCQ Sulfate Regular dose, HCQ Sulfate Loading Dose or CQ	Placebo	RT–PCR results | Progression of symptoms | Mortality
NCT04447534	18 yr older	CQ	Zinc	Number of patients with negative PCR
NCT04346667	20-50 yr	HCQ Sulfate Regular dose, HCQ Sulfate Loading Dose or CQ	Placebo	RT–PCR tests | Progression of symptoms | Development of Symptoms | Adverse events
NCT04341727	18 yr older	HCQ Sulfate or Azithromycin	CQ Sulfate	Hours to recovery | Time to fever resolution
NCT04346329	18 yr older	HCQ	Placebo	Adverse effects | Immune score | COVID-19 prevention | Clinical response
NCT04371406	18-75 yr	HCQ and Azithromycin	Dietary Supplement: Azinc	Rate of patients with the occurrence of an unfavorable outcome between randomization and day 14 | Primary outcome of ancillary virological study: The evolution of viral load between day 0 and day 14 | The all-cause mortality rate at day 14 | The all-cause mortality rate at day 28 | Rate of patients with the occurrence of an unfavorable outcome between randomization and day 28 | The rate of use of mechanical ventilation at day 14 | The rate of use of mechanical ventilation at day 28 | The Intensive Care Unit admission rate at day 14 | The Intensive Care Unit admission rate at day 28 | Number of days of hospitalization for any cause between day 0 and day 14 | Number of days of hospitalization for any cause between day 0 and day 28 | The time to resolution of all COVID symptoms at day 14 | The time to resolution of all COVID symptoms at day 28 | The rate of use of oxygen therapy at day 14 | The rate of use of oxygen therapy at day 28 | The rate of use of secondary antibiotic therapy (after day 2) at day 14 | The rate of use of secondary antibiotic therapy (after day 2) at day 28 | Clinical status at day 14 | Clinical status at day 28 | Number of serious adverse events at day 14 | Number of serious adverse events at day 28 | Number of adverse events at day 14 | Number of adverse events at day 28 | The rate of patients with treatment withdrawal | Ancillary virological study: The rate of patients with a negative viral load at day 8 | Ancillary virological study: The rate of patients with a negative viral load at day 14
NCT04340544	18-99 yr	HCQ	Placebo	Difference in the time to resolution of clinical signs and symptoms of mild COVID-19 treated with HCQ or placebo as assessed by daily self-assessment | Difference between HCQ- and placebo-treated patients on an ordinal outcome scale until day 28 (death, admission to intensive care, hospitalization, continuing disease, recovered) | All-cause mortality within 28 d
NCT04342221	18-99 yr	HCQ	Placebo	Effect of HCQ on in *vivo* viral clearance
NCT04330144	18-99 yr	HCQ	No intervention	The rate of COVID-19
NCT04384380	20-79 yr	HCQ	No intervention	Time to a negative RT–PCR test | Virological assessment | Number of

				participants with treatment-related adverse events as assessed by the CTCAE v.4.0
NCT04374903	18 yr and older	HCQ and azithromycin	HCQ	Time to Clinical improvement (TTCI) | Clinical failure defined as death or the need for intubation and mechanical ventilation | Adverse effects | QT interval prolongation | Failure to continue assigned therapy | Time to viral clearance
NCT04347512	18 yr and older	HCQ and azithromycin	Placebo	The rate of patients reaching a significant hypoxemia, in each arm.
NCT04391127	16-90 yr	HCQ or Ivermectin	Placebo	Mean days of hospital stay | The rate of respiratory deterioration, the requirement of invasive mechanical ventilation or death | Mean oxygenation index delta | Mean time to viral PCR negativity
NCT04363866	18 yr and older	HCQ	Placebo	Clinical status at Day 5 assessed by a 6-Point Ordinal Scale | Number of participants with detectable SARS-CoV-2 virus from day 0 to day 28 and at day 5 | Toxicity of the study drug assessed by the incidence of adverse events
NCT04443725	18-65 yr	HCQ	Standard treatment	Virological cure
NCT04344951	18-90 yr	CQ	Standard treatment	50% reduction in the symptom score for patients with lower respiratory tract infections | Lack of progression for patients with upper respiratory tract infections | Comparison of the primary endpoint with respective patients not receiving the treatment | Serious respiratory failure until Day 14. This was compared with respective patients not receiving the treatment | Frequency of AEs and SAEs
NCT04359095	18 yr and older	HCQ or Lopinavir/Ritonavir Pill or Azithromycin	Standard treatment	Mortality | Number of participants with treatment-related severe adverse events as assessed by the NCORP Guidance for Collection of Adverse Events Related to COVID-19 Infection | Time to death | Number of participants transferred to the intensive care unit (ICU) | Number of participants that need mechanical ventilation support with endotracheal intubation | Number of participants cured as assessed by nasopharyngeal swabs, oropharyngeal swabs, and blood aspiration for COVID-19 (RT–PCR) without clinical symptoms and normal chest X ray | Number of participants with any adverse event related to treatment as assessed by the NCORP Guidance for Collection of Adverse Events Related to COVID-19 Infection
NCT04321278	18 yr and older	HCQ + azithromycin	HCQ	Evaluation of clinical status | All-cause mortality | Number of days free from mechanical ventilation | Duration of mechanical ventilation | Duration of hospitalization | Other secondary infections | Time from the start of treatment to death | Medium- and long-term outcomes of SARS-CoV-2 infection on morbimortality, daily life activities, mental health, and quality of life | Assessment of whether the tested therapies may be affected by leucocyte phenotype
NCT04316377	18 yr and older	HCQ	No intervention	Rate of decline in SARS-CoV-2 viral load | Change in National Early Warning Score scores | Admission to the intensive care unit | In-hospital mortality | Duration of hospital admission | Mortality at 30 and 90 d | Clinical status | Change in C-reactive protein concentrations | Change in alanine aminotransferase concentrations | Change in aspartate aminotransferase concentrations | Change in bilirubin concentrations | Change in the estimated glomerular filtration rate | Change in cardiac troponin concentrations | Change in natriuretic peptide concentrations
NCT04331470	15-100 yr	Levamisole Pill + Budesonide+Formoterol inhaler	Lopinavir/Ritonavir + HCQ	Clear chest CT-scan | PCR test | Physical status of the patient
NCT04325893	18 yr and older	HCQ	Placebo	Number of deaths from any cause, or the need for intubation and mechanical ventilation during the 14 d following inclusion and the start of treatment | Number of deaths from any cause, or the need for intubation and mechanical ventilation during the 28 d following inclusion and the start of treatment | Clinical evolution on the WHO Ordinal Scale for Clinical Improvement for COVID-19 between day 0 and day 14 | Clinical evolution on the WHO Ordinal Scale for Clinical Improvement for COVID-19 between day 0 and day 28 | Number of all-cause mortalities at day 14 | Number of all-cause mortalities at day 28 | Rate of positive SARS-CoV-2 RT–PCR nasopharyngeal samples at day 5 | Rate of positive SARS-CoV-2 RT–PCR nasopharyngeal samples at day 10 | The rate of venous thromboembolic events at day 28, documented and confirmed by an adjudication committee | Number of all-cause mortalities at day 28 in patients aged 75 yr and older | Clinical evolution on the WHO OSCI scale for COVID-19 between day 0 and day 28 for patients aged 75 yr or older | Rate of severe adverse events at day 28 | Number of all-cause mortalities at day 14 in patients aged 75 yr and older
NCT04353037	50-75 yr	HCQ	Placebo	Sub Study 1: Patients | Sub Study 2: Health Care Workers | Sub Study

				1: Patients: Rate of secondary infection of coinhabitants | Sub Study 1: Patients: Adverse Events | Sub Study 1: Patients: Negative for COVID-19 | Sub Study 2: Health Care Workers: Number of shifts missed | Sub Study 2: Health Care Workers: Rate of adverse events | Sub Study 2: Health Care Workers: Rate of hospitalization
NCT04351724	18-99 yr	CQ or HCQ	Placebo	Sustained improvement (> 48 h) of one point on the WHO scale | Time to improvement on the WHO scale | Mean change in the ranking on an ordinal scale from baseline | Time to discharge or a National Early Warning Score (NEWS) (maintained for 24 h), whichever occurs first | Change from baseline in the National Early Warning Score (NEWS) | Oxygenation-free days | Incidence of new oxygen use during the trial | Duration of oxygen use during the trial | Ventilator-free days until day 29 | Incidence of new mechanical ventilation use during the trial | Duration of mechanical ventilation use during the trial | Viral load/viral clearance | Duration of hospitalization | Mortality | Obesity – mortality | Obesity - duration of hospitalization | Obesity - ICU admission | Obesity - new oxygen use | Drug–drug interactions with lopinavir/ritonavir | Renin Angiotensin System (RAS) fingerprint
NCT04359316	18 yr and older	HCQ	Azithromycin	Time to clinical improvement | Mortality | SpO_2 improvement | Incidence of new mechanical ventilation use | Duration of hospitalization | Cumulative incidence of serious adverse events
NCT04334148	18 yr and older	HCQ	Placebo oral tablet	Number of participants with clinical COVID-19 infection | Number of participants with COVID-19 viral shedding | Safety as measured by the number of adverse events

CQ: Chloroquine; HCQ: Hydroxychloroquine; COVID-19: Coronavirus disease 2019; SARS-CoV2: Severe acute respiratory syndrome coronavirus 2.

However, as more standardized clinical trials were published, doubts about the efficacy of CQ/HCQ began to increase. On April 14, 2020, a multicenter open-label randomized clinical trial conducted at Ruijin Hospital showed that HCQ did not improve the rate of negative conversion of SARS-CoV-2 nucleic acid tests. This was the first clinical trial in which CQ/HCQ was shown to be ineffective[5]. On May 7, 2020, the New England Journal of Medicine (NEJM) published an important observational study reporting the clinical efficacy of HCQ for the treatment of COVID-19. Our team also confirmed this conclusion[6]. The conclusion was that there was no obvious effect[7]. Since then, more scholars have warned that HCQ/CQ has serious side effects[8,9]. This article reviews the published RCTs related to CQ and HCQ (Table 2).

ETHICAL CHALLENGES FOR HCQ/CQ OFF-LABEL USE FOR COVID-19

The results of existing clinical trials show that there are still some problems with the methodologies. For example, the controlled trials did not use randomization. The populations were not generally representative (the subjects of some trials were young), and the combined dose was too low to thoroughly explore the effectiveness of the drug; however, adverse events, such as cardiotoxicity, have occurred with high doses and drug combinations. Therefore, a well-designed clinical trial to clarify the safety and effectiveness of HCQ/CQ and to guide the development of drugs for the treatment of COVID-19 is needed. Simultaneously, obtaining ethical approval before conducting clinical trials is very important.

We found that many clinical trials lacked a solid ethical basis in the ethical review of studies involving the treatment of COVID-19 with HCQ/CQ during the pandemic.

ETHICAL RECOMMENDATIONS FOR CONDUCTING CLINICAL TRIALS WITH HCQ/CQ FOR COVID-19

In addition to applying for standardized ethical review and adhering to the "Key Guidelines on the Ethical Acceptability of COVID-19 Human Challenge Tests" issued by the WHO, postmarketing studies of clinical drugs initiated by researchers need to consider the following.

Paying attention to the scientific basis of the research

Scientificity is essential to the effectiveness of clinical research results. To research the off-label use of CQ and HCQ, it is necessary to carefully study the instructions for these drugs, obtain and consider the latest supplementary instructions for their use, and design the research plan accordingly.

Table 2 Published randomized controlled trials related to chloroquine and hydroxychloroquine use for coronavirus disease 2019

DOI		Number of subjects	Patients' age (mean ± SD)	Basic diseases (%)	Treatment plan
10.3785/j.issn.1008-9292.2020.03.03	Experimental group	15	50.5 ± 3.8	40.00%	Routine treatment + oral HCQ sulfate days 1-5, 400 mg QD
	Control group	15	46.7 ± 3.6	33.30%	Routine treatment
10.1101/2020.03.22.20040758	Experimental group	31	45.2 ± 14.7	NA	Standard treatment + oral HCQ sulfate days 1-5, 200 mg bid
	Control group	31	44.1 ± 16.1	NA	Standard treatment
10.1101/2020.04.10.20060558	Experimental group	75	48.0 ± 14.1	37.30%	Standard care + oral HCQ sulfate days 1-3, 1200 mg QD; Day 4 – 800 mg QD
	Control group	75	44.1 ± 15.0	22.70%	Standard care
10.1101/2020.04.10.20060699	Experimental group	84	59 ± 48-67	NA	Standard care + oral HCQ sulfate day 1 - 600 mg QD
	Control group	97	63 ± 53-68	NA	Standard care

Routine treatment includes bed rest, oxygen inhalation, symptomatic support treatment, the use of antiviral drugs recommended in the "diagnosis and treatment plan", if necessary, antibiotics, *etc*. Standard treatments include oxygen therapy, antiviral drugs, antibiotics and immunoglobulins, with or without corticosteroids. The minimum requirements for standard care include intravenous infusion, oxygen supply, regular laboratory tests and severe acute respiratory syndrome coronavirus 2 tests, hemodynamic monitoring and intensive care, and the provision of symptomatic drugs. HCQ: Hydroxychloroquine; NA: Not available.

Research design

When considering using CQ and HCQ to treat COVID-19, it is necessary to fully consider the indications, usages, dosages, precautions, adverse reactions, contraindications, drug interactions and possible risks. In view of the above considerations, researchers should refine their plans and measurements, clarify the specific indicators, and, for the long-term follow-up of the clinical responses, develop medical countermeasures. At the same time, in accordance with the scientific requirements, a gold standard for evaluating interventions involving CQ and HCQ needs to be established, and alternative research designs, such as adaptive designs and stepwise designs, should be explored. Before using alternative research designs, the advantages and disadvantages must be carefully evaluated to minimize the risk to the subjects.

Sample size and estimation method

The sample sizes needed in studies of CQ and HCQ are uncertain. According to the developing trends of the pandemic, it is necessary to recruit a large numbers of clinical research subjects; research should not be wasted due to an insufficient sample size. At present, countries are gradually gaining control over the pandemic, and it is also important to ensure that there are enough subjects in CQ and HCQ trials to prevent the unnecessary exposure of subjects to risk.

Criteria for patient inclusion, exclusion and early withdrawal

When determining patients for inclusion, it is important to consider that CQ should be used with caution in patients with the following conditions: Liver and kidney insufficiency, heart disease, severe multitype erythema, hematoporphyria, psoriasis, and psychosis. Other considerations include the following: (1) "Providers should be careful when applying it for patients with liver disease"; (2) "It is particularly dangerous for patients with porphyria"; (3) "Patients lacking glucose 6-phosphate dehydrogenase are at great risk of hemolysis"; (4) "Children are particularly sensitive to the toxicity of this drug"; and (5) "It can aggravate the onset of psoriasis or promote the recurrence of psoriasis". The clinical precautions needed when using HCQ are clear: "All patients should undergo ophthalmological and ECG examinations" and "Patients with the following conditions should increase their frequency of eye examinations": (1) Patients with a daily dose exceeding the ideal body weight of 6.5 mg/kg (using the absolute body weight as a dosing guide can cause overdosing in obese patients); (2) Patients with renal insufficiency; (3) Patients with a cumulative dose exceeding 200 g; and (4) Patients with adverse reactions". In addition, precautions in the "elderly" population should be fully considered with regard to patient exclusion or as early withdrawal criteria to prevent their incorrect inclusion. At the same time, there must be a withdrawal standard that takes into account the rapid progression of the disease and sudden changes in each stage to protect the safety and rights of the subjects to the greatest extent. All

patients who meet the criteria should enter the selection process for screening. Selected patients must strictly abide by a program's selection and exclusion criteria. Criteria that are too loose will lead to the inclusion of patients who are not suited for the program. Criteria that are too strict actually added new exclusion criteria and eventually led to so-called "super selection". There will be bias in both cases. To ensure the speed and quality of patient selection, although it is possible to mobilize more doctors to recommend patients, it is best to focus on a few doctors who understand the plan and are available at any time. It is important for these doctors to ask for clarification when there is a paradox in the exclusion criteria. When seeking clarification, the PI of a unit should be contacted before the inspector. If there is a period of uncertainty regarding the inclusion of a patient in a trial, the treatment of the patient's condition should be the primary focus, and the diagnosis and treatment should not be delayed due to selection. In the event of serious adverse reactions such as cardiotoxicity, subjects should be considered for early withdrawal. We should also pay attention to people with rare diseases where off-label drugs for COVID-19 might lead to severe complications, such as patients with neuromuscular diseases[10].

Evaluation indicators and standards

It is important to distinguish among mild, severe, slowly developing, and urgent symptoms of COVID-19 to determine the status of the subjects and the specific timing and conditions indicating the use of CQ and HCQ. For example, patients with mild COVID-19 should receive the medication at the beginning of the diagnostic process; when hospitalized, patients with severe COVID-19 should receive it before intubation; and patients experiencing a life-threatening emergency should receive it after intubation. In the above situation, the corresponding evaluation index should be set after the medication is administered. The main evaluation index used for patients with mild COVID-19 is the cure rate or the rate of conversion from severe COVID-19; the main evaluation indicator for critical patients is the case fatality rate. In emergencies, the clinical recovery time can be used as a surrogate endpoint. At the same time, the dosage of a patient's medication at each stage, the rate of ventilator use after drug treatment, and whether drug treatment was combined with other medications should be considered important evaluation indicators. It is necessary to compare the evaluation indicators among patients with various symptoms who have and have not been treated with CQ and HCQ to comprehensively determine the benefits of the medications.

Assessing risks and potential benefits, and fully informing subjects of the risks of participating in the research

We need to reasonably evaluate and anticipate the risks and benefits of the research. The expected benefits should be greater than the risks, and the subjects should be fully informed of the risks involved in the research. Appropriate strategies should be adopted as much as possible to minimize the risks to patients. It is important to identify the possible risks and symptoms of adverse events in each stage of the process related to treatment with CQ and HCQ to formulate targeted risk mitigation measures to carefully control and reduce the risks.

There are clinical trials reporting that taking high doses of CQ and HCQ carries the risk of clinical arrhythmia. According to the reports, a total of 81 subjects participated in a randomized double-blind HCQ trial for the treatment of COVID-19 in Brazil. Approximately half of the patients took 450 mg twice a day for 5 consecutive days, while the other half took 600 mg a day (high-dose group). On the third day of the trial, some patients in the high-dose group experienced severe arrhythmia, and 11 people died; the investigator had to terminate the trial as soon as possible[11]. In addition, there have been studies showing that the combination of HCQ or CQ with azithromycin can cause cardiac safety issues; one such study was an analysis of HCQ use in more than 950000 patients from 6 countries. The results showed that the current HCQ recommended dose for rheumatoid arthritis is safe; when azithromycin is used at the same time, the QT interval may be prolonged or even torsade de pointes tachycardia, resulting in sudden death. This suggests that caution should be used when combining medications. Current reports show that SARS-CoV-2 may affect the heart muscle and cause myocarditis. Individual autopsy reports suggest that the myocardium is infiltrated by interstitial mononuclear inflammatory cells, indicating that the heart tissue is infected. Severe myocarditis with decreased myocardial contractile function has also been reported in COVID-19 patients. Studies of cardiac biomarkers have also shown that the incidence of cardiac damage in hospitalized patients is high. COVID-19-induced electrolyte disorders (such as hypokalemia and hypomagnesemia) should not be understated, as they can explain why COVID-19 patients are at high risk for ventricular arrhythmias when treated with HCQ. The cytokine storm can also have a prolonging effect on the QT interval[12].

However, there are major uncertainties about the pathogenesis of COVID-19. Despite our efforts to reduce risks, serious harm may still occur. Therefore, subjects should be provided with high-quality supportive care (including necessary intensive care), long-term follow-up (to detect any lasting injury), and adequate compensation for any injury that occurs to fully protect their rights and interests.

STRENGTHENING CONSULTATION AMONG STAKEHOLDERS

Clinical research should focus on consulting with and soliciting the opinions of stakeholders (subjects, researchers, ethics committee members, *etc*.). For example, when researching the off-label use of CQ and HCQ, it is necessary to ask the CQ and HCQ drug manufacturers for the latest supplementary instructions regarding their use. Research-related risks and potential benefits should be presented in a transparent manner to participants; the opinions of subjects, people interested in the research and relevant experts should be incorporated; and the acceptability of the clinical research to the public and the acceptance of the off-label use of CQ/HCQ by the research subjects should be comprehensively considered. At the same time, consultations with local and international researchers, ethics committee members, decision makers, and other relevant experts should also be conducted.

Promoting research coordination

Coordinated research is intended to ensure that clinical research-related public health benefits are achieved with the greatest possible safety and efficiency. Therefore, research should be coordinated with public health agencies to prevent unduly compromising the local public health response to COVID-19. Research should also be fully supervised by the relevant authorities (including the World Health Organization when appropriate), and adequate communication and coordination with regulatory agencies should be ensured to maximize safety. During early coordination with regulatory agencies, attention should also be paid to the data and results regarding research on the off-label use of CQ and HCQ.

Paying attention to the qualifications of the research team

The research team is the main group involved in conducting drug trials. With regards to drug research conducted during a pandemic, the clinical qualifications, scientific research ability and industry influence of the team members determine the effectiveness of the research.

In terms of personnel qualifications, the main investigator should have clinical experience in the use of CQ, HCQ, *etc*. The research team members should have the appropriate qualifications and clinical research experience and should have received training on drug clinical trial quality management practices and infectious disease protective measures. In addition, a certain number of clinically experienced pharmacists and nursing staff should participate.

In terms of the division of responsibilities, the main researchers should adequately delegate the responsibilities and coordinate the research team, and reasonably allocate the time and energy needed for the clinical research and clinical treatment, including designing the research plan, obtaining informed consent, screening patients for enrollment, acquiring clinical specimens, collecting data in the field, filling in case report forms, performing the statistical analysis, *etc*. All processes should be carried out by the specific personnel responsible. The China national medical aid team in Hubei can be considered as an example. The clinical trial is led by the academician, and the vice president is directly responsible for the trial. The chief physician of the Department of Respiratory Medicine and Critical Care implements the specific treatments and monitors changes in the patients' conditions, and the clinical pharmacology trial institution conducts the trial. With regard to data management and analysis, the entire team has a comprehensive relevant professional background, and there is a clear division of labor and a mechanism to ensure smooth communication and collaboration.

Respecting the subjects' choices

In addition to referring to the criteria for the inclusion, exclusion and withdrawal of subjects specified in the study design, the selection of subjects should also follow the principle of fairness. The principle of fairness is one of the four basic principles of medical ethics. Fairness in research plays an important role in maintaining trust in the relationship between the public and medical researchers. During a pandemic, the principle of fairness is particularly important.

Researchers, sponsors and ethics committees need to ensure that the risks and benefits to subjects are fairly balanced. During a sudden infectious disease pandemic, potentially effective interventional clinical research may be limited. Therefore, researchers should recruit subjects fairly and pay special attention to the inclusion or exclusion of subjects from special groups (such as medical personnel with confirmed infections). There should be sufficient and reasonable rationale behind the selection of subjects. Equity is also reflected in the fact that the subjects should have equal access to the results of the research, and the subjects' welfare should be ensured after the trial.

EXPERT REVIEW

Clinical trials related to SARS-CoV-2 should be included in an independent review category, in addition to or in combination with local ethical review standards, similar to other types of research. Such trials may be controversial or involve higher risks and levels of uncertainty. An independent ethical review committee should include members with relevant scientific knowledge and relevant knowledge of

clinical trial ethics. In all cases, the review process should involve a high level of the necessary knowledge and should be carried out quickly to improve the efficiency of the review process while strictly abiding by the review standards.

At the same time, the researchers and the ethics committee should regularly negotiate, whether before or during the research, and pay special attention to new data (especially data related to risks). In addition, the ethics committee should supervise the entire process of the clinical research and conduct a follow-up review. During the implementation of the trial protocol, the review and approval of important documents, the review of protocol violations, and the review of serious adverse events, it is important to pay close attention to the safety of the subjects. With regard to the subjects involved in the trials of the off-label use of CQ and HCQ, unanticipated adverse events and violations of ethical principles harmed the subjects. The research team should submit research progress reports during each phase with links to key reports, and the overall research process should conform to the requirements in the ethical approval documents with regard to follow-up frequency. A summary report should be submitted after the end of the project.

OBTAINING THE INFORMED CONSENT OF SUBJECTS

Adhering to the priority of patients' rights is the core principle of ethical review and the fundamental manifestation of medical ethics. It is a basic principle that cannot be neglected, regardless of the circumstances. In the case of a pandemic, the ethical review of research on the off-label use of CQ and HCQ still needs to prioritize the rights and interests of subjects and guarantee that subjects give their informed consent.

First, fully informed consent requires the explanation of the involved risks and possible benefits. Subjects should receive an explanation of the in vitro test results and possible positive effects of CQ and HCQ and an explanation of the adverse reactions and possible side effects, such as digestive tract symptoms, cardiovascular symptoms and ocular discomfort. The possibility of lifelong adverse consequences should be explained. Any application for exemption from the need to obtain informed consent or explain the risks due to inconvenience, a shortage of researchers, an increased opportunity for infection, or the lack of personal protective equipment needed when entering isolation wards are not in line with the principles of ethical review. In addition, due to the contagious nature of the disease, there are additional challenges related to the work environment and sanitation with regards to the signing of the informed consent form for off-label CQ and HCQ trials. The research team needs to comply with the principles of ethical review and obtain fully informed consent. For example, during the pandemic, researchers in Wuhan sent WeChat messages that contained the informed consent form signed by the patient and the electrocardiogram (ECG) results from mobile phones in the contaminated area to mobile phones in the clean area. Consent for participation for mechanically ventilated and sedated subjects who lack the capacity to sign the informed consent form can be obtained from their legal representative. No emotional rhetoric should be used under any circumstances to pressure or deceive subjects. Patients should be given sufficient time to consider their participation in a clinical research trial, and their decision regarding their participation in the trial should be respected.

CONCLUSION

Research must be both rigorous and prudent to ensure the best outcome, with the maximization of benefits as the core principle. Standardization of the application, implementation and ethical review processes are needed to prevent unnecessary risk.

FOOTNOTES

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