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A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19

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ABSTRACT

Purpose: COVID-19 (coronavirus disease 2019) is a public health emergency of international concern. As of this time, there is no known effective pharmaceutical treatment, although it is much needed for patient contracting the severe form of the disease. The aim of this systematic review was to summarize the evidence regarding chloroquine for the treatment of COVID-19.
Methods: PubMed, EMBASE, and three trial Registries were searched for studies on the use of chloroquine in patients with COVID-19.
Results: We included six articles (one narrative letter, one in-vitro study, one editorial, expert consensus paper, two national guideline documents) and 23 ongoing clinical trials in China. Chloroquine seems to be effective in limiting the replication of SARS-CoV-2 (virus causing COVID-19) in vitro.
Conclusions: There is rationale, pre-clinical evidence of effectiveness and evidence of safety from long-time clinical use for other indications to justify clinical research on chloroquine in patients with COVID-19. However, 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.

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1. Introduction

COVID-19 (Coronavirus Disease-2019) is a public health emergency of international concern. Patients contracting the severe form of the disease constitute approximately 15% of the cases [1]. As of this time there is no known specific, effective, proven, pharmacological treatment. In-vitro studies have suggested that chloroquine, an immunomodulant drug traditionally used to treat malaria, is effective in reducing viral replication in other infections, including the SARS-associated coronavirus (CoV) and MERS-CoV [2–4].

Chloroquine has been used worldwide for more than 70 years, and it is part of the World Health Organization (WHO) model list of essential medicines. It is also cheap and has an established clinical safety profile [3]. However, the efficacy and safety of chloroquine for treatment of SARS-CoV-2 (the new virus causing COVID-19) pneumonia remains unclear.

2. Methods

We performed a systematic review of the PubMed and EMBASE databases from inception to 1-March-2020 to find articles providing information on the efficacy and safety of chloroquine and chloroquine-related formulations in patients with SARS-CoV-2 pneumonia and articles describing related in-vitro studies. As much of the data on COVID-19 are coming from Asia, no language restrictions were imposed (see detailed search strategy in Supplement 1). The search was expanded using a snowballing method applied to the references of retrieved papers. We also searched the Chinese Clinical Trial Registry, Clinicatrial.gov and the International Clinical Trials Registry Platform (WHO ICTRP) to identify ongoing trials. Two authors (AC, MI) independently screened the databases and the trial registries and extracted relevant information (MI, GI). Discrepancies and doubts about relevance of the sources were solved by consensus with two more authors (AG, SE). We did not register the systematic review protocol because we anticipated the very limited available evidence on the topic and due to the urgency of the matter.

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Table 1
Characteristics of clinical trials studying the efficacy and safety of Chloroquine or related formulation in patients with new coronavirus.pneumonia (COVID-19).

ID	Recruiting Status	Number of centers and Study design	Country	Population (n patients)	Intervention Group(s)	Comparison Group(s)	Primary Outcomes
ChiCTR2000030417	Not yet recruiting	Single Center RCT	China	COVID-19 pneumonia (n = 30)	Chloroquine phosphate aerosolized inhalation solution	Water for injection atomized inhalation combined	Temperature normal for more than 3 days, respiratory symptoms, pulmonary imaging, test negativization
ChiCTR2000030054	Pending approval	Single Center RCT	China	Mild and common COVID-19 pneumonia (n = 100)	Hydroxychloroquine sulfate group: Hydroxychloroquine sulfate 0.2 g BID × 14 days Chloroquine phosphate group: First dose of chloroquine phosphate 1 g × 2 days, then 0.5 g × 12 days	Standard treatment	Clinical recovery time
ChiCTR2000030031	Recruiting	Single Center RCT	China	Mild and common COVID-19 pneumonia (n = 120)	2 tablets Chloroquine phosphate BID	2 tablets placebo BID	Time of conversion to be negative of novel coronavirus nucleic acid
ChiCTR2000029992	Pending approval	Single Center RCT	China	Severe COVID-19 pneumonia (n = 100)	Chloroquine phosphate group: Chloroquine phosphate 1.0 g × 2 days, then 0.5 g × 12 day from the third day Hydroxychloroquine sulfate group: Hydroxychloroquine sulfate 0.2 g BID x 14 days	Standard treatment	Clinical recovery time; Changes in viral load of upper and lower respiratory tract samples compared with the baseline
ChiCTR2000029988	Recruiting	Single Center RCT	China	Severe COVID-19 pneumonia (n = 80)	Chloroquine phosphate	Standard treatment	Time to Clinical Recovery
ChiCTR2000029975	Pending approval	Single CenterSingle-arm clinical trial	China	COVID-19 pneumonia (n = 10)	150 mg chloroquine phosphate dissolved in 5 ml of normal saline, q12h, inhaled by atomization for one week	No comparison group	Viral negative-transforming time; 30-day cause-specific mortality; Co-infections; Time from severe and critical patients to clinical improvement
ChiCTR2000029939	Recruiting	Single Center RCT	China	COVID-19 pneumonia (n = 100)	Chloroquine phosphate	Standard treatment	Length of hospital stay
ChiCTR2000029935	Recruiting	Single CenterSingle-arm clinical trial	China	COVID-19 pneumonia (n = 100)	Chloroquine phosphate	No comparison group	Length of hospital stay
ChiCTR2000029899	Recruiting	Single Center RCT	China	Mild and Common COVID-19 pneumonia (n = 100)	Hydroxychloroquine: Day1: first dose: 6 tablets (0.1 g/table), second dose: 6 tablets (0.1 g/table) after 6 h; Day 2–10: 2 tablets/day (0.1 g/table)	Phosphate chloroquine: Day1–3: 500 mg BID; Day4–10: 250 mg BID	Time to Clinical Recovery
ChiCTR2000029898	Recruiting	Single Center RCT	China	Severe COVID-19 pneumonia (n = 100)	Hydroxychloroquine Day1: first dose: 6 tablets (0.1 g/tablet), second dose: 6 tablets (0.1 g/tablet) after 6 h; Day2~10: 2 tablets/day (0.1 g/tablet)	Phosphate Chloroquine Day1–3: 500 mg BID; Day4–10: 250 mg BID	Time to Clinical Improvement
ChiCTR2000029868	Recruiting	Multi-Center RCT	China	COVID-19 pneumonia (n = 200)	Oral hydroxychloroquine sulfate tablets	Standard treament	Viral nucleic acid test
ChiCTR2000029837	Pending approval	Single Center RCT	China	Mild and common COVID-19 pneumonia (n = 120)	2 tablets Chloroquine phosphate BID	2 tablets placebo BID	Negative conversion rate of COVID-19 nucleic acid
ChiCTR2000029826	Pending approval	Single Center RCT	China	Critically ill COVID-19 pneumonia (n = 45)	2 tablets Chloroquine phosphate BID	2 tablets placebo BID	Mortality rate
ChiCTR2000029803	Pending approval	Single Center RCT	China	Close contacts with suspected or confirmed cases, and positive test of COVID-19 nucleic acid (n = 320)	Group A1: Hydroxychloroquine, small dose; Group A2: Hydroxychloroquine, high dose	Group B1: Abidol hydrochloride low dose; Group B2: Abidol hydrochloride high dose	Progression to suspected or confirmed disease within 24 days
ChiCTR2000029762	Recruiting	Single Center RCT	China	COVID-19 pneumonia (n = 60)	Hydroxychloroquine tablet	Standard treatment	Negative conversion rate of COVID-19 nucleic acid; lung inflammation absorption ratio
ChiCTR2000029761	Recruiting	Multi-Center RCT	China	Common COVID-19	Low-dose group: Low-dose hydroxychloroquine;	Standard treatment	Negative conversion rate of COVID-19 nucleic acid; lung

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Table 1 (*continued*)

ID	Recruiting Status	Number of centers and Study design	Country	Population (n patients)	Intervention Group(s)	Comparison Group(s)	Primary Outcomes
				pneumonia (n = 240)	Medium-dose group: Medium-dose hydroxychloroquine; High-dose group: High-dose hydroxychloroquine		inflammation absorption ratio
ChiCTR2000029741	Recruiting	Multi-Center RCT	China	Mild and common COVID-19 pneumonia (n = 112)	Chloroquine phosphate	Lopinavir/Ritonavir	All-cause mortality at day 28; length of stay; oxygen index during treatment; blood cell count; inflammation serum factors; coagulation indicators
ChiCTR2000029740	Recruiting	Single Center RCT	China	COVID-19 pneumonia (n = 78)	Oral intake hydroxycholoroquine 0.2 g BID	Standard treatment	Negative conversion rate of COVID-19 nucleic acid; prognosis; oxygen index; respiratory rate; lung radiography; temperature; count of lymphocyte; temperature; other infections
ChiCTR2000029609	Pending approval	Multi-Center Non-randomized controlled trial	China	COVID-19 pneumonia (n = 205)	Mild-moderate Chloroquine group: oral Chloroquine phosphate; Mild-moderate combination group: Chloroquine phosphate plus Lopinavir/ritonavir; Severe Chloroquine group: oral Chloroquine phosphate	Mild-moderate Lopinavir/Ritonavir group: oral Lopinavir/Ritonavir; Severe Lopinavir/Ritonavir group: oral Lopinavir/ritonavir	Negative conversion rate of COVID-19 nucleic acid
ChiCTR2000029559	Recruiting	Single center RCT	China	COVID-19 pneumonia (n = 300)	Group 1: Hydroxychloroquine 0.1 g oral BID; Group 2: Hydroxychloroquine 0.2 g oral BID	Placebo control group: Starch pill oral BID	Negative conversion rate of COVID-19 nucleic acid; T cell recovery time
ChiCTR2000029542	Recruiting	Single center prospective cohort study	China	COVID-19 pneumonia (n = 20)	Oral chloroquine 0.5 g BID for 10 days	Standard treatment	Negative conversion rate of COVID-19 nucleic acid; 30-day cause specific mortality
NCT04286503	Not yet recruiting	Multi-center RCT	China	Critically ill COVID-19 pneumonia (n = 520)	Carrimycin	lopinavir/ritonavir or Arbidol or Chloroquine phosphate	Fever to normal time; pulmonary inflammation resolution time at 30 day; negative conversion of COVID-19 nucleic acid at the end of treatment
NCT04261517	Not yet recruiting	Single center RCT	China	COVID-19 pneumonia (n = 30)	Hydroxychloroquine 400 mg/day for 5 days	Standard treatment	Mortality rate at day 14; Virological clearance rate of throat swabs, sputum, or lower respiratory tract secretions at day 3,5,7

For data entry, we used the definitions and the information provided by the investigators in the trial registries, if available. The number of patients in the Population columns refers to the reported sample size. In the 'Primary outcomes column' we reported only the primary outcomes, as described by the investigators; BID: twice per day; RCT: Randomized controlled trial.

3. Results

The initial search identified 234 sources (156 from PubMed, 73 EMBASE and 5 from other sources). Following screening of titles and abstracts and removing duplicates, we evaluated eight articles in full text. Among these, we found six relevant articles (one narrative letter, one research letter, one editorial, one expert consensus paper in Chinese, one national guideline document in Dutch and one in Italian) [3,5–9]. Twenty-three trials were found in the trial registries (Table 1).

4. Discussion

The research letter, written by a group of Chinese researchers, studied the effect of chloroquine in vitro, using Vero E6 cells infected by SARS-CoV-2 at a multiplicity of infection (MOI) of 0.05. The study demonstrated that chloroquine was highly effective in reducing viral replication, with an Effective Concentration $(EC)_{90}$ of 6.90 μM that can be easily achievable with standard dosing, due to its favourable penetration in tissues, including in the lung [6]. The authors described that chloroquine is known to block virus infection by increasing endosomial ph and by interfering with the glycosylation of cellular receptor of SARS-CoV. The authors also speculated on the possibility that the known immunomodulant effect of the drug may enhance the antiviral effect in vivo [6].

A narrative letter by Chinese authors reported that a news briefing from the State Council of China had indicated that "Chloroquine phosphate… had demonstrated marked efficacy and acceptable safety in treating COVID-19 associated pneumonia in multicentre clinical trials conducted in China" [5]. The authors also stated that these findings came from "more than 100 patients" included in the trials [5]. We sought for evidence of such data in the trial registries we reviewed and found none.

The Editorial written by French researchers, underlined the in-vitro efficacy of chloroquine in other viral infections, especially SARS (whose disappearance resulted in limited further research). They also discussed the potentially favourable risk-benefit balance, the high safety, and the low expenditure of such treatment in the context of the current COVID-19 outbreak [3]. Since cases were reported in 85 countries so far (5th March 2020), the low cost of chloroquine is a major benefit for both the highly stressed healthcare systems of involved high-income countries and the underfunded heathcare systems of middle- and low-income counties [10].

The expert consensus was published on 20th February by a multicentre collaboration group of the Department of Science and

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Technology of Guangdong Province and Health Commission of Guangdong Province paper and related specifically to the use of chloroquine phosphate [7]. No information was provided on the method used to achieve consensus [7]. Based on in vitro evidence and still unpublished clinical experience, the panel recommended chloroquine phosphate tablet, at a dose of 500 mg twice per day for 10 days, for patients diagnosed as mild, moderate and severe cases of SARS-CoV-2 pneumonia, provided that there were no contraindications to the drug. The panel recommended using several precautions, including blood testing to rule out the development of anemia, thrombocytopenia or leukopenia as well as serum electrolyte disturbances and/or hepatic and renal function dysfunction. Also recommended were routine electrocardiography to rule out the development of QT interval prolongation or bradycardia and patient interviews to seek the appearance of visual and/or mental disturbance/deterioration. The panel recommended avoiding concurrent administration of other drugs known to prolong the QT interval (i.e. chinolones, macrolides, ondansetron) as well as various antiarrhythmic, antidepressant and antipsychotic drugs [7].

The Dutch Center of Disease control (CDC), in a public document on its website, suggested to treat severe infections requiring admission to the hospital and oxygen therapy or admitted to the ICU with chloroquine, [8]. However, the document also stated that treating patients only with optimal supportive care is still a reasonable option, due to lack of supportive evidence. The suggested regimen in adults consists of 600 mg of chloroquine base (6 tablets A-CQ 100 mg) followed by 300 mg after 12 h on day 1, then 300 mg × 2/die per os on days 2–5 days. This document also underlined 1) the needs for stopping the treatment at day 5 to reduce the risk of side effects, considering the long half-life of the drug (30 h); 2) the need to differentiate between regimens based on chloroquine phosphate and chloroquine base since 500 mg of the first correspond to 300 mg of the second [8].

Another guideline document by the Italian Society of Infectious and Tropical disease (Lombardy section) recommend the use of chlorochine 500 mg × 2/die or hydroxychloroquine 200 mg die for 10 days, although the treatment may vary from 5 to 20 days according to clinical severity. The suggested target population ranged from patients with mild respiratory symptoms and comorbidities to patients with severe respiratory failure [9].

Our search also identified ongoing 23 trials, all in China (Table 1). The trials varied in study design, severity of the disease in the target population and in dosing and duration of the treatment. Indeed, the trial registrations varied also in quality of the reported information. That so many such studies are being conducted in parallel suggests that that the scientific community is making a huge effort to clarify this question, but this effort is probably insufficiently coordinated. In support of this observation, the Chinese authorities have recently issued a directive to regulate and coordinate clinical trials studying potential pharmacological treatments for COVID-19 [11]. The results of these trials will be the first available on humans, since studies published to date on the characteristics and management of patients with COVID-19 did not report data about chloroquine use [1,12–15]. Of note, the WHO published a generic protocol for randomized clinical trials to investigate the clinical efficacy and safety of drugs in hospitalized patients with COVID-19 (i.e. a "master template" for researching drugs in this setting) [16].

The vital ethical issue is whether administration of chloroquine in the setting of COVID-19 is experimental, and therefore requires ethical trial approval, or off-label (i.e. ethically justifiable as the best available treatment). Additional information on chloroquine will soon be released in the context of the evolving outbreak. Timely release of this information can be of importance due to the growing number of infected patients, and the absence of licensed specific drugs. Meanwhile, the recommendations for "Clinical management of severe acute respiratory infection when novel coronavirus (2019-nCoV) infection is suspected", published by the WHO, confirm that there is currently no evidence from RCTs to inform on specific drug treatment of COVID-19 and that unlicensed treatments should be administered only in the context of ethically-approved clinical trials or the Monitored Emergency Use of Unregistered Interventions Framework (MEURI), under strict monitoring [17]. The WHO therefore seems to view chloroquine as experimental. The authors tend to agree with this viewpoint. But even off-label use of chloroquine may be accompanied by several concerns; the first is patient safety. Such use should be accompanied by close monitoring. An epidemic is hardly the ideal setting to do this. The ethical approach to off-label drug use also differs between countries, raising questions regarding equity. Finally, chloroquine remains a pivotal drug in the treatment of Malaria in many places in the world. Off label drug use can create major drug shortages [18].

5. Conclusion

There is sufficient pre-clinical rationale and evidence regarding the effectiveness of chloroquine for treatment of COVID-19 as well as evidence of safety from long-time use in clinical practice for other indications [3] to justify clinical research on the topic. The current circumstances justify prioritization of ethical review of study proposals above other, less pressing, research topics (i.e. fast track institutional ethical review). Although the use of chloroquine may be supported by expert opinion, clinical use of this drug in patients with COVID-19 should adhere to the MEURI framework or after ethical approval as a trial as stated by the WHO. Data from high-quality, coordinated, clinical trials coming from different locations worldwide are urgently needed.

Authors' contribution

AC conceived the content, retrieved the data, wrote the manuscript and approved the final version. MI retrieved the data, wrote the manuscript and approved the final version. GI retrieved the data, wrote the manuscript and approved the final version. AG conceived the content, helped in data extraction, revised the manuscript critically and approved the final version. SE conceived the content, helped in data extraction, wrote the manuscript and approved the final version.

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Declaration of Competing Interest

AC, GI, MI, AG, SE declare to have no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2020.03.005.

References

[1] Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. Jama 2020. https://doi.org/10.1001/jama.2020.2648.

[2] Savarino A, Boelaert JR, Cassone A, Majori G, Cauda R. Effects of chloroquine on viral infections: an old drug against today's diseases? Lancet Infect Dis 2003;3:722–7.

[3] Colson P, Rolain J-M, Raoult D. Chloroquine for the 2019 novel coronavirus SARS-CoV-2. Int J Antimicrob Agents 2020:105923.

[4] https://www.who.int/blueprint/priority-diseases/keyaction/Table_of_therapeutics_Appendix_17022020.pdf?ua=1. Accessed on 2nd March 2020.

[5] Gao J, Tian Z, Yang X. Breakthrough: chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. Biosci Trends 2020. https://doi.org/10.5582/bst.2020.01047.

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[6] Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res 2020. https://doi.org/10.1038/s41422–020–0282–0.
[7] 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 2020;43 E019–9.
[8] https://lci.rivm.nl/covid-19/bijlage/behandeladvies. (Accessed on 6th March 2020).
[9] http://www.simit.org/medias/1555-covid19-linee-guida-trattamento-01mar.pdf. (Accessed on 6th March 2020).
[10] https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports/. (Accessed on 5th March 2020).
[11] http://www.xinhuanet.com/english/2020-02/28/c_138828090.htm. (Accessed on 2th March 2020).
[12] Guan W-J, Ni Z-Y, Hu Y, Liang W-H, Ou C-Q, He J-X, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med 2020. https://doi.org/10.1056/NEJMoa2002032 NEJMoa2002032.
[13] Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. Jama 2020. https://doi.org/10.1001/jama.2020.1585.
[14] Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med 2020. https://doi.org/10.1016/S2213-2600(20)30079-5.
[15] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497–506.
[16] https://www.who.int/blueprint/priority-diseases/key-action/multicenter-adaptive-RCT-of-investigational-therapeutics-for-COVID-19.pdf?ua=1. (Accessed on 6th Mrch 2020).
[17] https://www.who.int/docs/default-source/coronaviruse/clinical-management-of-novel-cov.pdf. (Accessed on 6th March 2020).
[18] Lenk C, Duttge G. Ethical and legal framework and regulation for off-label use: European perspective. Ther Clin Risk Manag 2014;10:537–46.

Please cite this article as: A. Cortegiani, G. Ingoglia, M. Ippolito, et al., A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19, Journal of Critical Care, https://doi.org/10.1016/j.jcrc.2020.03.005