CADTH COVID-19 PANDEMIC

COVID-19 CADTH HEALTH TECHNOLOGY REVIEW

Chloroquine and Hydroxychloroquine, With or Without Azithromycin, for COVID-19: A Brief Overview

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To produce this report, CADTH used a modified approach to the selection, appraisal, and synthesis of the evidence to meet decision-making needs during the COVID-19 pandemic. Care has been taken to ensure the information is accurate and complete, but it should be noted that international scientific evidence about COVID-19 is changing and growing rapidly.

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Key Message

- There is currently no evidence from clinical trials regarding the efficacy of chloroquine or hydroxychloroquine for the prevention of COVID-19.
- At this time, evidence from clinical trials regarding the efficacy of chloroquine or hydroxychloroquine monotherapy for the treatment of COVID-19 is limited and associated with important uncertainty.
- At this time, evidence from clinical trials regarding the efficacy of chloroquine or hydroxychloroquine combined with azithromycin for the treatment of COVID-19 is limited and associated with important uncertainty.

Background

Chloroquine and hydroxychloroquine have been identified as potential treatments for COVID-19. This is based on two observations: first, in vitro data showing that chloroquine and hydroxychloroquine inhibit Coronaviridae (including severe acute respiratory syndrome [SARS] and severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]); second, recent preliminary — though contradictory — results from small clinical trials performed in China and France that assessed the use of chloroquine and hydroxychloroquine in the treatment of patients with COVID-19.[1] Some clinical trials have combined chloroquine or hydroxychloroquine with the antibacterial azithromycin.[2] Azithromycin is a broad-spectrum macrolide antibiotic with activity against gram-positive and atypical bacteria.[3] The combination of azithromycin with chloroquine has been previously studied for the treatment of malaria.[3]

Questions of Interest

There are three questions of interest in this brief overview; these are:

1. What is the clinical effectiveness of chloroquine and hydroxychloroquine in the prevention of COVID-19?
2. What is the clinical effectiveness of chloroquine and hydroxychloroquine in the treatment of COVID-19?
3. What is the clinical effectiveness of either chloroquine or hydroxychloroquine in combination with azithromycin in the treatment of COVID-19?

Methods

This review is not based on a systematic literature search. The rapid response report on chloroquine and hydroxychloroquine for COVID-19 posted on April 4, 2020, by Quebec's Institut national d'excellence en santé et en services sociaux (INESSS)[2] was a key source of the information presented in this brief overview. INESSS conducted its literature search on March 31, 2020, using the following databases: MEDLINE, EMBASE, Trip Database, Cochrane, Google, medRxIV, and ClinicalTrials. Further information on the methods used by INESSS is available in its report.[2] Additional articles and publications of interest were also reviewed by CADTH to complement the information from the INESSS report and provide an overview of the more notable studies on the use of chloroquine and hydroxychloroquine, with or without azithromycin, for COVID-19.

Summary of Findings

Pre-clinical Studies

The alkaline natures of chloroquine and hydroxychloroquine may contribute to their antiviral effect, as it appears that this property inhibits the pH-dependant steps of viral replication, including for coronaviruses.[2,4] Recent in vitro studies provide some support for the antiviral effects of chloroquine and hydroxychloroquine on strains of the coronavirus associated with COVID-19 and some synergistic effect of combining hydroxychloroquine and azithromycin to reduce SARS-CoV-2 replication.[2] This synergistic effect was observed at concentrations that can be achieved in pulmonary tissue levels in humans.[2]

Clinical Studies

According to the recent INESSS rapid response report, there are 39 ongoing clinical trials involving chloroquine and hydroxychloroquine, including 29 trials investigating the use of hydroxychloroquine for the management of COVID-19, five trials investigating hydroxychloroquine in combination with azithromycin, four trials investigating chloroquine, and one trial investigating chloroquine in combination with azithromycin. Among these trials, 13 are evaluating hydroxychloroquine for either post-exposure prophylaxis or prevention of COVID-19, specifically in exposed health care professionals.[2]

Prevention of COVID-19

There are no completed clinical trials that assess the efficacy of chloroquine or hydroxychloroquine for the prevention of COVID-19. Accordingly, until the results from currently ongoing trials on either post-exposure prophylaxis or prevention of COVID-19 are available, the clinical effectiveness of chloroquine and hydroxychloroquine in the prevention of this disease is unknown.

Treatment of COVID-19

The INESSS report presents the results of five recent clinical trials.[2] Of these studies, the results from two trials were published in a journal.[5,6] The results from another clinical trial were posted on the medRxiv platform prior to being peer-reviewed.[7] The results from the other trials were mostly available as abstracts.[2,8,9] Accordingly, interpretation of these results warrants caution as findings from three of these trials are either interim or have not been peer-reviewed.

Interim results were reported for approximately 100 patients enrolled in a series of ongoing chloroquine clinical trials in different hospitals in China (Gao [2020], per the INESSS report).[2] No information on the design of these trials is available. The results were reported qualitatively without presenting statistical results. Noting the limitations of these studies, findings indicate that the use of chloroquine reduced disease progression, enhanced viral clearance, improved findings from thoracic imaging, and reduced exacerbation of pulmonary symptoms. No serious adverse events were reported.[2,4,8]

A randomized pilot study was conducted in patients with a confirmed diagnosis of COVID-19, but with non-severe disease at baseline (Chen J [2020], per the INESSS report).[2] Thirty patients from the Shanghai Public Health Clinical Center were randomized (1:1) to either hydroxychloroquine 400 mg daily for five days plus standard of care (supportive care, interferon, and antiviral drugs) or standard care. No differences in virologic cure were observed after seven days of treatment, with 86.7% (13) of patients who received

hydroxychloroquine having a negative viral ribonucleic acid–based test, compared with 93.3% (14) of patients in the control group (P > 0.05).[2,4,9] There were also no statistical differences between treatment and control groups with respect to:

- median time from hospital admission and negative testing (4 [1 to 9] versus 2 [1 to 4] days; P > 0.05)
- median time to normalization of body temperature following hospital admission (1 [0 to 2] versus 1 [0 to 3] days), no P value
- radiological progression (CT scan) (33.3% [five patients] versus 46.7% [seven patients]), no P value
- transient diarrhea and abnormal hepatic function (26.7% [four patients] versus 20% [three patients]; P > 0.05).[2,4,9]

The results from a randomized double-blind trial conducted in 62 patients with confirmed COVID-19 were recently posted prior to peer review publication (Chen Z [2020], per the INESSS report).[2] Patients were admitted between February 4, 2020, and February 28, 2020, to the Renmin Hospital of Wuhan University. All patients received standard of care therapy (i.e., oxygen, antiviral drugs, antibacterial drugs, and immunoglobulin, with or without corticosteroids). Patients were randomized (1:1) to either hydroxychloroquine 200 mg twice daily for five days (n = 31) or to control (n = 31). Both the body temperature recovery time (2.2 days versus 3.2 days; P = 0.0008) and the cough remission time (2.0 days versus 3.1 days; P = 0.0016) were shorter in the hydroxychloroquine group compared with the control group. The proportion of patients with radiologically (chest CT scan) improved pneumonia was 80.6% (25 of 31 patients) in the hydroxychloroquine group compared with 54.8% in the control group (17 of 31 patients); no P value provided. Disease exacerbation was reported in two patients (6.5%) in the hydroxychloroquine group compared with nine patients (29%) in the control group, no P value provided. Four patients progressed to severe disease; all were in the control group. Mild adverse reactions were reported in two patients in the hydroxychloroquine group; one patient experienced mild rash and another experienced mild headache.[2,7]

The results of an open-label non-randomized trial conducted by the University Hospital Institute Méditerranée Infection in Marseille (France) are described in the INESSS report (Gautret [2020a], per the INESSS report).[2] This study evaluated the effect of hydroxychloroquine 200 mg administered three times daily for 10 days on respiratory viral loads in patients who are hospitalized with confirmed COVID-19. All patients in the intervention group were treated in a single center located in Marseille. The control group was composed of patients not treated with hydroxychloroquine from other treatment centers located in four cities in southern France, as well as patients from Marseille who refused to participate in the study. All patients were 12 years of age or older with polymerase chain reaction–documented SARS-CoV-2 carriage in nasopharyngeal sample at admission independently of their clinical status. Patients taking hydroxychloroquine were also eligible to receive azithromycin (500 mg for one day followed by 250 mg per day the next four days) based on the judgment of the treating physician. This study enrolled 42 patients (26 patients in the intervention group and 16 in the control group) but only 36 were included in the analysis. Of the 36 patients, six were asymptomatic, 22 had upper respiratory tract infection, and eight had lower respiratory tract infection. Among the 26 patients taking hydroxychloroquine, six dropped out because of early treatment cessation. Three of these patients were transferred to the intensive care unit; one patient died, one patient with a negative test left the hospital, and another stopped treatment because of nausea. After six days of treatment, 70% (14 out of 20) of patients taking hydroxychloroquine showed a

reduction of the viral load compared to 12.5% (2 out of 16) in the control group (P = 0.001). Among the six patients using the hydroxychloroquine and azithromycin combination, 100% had a negative virologic test after six days, compared with 57.1% of patients on hydroxychloroquine only and 12.5% in the control group (< 0.001).[2,5,10] Concerning this study, the INESSS report noted the following five limitations:

- There was no random allocation of patients.
- There were no planned adjustments for confounding factors in the statistical analysis.
- The control group was composed of patients who did not accept participation in the trial or who were from other hospitals.
- Data related to the six patients who dropped out of the study were excluded from the statistical analysis, which may lead to overestimating the effect of the intervention.
- There was a lack of correlation between nasopharyngeal virologic clearance, pulmonary virologic clearance, and clinical symptom resolution.[2]

Other important limitations identified for this study include a small sample size, the variable baseline viral loads between hydroxychloroquine monotherapy and combination therapy groups as well as the fact that no clinical or safety outcomes were reported.[4]

The results from the other study conducted by the University Hospital Institute Méditerranée Infection in Marseille as an extension of the aforementioned nonrandomized controlled trial were also reported in the INESSS report (Gautret [2020b], per the INESSS report).[2] Eighty patients with a confirmed diagnosis of COVID-19 were followed; the six patients treated with hydroxychloroquine and azithromycin in the previous trial were also included. Patients were treated with hydroxychloroquine 200 mg three times daily for 10 days in combination with azithromycin 500 mg administered on the first day followed by azithromycin 250 mg daily for four days. The following key findings were reported:[2,6]

- A total of 81.3% (65 out of 80) of patients had positive outcomes and were discharged after a mean hospitalization duration of 4.1 days. Three patients were transferred to the intensive care unit.
- Nasopharyngeal viral load was negative for 83% of patients after seven days of treatment and 93% of patients after eight days of treatment.
- There was a reduction in the proportion of patients presumed to be contagious (based on polymerase chain reaction testing) after six days of treatment; there were no contagious patients after 12 days.
- Respiratory cultures were negative after five days of treatment in 97.5% of patients.
- There were few adverse events reported and those that occurred were generally mild.

The INESSS report noted that, in addition to the lack of a control group, this study shares many of the methodological limitations of the preceding non-randomized clinical trial conducted by the same group.[2]

Other Considerations

While it seems that few adverse events were reported in the trials discussed in the previous section, there is potential for harm with these therapies. Use of chloroquine and hydroxychloroquine may be associated with cardiac arrhythmia, retinopathy, hypoglycemia, and hematological abnormalities. With respect to cardiac arrhythmia, chloroquine and hydroxychloroquine may prolong the QT/QTc interval on the electrocardiogram, which may

increase the risk of a potentially life-threatening type of arrhythmia called torsade de pointes.[1,2,11 12] Use of chloroquine and hydroxychloroquine has also been associated with onset of neuropsychiatric adverse events such as agitation, insomnia, confusion, hallucinations, and psychosis.[1,2,11,12] Use of azithromycin may be associated with adverse events as well; most are gastrointestinal in nature. Less common but more serious ones would include angioedema and cholestatic jaundice. In rare cases, azithromycin use may be associated with severe allergic reactions.[13] In addition, the potential for drug interactions needs to be kept in mind. In particular, caution is warranted when azithromycin is administered to a patient with a history of a significant cardiac repolarization disorder or who is taking other drugs that cause a prolonged QT/QTc interval.[13]

Health Canada has recently approved two studies assessing the efficacy of hydroxychloroquine in the prevention of COVID-19 (Table 1).[14] Another Canadian clinical trial is assessing the effect of hydroxychloroquine for the treatment of COVID-19 (i.e., the ALBERTA HOPE COVID-19 for the Prevention of Severe COVID19 Disease [NCT04329611]). This double-blind, placebo-controlled, randomized clinical trial will determine if hydroxychloroquine administered for five days reduces the occurrence of severe COVID-19 disease in adults. In this study, hydroxychloroquine will be administered as 400 mg orally twice on the first day (loading dose) followed by 200 mg orally twice daily for four days. This trial is set to be initiated mid-April 2020 with an estimated study completion date of August 31, 2020.[15]

Table 1: Hydroxychloroquine for COVID-19 Clinical Trials Approved by Health Canada[14]

Trial name, protocol number (control number)	Title	Interventions	Authorization holder	Authorization date	Clinicaltrials.gov link
COVID19 PEP RCT - Canada, 2020-6549 (237355)	Post-exposure Prophylaxis or Preemptive Therapy for SARS-Coronavirus-2: A Pragmatic Randomized Clinical Trial (COVID19 PEP RCT - Canada)	Hydroxychloroquine (800 mg orally once, followed in 6 to 8 hours by 600 mg, then 600 mg once a day for 4 consecutive days)[16]	Research Institute of the McGill University Health Centre	March 25, 2020	NCT04308668[a]
HEROS-1 (237851)	Protecting Frontline Health Care Workers from COVID-19 with Hydroxychloroquine Pre-Exposure Prophylaxis: A randomized, Placebo-controlled Multi-Site Trial in Toronto, Canada	Hydroxychloroquine	University Health Network	April 3, 2020	NA

NA = not available; PEP = post-exposure prophylaxis; RCT = randomized controlled trial; SARS = severe acute respiratory syndrome.

[a] Estimated completion date: May 12, 2020.[16]

With respect to clinical practice, despite the still limited evidence available and statements from several professional organizations discouraging the use of hydroxychloroquine for COVID-19, an increase in the number of prescriptions for this drug has been observed in Canada.[17] This increase is impacting the Canadian supply of hydroxychloroquine for the treatment of lupus erythematosus and rheumatoid arthritis, potentially resulting in shortages for patients using this drug for proven indications.[17]

Conclusion

Evidence available at this time regarding the efficacy of chloroquine or hydroxychloroquine, used with or without azithromycin, in COVID-19 is limited both in terms of quantity and quality. The clinical studies described in this report are associated with several limitations, such as small sample size; lack of a control group; and lack of information on the comorbidities of the enrolled patients. Details on the design of some of these studies are not available.

There is currently no evidence regarding the efficacy of chloroquine or hydroxychloroquine for the prevention of COVID-19. With respect to treating COVID-19, current evidence regarding the clinical efficacy of chloroquine or hydroxychloroquine, used with or without azithromycin, has major limitations and is associated with inconsistent and uncertain findings. As such, at this time, no conclusions can be made regarding the use of these therapies for the treatment of COVID-19. However, several trials are currently underway, including some Canadian trials, and there may be more definitive answers provided in the future to the questions of interest to this brief overview.

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