Prevention and treatment of COVID-19 with chloroquine or hydroxychloroquine

Key Points:

- There is insufficient evidence that chloroquine or hydroxychloroquine will prevent or treat COVID-19
- Preliminary analysis of the largest data to date shows that treatment with hydroxychloroquine has no significant effect on disease morbidity or mortality[1]
- Use of chloroquine or hydroxychloroquine in COVID-19 patients may be associated with significant adverse effects
- Use of chloroquine or hydroxychloroquine for COVID-19 should be restricted to use in clinical trials until more data are available

Background:

Globally, there are reports of physicians prescribing chloroquine or hydroxychloroquine to otherwise healthy patients for the prevention and treatment of COVID-19. This practice threatens the Canadian supply of these drugs for patients who receive these medications on an ongoing basis (e.g., systemic lupus erythematosus, rheumatoid arthritis).

While evidence has been mostly conflicting and of low quality (e.g., small sample size, absence of a control group, significant baseline differences between control and intervention groups, or varying dosage regimens), recent analysis of the largest data to date (UK's Recovery trial) shows that hydroxychloroquine is not effective in the **treatment** of hospitalized COVID-19 patients.[1] The effectiveness of hydroxychloroquine or chloroquine in **pre- or post-exposure prophylaxis** has not been determined and is currently being assessed in clinical trials. Preliminary studies report significant adverse effects associated with the use of chloroquine or hydroxychloroquine in COVID-19 patients, including possible increase in mortality in patients with COVID-19.[2,3,4] Studies also have shown an increased risk of QTc prolongation, especially when combined with azithromycin.[1,2,3,5,6,7,8,9,10] Concerns over these significant adverse effects initially prompted the World Health Organization (WHO) to temporarily stop the hydroxychloroquine arm of the Solidarity trial;[11] however, following a review of available data on the safety of hydroxychloroquine, the WHO has resumed the study of hydroxychloroquine.[12] Similarly, following analysis of interim data from UK's large Recovery trial, the safety board found no sign of harm to study participants. Until more data become available, the use of these agents is considered strictly experimental and as such should be undertaken only through a clinical study.[13,14,15]

Clinical Studies:

In vitro studies suggest that chloroquine and hydroxychloroquine possess antiviral activity against COVID-19.[16] The following section summarizes studies based on those that found benefit and those that found harm or no benefit.

The following studies support the use of hydroxychloroquine/chloroquine for outcomes specified:

Pre- and post-exposure prophylaxis:

- In a large case-control study conducted in India, lower rates of polymerase chain reaction (PCR) confirmed SARS-CoV-2 was observed in health-care workers who received hydroxychloroquine.[17]

Viral load and time to viral RNA clearance:

Interpret with caution as these findings do not prove clinical benefit (i.e., progression of pneumonia, reduction in mortality or duration of hospitalization associated with COVID-19).

- A small open-label study conducted in France has shown that hydroxychloroquine (alone or in combination with azithromycin) may be effective in reducing viral load in nasopharyngeal samples.[18]
- A subsequent observational study by the same group in patients with mild COVID-19 disease suggests that the combination of hydroxychloroquine and azithromycin may reduce viral load.[19]
- An observational study with historical controls suggests that chloroquine shortens the time for viral clearance as well as the duration of fever in patients with mild disease.[20]
- In a small randomized trial with active comparator (lopinavir/ritonavir), treatment with chloroquine was associated with faster viral clearance than treatment with lopinavir/ritonavir.[21]

Fever, cough or pneumonia:

- In a small randomized controlled trial, hydroxychloroquine-treated patients with mild COVID-19 disease had shorter duration of fever and cough (median difference of 1 day between control group and hydroxychloroquine-treated group).[22] Hydroxychloroquine-treated patients were also more likely to exhibit radiologic improvement of pneumonia.[22]

Duration of hospitalization or mortality:

- A retrospective study conducted in China suggests that treatment with hydroxychloroquine may lower mortality in critically ill patients, possibly through a reduction in IL-6.[23]

- ~~*Similarly, a retrospective study in France suggests that the combination of hydroxychloroquine and azithromycin may reduce mortality.*~~[24] [retracted]
- Compared with lopinavir/ritonavir, chloroquine use was associated with shorter duration of hospitalization.[20]
- A large retrospective study conducted in the United States suggests that treatment with hydroxychloroquine in hospitalized patients is associated with reduced mortality.[25]

In contrast, the following studies found no benefit for the use of hydroxychloroquine/chloroquine for outcomes specified:

Pre- or post-exposure prophylaxis of COVID-19:

- A retrospective database study conducted in the United States found that patients treated with hydroxychloroquine for rheumatic or autoimmune diseases had the same risk as controls for acquiring COVID-19.[26]
- A double-blind randomized controlled trial found that hydroxychloroquine was not effective in preventing post-exposure (moderate- and high-risk exposure to confirmed COVID-19 case) COVID-19 illness.[27]

Viral load and time to viral RNA clearance:

- A randomized controlled trial conducted in China showed that treatment with hydroxychloroquine did not have a significant effect on nasopharyngeal viral load.[28]
- In an open-label randomized controlled trial, hydroxychloroquine did not have a significant effect on time to viral RNA clearance.[29]
- Similar findings were obtained in retrospective cohort studies; chloroquine[30] and hydroxychloroquine[31] were not associated with increased viral clearance.
- A small retrospective study suggests that, compared to standard care, hydroxychloroquine use is associated with delayed viral clearance.[32]

Duration of hospitalization or mortality:

- A small study used medical records of patients to compare disease progression and mortality in patients who received hydroxychloroquine with those who did not.[33] Hydroxychloroquine was not effective in reducing mortality, transfer to ICU or development of acute respiratory distress syndrome.[33]
- A retrospective study conducted in the United States showed that the use of hydroxychloroquine alone or in combination with azithromycin was associated with increased mortality.[34]
- In contrast, another retrospective study in the United States reported that hydroxychloroquine did not lower or increase the risk of death.[35]
- ~~A large multinational data registry study of 96 032 patients across 671 hospitals found that the use of hydroxychloroquine or chloroquine, alone or in combination with a macrolide, was associated with a significant increase in mortality and ventricular arrythmias.~~[4] [retracted]
    - *The data and methodology used in this study have been questioned and the publishing journal,* The Lancet*, has issued a statement of concern about this paper.*[36] *The authors have subsequently retracted this paper.*
- Preliminary analysis of data from UK's Recovery trial (1542 hospitalized patients randomized to hydroxychloroquine and compared with 3132 patients randomized to usual care alone), showed that hydroxyxhloroquine is ineffective in reducing mortality, duration of hospitalization and disease outcomes.[1] The investigators have therefore stopped enrolling patients to the hydroxychloroquine arm of the Recovery trial.[1] Similarly, both the WHO and the NIH have halted the hydroxychloroquine arms of the trials (Solidarity and ORCHID trial, respectively).[37, 38]

Recommendation:

Pharmacists must use their professional judgment to question the appropriateness of any prescriptions they receive for chloroquine or hydroxychloroquine that are outside the usual indications. This is important to protect patients from unnecessary adverse effects and to protect the supply of these medications for those patients who rely on them for treatment of medical conditions (e.g., systemic lupus erythematosus, rheumatoid arthritis) for which they are indicated.

The COVID-19 situation is evolving, and data collection is ongoing. The evidence regarding the use of chloroquine or hydroxychloroquine in the treatment of COVID-19 will be reviewed as it becomes available and this statement will be updated accordingly.

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Updated to reflect evolving evidence:

- 29 March 2020 to include references 19 and 26
- 2 April 2020 to include reference 22

- 17 April 2020 to include references 2, 3, 5, 15, 29, 31 and 33
- 13 May 2020 to include references 6, 7, 8, 9, 10, 20, 21, 23, 24, 28, 30, 31, 32 and 35
- 26 May 2020 to include references 4 and 11; reference 24 has been retracted
- 5 June 2020 to include references 12, 27 and 34; reference 4 has been retracted
- 7 June 2020 to include reference 1
- 15 June 2020 to include reference 17
- 23 June 2020 to include references 37 and 38
- 10 July 2020 to include reference 25

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