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MINI REVIEW

Integrative Clinical Medicine & Therapeutics

Hydrooxychloroquine for the SARS-Cov-2 Infection: Current Evidences and Way Forward

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Abstract

Despite limited and conflicting data on the use of Chloroquine and hydroxychloroquine in patients with Covid-19, the U.S. Food and Drug Administration (FDA) authorized the emergency use of these drug on March 28, 2020 given the clinical trials are unavailable or infeasible. Hydroxychloroquine, alone or in combination with azithromycin, is being widely used in Covid-19 therapy based on anecdotal and limited observational evidence. This commentary reviews its use for treatment and prophylaxis for SARS-COV-2 infections based on scientific evidences.

Hydroxychloroquine is a less toxic metabolite of the antimalarial drug chloroquine and is used as an immunomodulator for the treatment of autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus [1-3]. Chloroquine and hydroxychloroquine have been demonstrated to inhibit viral infection in cell culture [4-6], leading investigators to hypothesize that they may have an in vivo antiviral effect. Despite the absence of good controlled clinical trial evidence of its effectiveness, hydroxychloroquine has gained widespread use in the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.

In other times, the absence of good clinical data would have precluded such use of a drug in patients. However, during this difficult time of the coronavirus disease 2019 (COVID-19) pandemic, news reports on the scant data that currently exists on the use of hydroxychloroquine for SARS-CoV-2 and the endorsement of hydroxychloroquine by the President of the United States has influenced the public perception of its effectiveness and the medical response. On March 28, 2020, the US Food and Drug Administration issued an emergency use authorization for hydroxychloroquine for patients with COVID-19 [7].

Research conducted during and after the 2003 SARS-CoV-1 outbreak in China demonstrated in vitro antiviral effects of chloroquine and hydroxychloroquine against this virus [4,8]. Chloroquine [2,9] and hydroxychloroquine [2,10] have been shown to also inhibit SARS-CoV-2 growth in cell culture.

In February 2020, it was announced by China that chloroquine was found to be more effective than control treatment in clinical trials of patients with COVID-19 [11]. Officials announced that chloroquine treatment prevented worsening of pneumonia, improved findings on lung imaging, facilitated conversion to virus-negative status, and reduced disease duration, without significant side effects [11], leading to a panel recommendation in that country for its use in COVID-19 [12]. This soon led to the global use of hydroxychloroquine for COVID-19 [13].

Gautret, et al. subsequently published a study that set out to examine the effect of hydroxychloroquine (200 mg 3 times a day for 10 days) on nasopharyngeal SARS-CoV-2 viral load in patients with confirmed infection [14]. They enrolled 26 hospitalized patients with COVID-19 infection at a single hospital to receive hydroxychloroquine; they also enrolled 16 patients with COVID-19 infection who refused inclusion or did not meet inclusion criteria at that hospital, as well as patients at 3 other hospitals, as controls.

Of the 26 patients who received hydroxychloroquine, 6 were not included in the final analysis; they were considered lost to follow-up because of transfer to the intensive care unit (ICU; 3 patients), death (1 patient), leaving hospital (1 patient), and stopped treatment (1 patient). The average age of the group receiving hydroxychloroquine was older than the control group (not quite statistically significant); there was not a statistically significant difference in clinical status. Six patients in the hydroxychloroquine-treated group also received azithromycin to prevent bacterial superinfection [14].

The investigators found that on days 3, 4, 5, and 6 there was a statistically significant difference in the number of patients with a negative viral load between the 2 groups, such that by day 6 the viral load was negative in 70% of patients in the hydroxychloroquine-treated group vs 12.5% in the control group [14].

The researchers went on to compare the hydroxychloroquine-treated group (n = 14) with the hydroxychloroquine plus azithromycin-treated group (n = 6). They found a significant difference in the number of patients with a negative viral load on days 3, 4, 5, and 6 in favour of the combination treatment, with 100% of patients in the combination group virus-negative compared with 57.1% in the hydroxychloroquine-alone group on day 6 [14]. Of note, however, of the 6 patients in the hydroxychloroquine-treated group who did not have a negative viral load at day 6, four participants demonstrated a higher viral load on day 0 than any of the patients who received hydroxychloroquine plus azithromycin [14], implying that initial viral load may have played an important role in day 6 viral load.

Subsequent to this study, another group from France reported on 11 consecutive patients who received hydroxychloroquine plus azithromycin dosed as per the Gautret study [15]. Of these patients, 1 died and 8 of the remaining 10 had persistent positive SARS-CoV-2 viral loads at days 5 and 6 [15].

In another study conducted in China, 30 patients were randomly assigned to receive hydroxychloroquine (400 mg/d for 5 days) or control standard treatment; clinical findings were similar between the groups at study onset [16]. In this study, there was no difference in viral load between the 2 groups on day 7, with 86.7% of the study group and 93.3% of the control group reported as being virus-negative [16].

Most recently, a report by Chen et al presented data from a study including 62 patients with non-severe, noncritical COVID-19 who were randomly assigned to receive hydroxychloroquine (200 mg twice a day for 5 days) or standard treatment.[17] Results showed that duration of fever (2.2 vs 3.2 days) and cough (2.0 vs 3.1 days) was shorter among members of the group receiving hydroxychloroquine, and that more patients receiving hydroxychloroquine had improved findings on chest computed tomographic imagingy.[17] The study authors also noted that of the 62 patients enrolled, 4 patients, all in the standard treatment group, demonstrated progression to severe infection [17].

Given the encouraging in vitro data against a host of viruses, animal models have been used to study the efficacy of chloroquine in treating a variety of non-COVID-19 viral infections, and results have been variable [18]. Human trials of chloroquine for the prevention or treatment of influenza [19], dengue [20], and chikungunya [21,22] viruses have not demonstrated efficacy. The evidence thus far for the use of hydroxychloroquine in the treatment of human infection with SARS-CoV-2 is based on encouraging in vitro data, very small clinical studies, and anecdotal observation.

The randomized study by Chen, et al. [17] was small and did not include patients with severe disease. It is notable, however, that only 4 of 62 patients progressed from non-severe disease to severe disease, implying that the study population had quite mild illness. The other randomized study reported [16] examined viral loads and did not find a difference in viral load between hydroxychloroquine-treated and untreated patients at day 7. Conversely, Gautret, et al. noted improved viral loads among patients in the hydroxychloroquine-treated group compared with untreated patients. However, this was a small, nonrandomized study in which the control group was culled from several hospitals with likely differing standard therapies, and 4 patients in the hydroxychloroquine group who required care in an intensive care unit or died were not included in the analysis [14]. The study that evaluated azithromycin was observational in nature and few conclusions could be surmised from the set of azithromycin data [14]. It should also be noted that there is concern for QTc prolongation and torsades de pointes with even short-term use of hydroxychloroquine for COVID-19 [23].

Hence, larger and well-designed randomized controlled trials are required to better understand if hydroxychloroquine has a role in the treatment or prophylaxis of COVID-19. In the United States and elsewhere, several such trials are ongoing and hopefully data will be available soon [24].

References

1. Schrezenmeier E, Dorner T. Mechanisms of action of hydroxychloroquine and chloroquine: implications for rheumatology. *Nature Rev*. 2020; 16: 155-166.
2. Lee SJ, Silverman E, Bargman JM. The role of antimalarial agents in the treatment of SLE and lupus nephritis. *Nat Rev Nephrol*. 2011; 7: 718-729.
3. Liu J, Cao R, Xu M, Wang Xi, Zhang H, et al. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. *Cell Discovery*. 2020; 6: 16.
4. Colson P, Rolain J-M, Lagier J-C, Brouqui P, Raoult D, et al. Chloroquine and hydroxychloroquine as available weapons to fight COVID-19. *Int J Antimicrob Agents.* 2020; 55: 105932.
5. Rolain J-M, Coilson P, Raoult D. Recycling of chloroquine and its hydroxyl analogue to face bacterial, fungal and viral infections in the 21st century. *Int J Antimicrob Agents.* 2007; 30: 297-308.
6. Savarino A, Boelaert JR, Cassone A, Majori G, Cauda R. Effect of chloroquine on viral infections: an old drug against today's diseases. *Lancet Infect Dis*. 2003; 3: 722-727.
7. Lenzer J. Covid-19: US gives emergency approval to hydroxychloroquine despite lack of evidence. *British Med J*. 2020.
8. Keyaerts E, Vijgen L, Maes P, Neyts J, Ranst MV. In vitro inhibition of severe acute respiratory syndrome coronavirus by chloroquine. *Biochem Biophys Res Comm*. 2004; 323: 264-268.
9. Wang M, Cao R, Zhang L, Yang X, Liu J, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019 nCoV) in vitro. *Cell Res*. 2020; 30: 269-271.
10. Yao X, Ye F, Zhang M, Cui C, Huang B, et al. In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). *Clin Infect Dis*. 2020.
11. 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.

12. Zhonghua Jie He He Hu Xi Za Zhi. 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 [in Chinese]. 2020; 43: 185-188.
13. Devaux CA, RolaIn J-M, Colson P, Raoult D. New insights on the antiviral effects of chloroquine against coronavirus: what to expect for COVID-19?. *Int J Antimicrob Agents*. 2020. 55: 105938.
14. Gautret P, Lagier JC, Parola P, Hoang VT, Meddeb L, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Int J Antimicrob Agents*. 2020: 105949.
15. Molina J, Delaugerre C, Le Goff Breno J, Mela-Lima B, Ponscarme D, et al. No evidence of rapid antiviral clearance or clinical benefit with the combination of hydroxychloroquine and azithromycin in patients with severe COVID-19 infection. *Med Mal Infect*. 2020; 50: 384.
16. Chen J, Liu D, Liu L, Liu P, Qingnian Xu, et al. A pilot study of hydroxychloroquine sulfate in patients with common 2019 coronavirus disease-19 (COVID-19) [in Chinese]. *J Zhe Jiang University (Medical Sciences)*. 2020; 49: 215-219.
17. Chen Z, Hu J, Zhang Z, Jiang SS. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. *Med Rxiv*. 2020.
18. Touret F, de Lamballerie X. Of chloroquine and COVID-19. *Antiviral Res*. 2020.
19. Paton NI, Lee L, Xu Y, Ooi EE, Cheung YB, et al. Chloroquine for influenza prevention: a randomized, double-blind, placebo controlled trial. *Lancet Infect Dis*. 2011; 11: 677-683.
20. Tricou V, Minh NN, Van TP, Lee SJ, Farrar J, et al. A randomized controlled trial of chloroquine for the treatment of dengue in Vietnamese adults. *PLOS Negl Trop Dis*. 2010; 4: e785.
21. De Lamballerie X, Boisson V, Reynier JC, Enault S, Charrel RN, et al. On chikungunya acute infection and chloroquine treatment. *Vector Borne Zoonotic Dis*. 2008; 8.
22. Roques P, Thiberville S-D, Dupuis-Maguiraga L, Lum FM, Labadie K, et al. Paradoxical effect of chloroquine treatment in enhancing chikungunya virus infection. *Viruses.* 2018; 10: 268.
23. Giudicessi JR, Noseworthy P, Friedman PA, Ackerman MJ. Urgent guidance for navigating and circumventing the QTc prolonging and torsadogenic potential of possible pharmacotherapies for COVID-19. *Mayo Clin Proc.* 2020; 95: 1213-1221.
24. United States National Library of Medicine. *Clinical Trials.* Accessed April 28, 2020.
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Rec: Mar 15, 2020; Acc: Apr 25, 2020; Pub: Apr 27, 2020

Int Clin Med Therp. 2020;2(1):10
DOI: 10.36879/ICMT.20.000110

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