

HYDROXYCHLOROQUINE (HCQ) AND CHLOROQUINE (CQ)

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Introduction

Hydroxychloroquine (HCQ) and Chloroquine (CQ) are well-known drugs for their effectiveness in treating malaria and autoimmune diseases. The hydroxyethyl group of HCQ makes it more soluble, less toxic, with lesser side effects and hence safer than CQ.¹

Mechanism of Action

HCQ and CQ inhibit viral entry by inhibition of synthesis of sialic acid and by disruption of protein glycosylation interfering viral attachment and entry.^{2,3} They interfere with viral release into host cell by increasing endosomal pH, blocking the proteases responsible for coronavirus/endosomal fusion that release virus into cell.^{2,4} HCQ reduces viral infectivity by inhibiting protein glycosylation and maturation of viral protein.^{2,5} HCQ's immune modulation is demonstrated by reduction of Toll-like Receptors and cGAS-STING signaling which reduce the release of proinflammatory cytokines.^{2,6}

Efficacy and Safety of HCQ and CQ on COVID-19

*Efficacy and Safety of HCQ or CQ **Monotherapy** for COVID-19*

There are 3 randomized controlled trials and 2 observational studies completed on the efficacy and safety of hydroxychloroquine for COVID-19. Improvement in CT scan findings were observed among those who received standard of care and hydroxychloroquine compared to those who received standard of care alone.^{7,8} No significant differences with the time of normalization of temperature were detected nor with the reduction of admissions to ICU or deaths in the two treatment groups.^{7,8,9} There were differences however in the standard of care used for the 3 studies. Use of co-therapies (immunoglobulin, corticosteroids and other antimicrobials) was the standard of care for the study of Chen.⁷

In an observational study of 1376 patients admitted due COVID-19, hydroxychloroquine administration was not associated with intubation or death (hazard ratio, 1.04, 95% confidence interval, 0.82 to 1.32).¹⁰

A parallel, double-masked randomized, phase IIb clinical trial of 81 adult patients with severe COVID-19 was stopped due to high mortality rate (39%; 16 of 41 patients) among those who received high dose CQ (600 mg CQ; 4 × 150 mg tablets twice daily for 10 days; total dose 12 g).¹¹

The WHO in July 2020, upon the recommendation of the Solidarity Trial, agreed to discontinue the trials on the use of Hydroxychloroquine (versus the standard of care) and Lopinavir/Ritonavir (versus standard of care) only in

hospitalized patients with COVID-19. However, evaluations on its use in non-hospitalized and pre- and post-exposure prophylaxis are not affected by this decision.¹²

A living systematic review and network meta-analysis done to compare the effects of treatments for COVID-19 showed that hydroxychloroquine might reduce the symptom duration of illness (-4.5 days, low certainty) but also has an increased risk of developing adverse events.¹³ A randomized trial of HCQ as post exposure prophylaxis did not differ significantly between participants with HCQ (11.8%) and placebo (14.3%); the absolute difference was -2.4% (95% CI, -7.0 to 2.2; P=0.35). Side effects were more common with HCQ (40.1% vs 16.8%), though not serious.¹⁴

Efficacy of Hydroxychloroquine and Azithromycin for COVID-19

There is only one open-label clinical trial¹⁵ and 2 observational studies.^{16,17} on the use of hydroxychloroquine and azithromycin for patients with COVID-19. The use of the combination therapy was associated with a reduction in the viral RNA load, however results of the study should be interpreted with caution due to the methodologic concerns and a small sample size.¹⁵

In contrast, a recent multicenter, randomized, open label, three group, controlled trial involving hospitalized patients with suspected or confirmed COVID-19 concluded that the use of hydroxychloroquine, alone or with Azithromycin, did not improve clinical status of the patients.¹⁸

The Philippine Society for Microbiology and Infectious Diseases (PSMID) has recommended in their interim guidelines NOT to use HCQ except in context of a clinical trial. This holds for post-exposure prophylaxis and in hospitalized, probable or confirmed COVID-19 cases with moderated to severe pneumonia. This recommendation also includes outpatients with early or mild COVID-19 disease.¹⁹

Several national and society guidelines (China, Italy, Netherlands, Belgium) have initially included HCQ in the management of COVID-19 pneumonia^{20,21, 22} before the WHO directives to stop the drug. The latest update of Belgium's guideline no longer recommends its off-label use for COVID-19, except within ongoing clinical registered trials.²² In a survey of Indian doctors, however, they are still following the national guidelines provided by The Indian National Task Force and they will still recommend HCQ in the management of COVID-19 patients both as prophylaxis and in mild to moderate COVID-19.²³ There are ongoing clinical trials on the use of HCQ or CQ as monotherapy or in combinations for patients with COVID-19.(Appendix 10)

Adverse Effects

The use of HCQ or CQ in patients with COVID-19 has been associated with QTc prolongation and torsades de pointes.^{9, 24} The development of acute renal failure among those given the combination of HCQ and azithromycin was a strong predictor of severe QTc prolongation.²⁴ Use of HCQ should be avoided or used with caution and partnered with close monitoring in those with prolonged

baseline QTc interval or on other agents that affect cardiac conduction. Other adverse effects reported among patients with COVID-19 given HCQ were rash, diarrhea, nausea, vomiting and increase in aspartate aminotransferase.^{7,8,15,16}

Conclusion

There is no high-quality evidence on the efficacy of HCQ and CQ either as monotherapy or in combination with other drugs for COVID-19. HCQ and CQ have the potential for toxicity and lethality when given at high doses. HCQ and CQ should NOT be used in hospitalized COVID-19 patients. Its use in the outpatient setting, for pre and post exposure during the pandemic as interim management for COVID-19 should be weighed versus the risks associated with them.

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