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## Uncontrolled mass use of hydroxychloroquine

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### ABSTRACT

Hydroxychloroquine (HCQ) has previously been shown to inhibit coronavirus replication in vitro. But antiviral properties mechanisms are not well known, HCQ is a weak base that accumulates in lysosomes, modifies their pH, and interferes with some enzymes. In the lack of confirmed efficacy, the initial potential risk is not to expose patients to adverse effects. However, results from preliminary clinical studies have drawn inconclusive results regarding the efficacy of HCQ in coronavirus disease 2019 (COVID-19), due to several important weaknesses in research methodologies. Hypokalemia often occurs in patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), possibly due to the particular tropism of SARS-CoV-2 with regard to Angiotensin-converting enzyme 2 (ACE2). The wide use of HCQ, even against medical advice, will show an impact on ongoing clinical trials. It is important that we can recruit COVID-19 patients in these research studies to generate appropriate data regarding drugs that show promising efficacy against COVID-19. Currently, only doctors should be allowed to prescribe HCQ, and treatment should be confined to hospital settings, with proper cardiac and therapeutic drug monitoring.



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### INTRODUCTION

In addition to being an antimalarial drug, hydroxychloroquine (HCQ) also exhibits anti-inflammation and immunomodulation by regulating the production of  $TNF\alpha$ , interferons, and some cytokines (Weber and Levitz, 2000; Müller-Calleja et al., 2017). HCQ inhibits replication in a variety of viruses (Miller and Lenard, 1981). Even anti-viral properties mechanisms are not well known, HCQ is a weak base that accumulates in lysosomes, modifies their pH, and interferes with some enzymes. Thus, HCQ can inhibit the pH-dependent entry of some

viruses into host cells, or even block the enveloped viruses replication by inhibition the glycosylation of envelope proteins (Savarino *et al.*, 2006). These in vitro anti-viral effects suggest the potential use of HCQ in the treating viral infections, against which there are no effective drugs, or against which drugs exist but cannot be seen globally, mostly in low-income countries (Savarino *et al.*, 2003).

## RISKS OF UNCONTROLLED MASS USE

In the lack of confirmed efficacy, the initial potential risk is not to expose patients to adverse effects. The common side effects are abdominal pain or diarrhoea, which seen in almost 10% of patients as well as pruritus and rashes. Headache, dizziness, and tinnitus have also been reported. Additionally, adverse psychiatric effects ranging from anxiety disorders and insomnia to psychotic decompensations are even reported. Psychotic side effects, such as hallucinations and delusions, are frequent than depression. Serious psychiatric effects resulting from HCQ treatment are infrequent within the structure of conventional prescription. Because of the anxiety-provoking nature of the coronavirus disease 2019 (COVID-19) pandemic, and the desire to limit the spread of the disease, the prevalence of these undesirable effects is likely to increase.

HCQ also induces adverse cardiac effects due to its inhibitory effect on the human *ether-a-go-go*-related gene (hERG) potassium ( $K^+$ ) channels, which repolarize phase 3 cardiomyocyte action potentials in potassium efflux. This effect increases the risk of a prolonged corrected QT interval (QTc) on a surface electrocardiogram (ECG) (Borsini *et al.*, 2012). Although this toxicity is dose-dependent and, cases of serious arrhythmias are shown at therapeutic doses. Risk factors for QTc prolongation that can facilitate such arrhythmias include a slow heart rate (<55 bpm) and female sex (Drici and Clément, 2001) as well as hypokalemia in combination with other drugs that lengthen the QTc.

Hypokalemia often occurs in patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), possibly due to the particular tropism of SARS-CoV-2 concerning Angiotensin-converting enzyme 2 (ACE2) (French Society of Pharmacology and Therapeutics, 2020). Additionally, diarrhoea and vomiting may accompany the infection. It is important to check serum  $K^+$  levels and rectify any hypokalemia before HCQ treatment, which can itself cause diarrhoea. Relatively, the combination of azithromycin, which causes QT prolongation, with HCQ, justifies reinforced monitoring with ECGs, mostly, initiation of therapy and within 3-4 h after

the administration of the first dose. It should then be monitored two times a week for the treatment duration or in the event of symptoms suggestive of dysrhythmia. The dose-limiting adverse effect of HCQ is the retinopathy risk, which affects 8% of treated patients, mostly at high doses (> 5 mg/kg) or prolonged treatment (> 5 years) (Jorge *et al.*, 2018).

HCQ is metabolized by cytochrome P450 (CYP) isoforms, especially 3A4/5, 2D6, and 2C8, there is an elevated risk of adverse effects with drugs that inhibit these CYPs. If it is COVID-19, interest should be taken with other anti-virals, such as the lopinavir/ritonavir (LPV/R), which inhibits CYP3A. In France, several cases of serious adverse cardiac effects have been linked to the treatment with HCQ in COVID-19 patients.

Remdesivir showed inhibition against SARS-CoV and MERS-CoV in human airway epithelial cells, at early stages of replication by inhibiting viral RNA synthesis (Yethindra, 2020). The LPV/R, a strategy that prescribed for many years to treat HIV patients; LPV/R in the presence of interferon- $\beta$ , an immunomodulatory and anti-viral drug, and HCQ. In this study, treatment with one of these drugs in the 29 days preceding randomization was a criterion for non-inclusion. The inability to quickly conclude the effectiveness of these different treatments would be extremely detrimental to public health. In the context of a pandemic, it is difficult to conduct randomized controlled trials until such pandemics are brought under control.

## USE OF HCQ IN COVID-19

At the present COVID-19 pandemic, in vitro data showed that HCQ has some anti-viral activity against SARS-CoV-2 compared to other drugs, with a lower half-maximal effective concentration for HCQ (0.72  $\mu$ M vs 5.47  $\mu$ M), showing that it is more potent (Yao *et al.*, 2020). HCQ should not be used, except in severe cases where patients have been hospitalized, and based on decisions made by doctors and under strict medical supervision. HCQ should not be prescribed to healthy people or for non-life-threatening cases of COVID-19.

HCQ is prescribed in treating autoimmune diseases (Mok, 2017). Within the framework of the management of COVID-19, high variability in concentrations is expected in the light of the people likely to be treated (i.e., old or dialysis patients) (Guilhaumou *et al.*, 2019). Additionally, given the short duration of the proposed treatment, steady-state concentrations may not be reached, thereby increasing pharmacokinetic variability. Based on our findings, we estimated that

the low threshold was 0.1  $\mu\text{g/mL}$  and 0.3  $\mu\text{g/mL}$  for plasma and total blood assay. These values may change depending on future data.

## CONCLUSION

HCQ showed *in vitro* activity against SARS-CoV-2, and high-quality research studies are conducted at present. It is important that we can recruit COVID-19 patients in these research studies to generate appropriate data regarding drugs that show promising efficacy against COVID-19. The absence of confirming benefits related to existing adverse effects of HCQ. Although it is relatively well tolerated at therapeutic doses and for a short time, it is a drug with a narrow therapeutic window and one that requires cardiac and pharmacological monitoring to limit the severe adverse effects already reported in COVID-19 patients. This is particularly true considering polypharmacy, especially with azithromycin. Therefore, HCQ treatment must be limited to use in clinical environments and under appropriate supervision.

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## Conflict of Interest

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## REFERENCES

- Borsini, F., Crumb, W., Pace, S., Ubben, D., Wible, B., Yan, G.-X., Funck-Brentano, C. 2012. In Vitro Cardiovascular Effects of Dihydroartemisinin-Piperaquine Combination Compared with Other Antimalarials. *Antimicrobial Agents and Chemotherapy*, 56(6):3261–3270.
- Drici, M.-D., Clément, N. 2001. Is Gender a Risk Factor for Adverse Drug Reactions? *Drug Safety*, 24(8):575–585.
- French Society of Pharmacology and Therapeutics 2020. ACE2, IEC/ARAI and COVID-19 infections. Therapies.
- Guilhaumou, R., Benaboud, S., Bennis, Y., Dahyot-Fizelier, C., Dailly, E., Gandia, P., Goutelle, S., Lefeuvre, S. 2019. Optimization of the treatment with beta-lactam antibiotics in critically ill patients—guidelines from the French Society of Pharmacology and Therapeutics (Société Française de Pharmacologie et Thérapeutique—SFPT) and the French Society of Anaesthesia and Intensive Care Medicine (Société Française d'Anesthésie et Réanimation—SFAR). *Critical Care*, 23(1).
- Jorge, A., Ung, C., Young, L. H., Melles, R. B., Choi, H. K. 2018. Hydroxychloroquine retinopathy — implications of research advances for rheumatology care. *Nature Reviews Rheumatology*, 14(12):693–703.
- Miller, D. K., Lenard, J. 1981. Antihistaminics, local anesthetics, and other amines as antiviral agents. *Proceedings of the National Academy of Sciences*, 78(6):3605–3609.
- Mok, C. C. 2017. Therapeutic monitoring of the immuno-modulating drugs in systemic lupus erythematosus. *Expert Review of Clinical Immunology*, 13(1):35–41.
- Müller-Calleja, N., Manukyan, D., Canisius, A., Strand, D., Lackner, K. J. 2017. Hydroxychloroquine inhibits proinflammatory signalling pathways by targeting endosomal NADPH oxidase. *Annals of the Rheumatic Diseases*, 76(5):891–897.
- Savarino, A., Boelaert, J. R., Cassone, A., Majori, G., Cauda, R. 2003. Effects of chloroquine on viral infections: an old drug against today's diseases. *The Lancet Infectious Diseases*, 3:722–727.
- Savarino, A., Trani, L. D., Donatelli, I., Cauda, R., Cassone, A. 2006. New insights into the antiviral effects of chloroquine. *The Lancet Infectious Diseases*, 6:67–69.
- Weber, S. M., Levitz, S. M. 2000. Chloroquine Interferes with Lipopolysaccharide-Induced TNF- $\alpha$  Gene Expression by a Nonlysosomotropic Mechanism. *The Journal of Immunology*, 165(3):1534–1540.
- Yao, X., Ye, F., Zhang, M., Cui, C., Huang, B., Niu, P. 2020. 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*.
- Yethindra, V. 2020. Role of GS-5734 (Remdesivir) in inhibiting SARS-CoV and MERS-CoV: The expected role of GS-5734 (Remdesivir) in COVID-19 (2019-nCoV) - VYTR hypothesis. *International Journal of Research in Pharmaceutical Sciences*, 11(SPL1):1–6.