# EDITORIAL

# COVID-19 and Chloroquine/Hydroxychloroquine: Is There Ophthalmological Concern?

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CHLOROQUINE (CQ) AND HYDROXYCHLOROQUINE (HCQ) are generic antiviral agents that have shown effectiveness against severe acute respiratory syndrome (SARS) virus infection, and in this time of pandemic, physicians are trying any plausible approach to therapy.[1] News reports have appeared recently about China starting trials with a variety of medications to treat coronavirus 2019 (COVID-19) infection, including both of those agents.[2] In fact, at least 10 trials have started now in different countries.[3] The Chinese are giving a course of CQ, 500 mg twice daily, for up to 10 days, or 400 mg of HCQ 4 times daily, and these extreme doses have raised concerns about retinal damage.

CQ and HCQ are well known to ophthalmologists because of retinal toxicity after long-term usage for systemic lupus erythematosus and other rheumatoid diseases. Retinopathy is seen infrequently before 10 or more years of usage at the American Academy of Ophthalmology (AAO) recommended dosage of <5 mg/kg/day real weight.[4] However, the doses proposed to treat COVID-19 are 4-5 times higher, and it is important that our specialty be informed whether there is ocular risk from these short-term treatments. Do we need to be worried, and what, if anything, should ophthalmology be doing?

Even though the Chinese COVID-19 doses are extremely high, they are used for a very brief period of time. High-dose HCQ has been used for other medical treatments. Some rheumatologists have been giving 1,200 mg/day for 6 weeks as a loading dose when starting HCQ therapy for systemic lupus erythematosus, and no visual losses have been reported, although detailed ophthalmologic examinations were not performed.[5,6] Two trials of treatment of myeloma and solid tumors used 1,200 mg/day for 4-8 weeks, and again no visual loss was reported.[7,8] The only high-dose ophthalmologic study by Leung and associates[9] followed 7 patients at 3-month intervals for 7-25 months while using 1,000 mg/day HCQ therapy for small-cell lung cancer. By patient weight, these doses were 3-5 times greater than that recommended by the AAO. Two patients developed subtle and suggestive changes on optical coherence tomography in the parafoveal ellipsoid zone after 11 and 17 months and definitive toxicity after 15 and 25 months. None of the other patients showed damage. Thus, evidence to date indicates that extreme doses do accelerate retinal toxicity but with a probable time course of many months rather than days.

As this is being written, other reports are coming out that may alter the landscape of CQ and HCQ usage, and more reports will show up by the time this one is published. For example, a prepublication just appeared of a small French trial of 22 COVID-19-positive patients using 600 mg/day HCQ for 10 days to reduce the viral load.[10] The number of polymerase chain reaction-positive cases fell nearly 50% relative to those of controls and dropped to nearly zero if azithromycin was added. The HCQ dosage of 600 mg/day is only approximately twice that recommended by the AAO, on average, and should present no risk of retinopathy in this time frame. News media are now also citing interest in the use of CQ or HCQ intermittently as prophylaxis, much like the use for malaria, although doses have not been mentioned.

Ophthalmologists should judge all of this evolving information in light of well-established knowledge about dose, weight, and duration as the primary determinants of risk of retinopathy.[11] Older studies used to cite 1,000 g/day as a "toxic" dose of HCQ, but measurements of absolute usage are misleading with respect to retinopathy because toxicity relates to *dose by weight*.[4,11] People come in all sizes, and 400 mg means something very different in terms of risk to a small woman than it does to a large man. Short-term trials (less than 2 weeks) will have negligible risk, even with doses 5-6 times the usual recommended maximum dosage of <5 mg/kg/day. Usage for a few months will still have very low risk with doses less than 3-4 times the usual level. However, if physicians suggest using these drugs for a year or more, I would strongly advise staying within the AAO recommendation and screening the patient annually.

The bottom line: I do not believe ophthalmic screening is necessary for COVID-19 patients who take CQ or HCQ for less than 2 weeks as antiviral therapy, because the likelihood of retinal damage is exceedingly low, even with high doses. In a time of pandemic with worldwide shortages of

Accepted for publication Mar 22, 2020.

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0002-9394/$36.00
https://doi.org/10.1016/j.ajo.2020.03.029

medical personnel, funds, hospital beds, equipment, screening tests, and proven therapy, it would be counterproductive (and raise inappropriate fears) to suggest the addition of labor-intensive and expensive eye examinations that are of low yield. However, as new protocols arise, these steps will need to be evaluated relative to the risk of retinopathy that their particular doses and durations of use may pose. Ophthalmologists will be most effective in this time of crisis by reassuring physicians and the public where retinopathy is not a serious concern with respect to CQ or HCQ usage for coronavirus.

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