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 SARS virus, 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 (COVID-19), including both of these agents.[2] In fact, at least 10 trials have started now in different countries.[3] The Chinese are giving typically up to a 10-day course of 500 mg CQ twice daily, or 400 mg HCQ four 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 (SLE) and other rheumatoid diseases. Retinopathy is infrequently seen before 10 or more years of usage at American Academy of Ophthalmology (AAO) recommended dosage of <5 mg/kg 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 worry, 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 had been giving 1200 mg/day for 6 weeks as a loading dose when starting HCQ for SLE, and no visual loss was reported although detailed ophthalmologic exams were not performed.[5,6] Two trials on treatment of myeloma and solid tumors used 1200 mg/day for 4-8 weeks, and again no visual loss was reported.[7,8] The only high-dose ophthalmologic study by Leung et al followed 7 patients at 3-month intervals for 7-25 months while using 1000 mg/day of HCQ for small-cell lung cancer.[9] By patient weight these doses were 3-5 times greater than the AAO recommendation. Two patients developed subtle and suggestive OCT changes in the parafoveal ellipsoid zone after 11 and 17 months, and definitive toxicity after 15 and 25 months. None of the others 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 will show up by the time this is published. For example, a pre-publication just appeared on a small French trial of 22 COVID-19 positive patients using 600 mg/day of HCQ for 10 days to reduce the viral load.[10] The number of PCR-positive cases fell nearly 50% relative to controls, and it dropped to nearly zero if azithromycin was added. This dose is only about 2 times AAO recommended levels on average and should have no risk of retinopathy in this time frame. News media are now also citing interest in using 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 retinopathy risk.[11] Older literature used to cite 1000 g/day as a "toxic" dose of HCQ, but measures of absolute usage are misleading with respect to retinopathy, since toxicity relates to *dose by weight*.[4,11] People come in all sizes, and 400 mg means something very different risk-wise to a small woman than to a large man. Short-term trials (under 2 weeks) will have negligible risk even with doses 5-6 times the usual 5 mg/kg/day maximum recommendation. Usage for a few months will still have very low risk with doses under 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 annually.

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 anti-viral therapy, since the likelihood of retinal damage is exceedingly low even with high doses. In a time of pandemic with world-wide shortages of 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 exams that

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are of low yield. However, as new protocols arise these will have to 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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REFERENCES

1. 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;11:105938.
2. Gao J, Zhenxue T, Yang X. Breakthrough: chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. *Biosci Trends* 2020;14(1):72–73.
3. Harrison C. Coronavirus puts drug repurposing on the fast track. *Nat Biotechnol* 2020; https://doi.org/10.1038/d41587-020-00003-1. [Epub ahead of print].
4. Marmor M, Kellner U, Lai TY, Melles RB, Mieler WF. Recommendations on screening for chloroquine and hydroxychloroquine retinopathy (2016 revision). *Ophthalmology* 2016;123(6):1386–1394.
5. Furst DE, Lindsley H, Baethge B, et al. Dose-loading with hydroxychloroquine improves the rate of response in early, active rheumatoid arthritis: a randomized, double-blind six-week trial with eighteen-week extension. *Arthritis Rheum* 1999;42(2):357–365.
6. Munster T, Gibbs JP, Shen D, et al. Hydroxychloroquine concentration-response relationships in patients with rheumatoid arthritis. *Arthritis Rheum* 2002;46(6):1460–1469.
7. Vogl DT, Stadtmauer EA, Tan KS, et al. Combined autophagy and proteasome inhibition: a phase 1 trial of hydroxychloroquine and bortezomib in patients with relapsed/refractory myeloma. *Autophagy* 2014;10(8):1380–1390.
8. Rangwala R, Chang YC, Hu J, et al. Combined MTOR and autophagy Inhibition: phase I trial of hydroxychloroquine and temsirolimus in patients with advanced solid tumors and melanoma. *Autophagy* 2014;10(8):1391–1402.
9. Leung LB, Neal JW, Wakelee HA, Sequist LV, Marmor MF. Rapid onset of retinal toxicity from high-dose hydroxychloroquine given for cancer therapy. *Am J Ophthalmol* 2015;160(4):799–805.
10. Gautret P, Lagier J-C, Parola P, Hoang VT, Meddeb L, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of anopen-label non-randomized clinical trial. *Int J Antimicrob Agents* 2020;20:105949.
11. Melles RG, Marmor MF. The risk of toxic retinopathy in patients on long-term hydroxychloroquine therapy. *JAMA Ophthalmol* 2014;132(12):1453–1460.