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PERSPECTIVE ARTICLE

Hydroxychloroquine and SARS-CoV-2 (COVID-19): An Old Problem and New Considerations in Ophthalmology

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Abstract:

The antimalarial hydroxychloroquine (HCQ) has been suggested as a potential drug for treatment and prevention against severe acute respiratory syndrome–coronavirus 2 (SARS–CoV-2). Currently, there is insufficient scientific evidence available on HCQ retinal toxicity associated with the current treatment regimen and dosing for COVID-19 patients. In the sight of the current public health crisis, our recommendations aim to reduce the probability of unfavorable HCQ treatment outcomes and emphasize the importance of monitoring and early detection for HCQ retinopathy by simple means and the need for correlating clinical observations with multimodal imaging. We, therefore, recommend the use of Threshold Amsler grid (TAG) as a screening tool for high risk COVID-19 patients as well as treated patients with visual symptoms. Clinical decisions should be made on an individual basis, taking into consideration any pre-existing liver and kidney disease as well as macular pathology.

Keywords: Hydroxychloroquine, Ocular toxicity, COVID-19, Pandemic, Screening, Short-term toxicity.

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In the midst of coronavirus disease 2019(COVID-19) pandemic, the antimalarials hydroxychloroquine(HCQ) and chloroquine(CQ) have been suggested as potential drugs for treatment and prevention against severe acute respiratory syndrome–coronavirus 2(SARS–CoV-2) [1]. Both drugs have been used extensively for malaria prophylaxis and treatment and remain an integral standard of care for autoimmune conditions, such as Systemic Lupus Erythematosus (SLE) and Rheumatoid Arthritis (RA) [2]. HCQ is a disease modifying antirheumatic agent and is currently included in the World Health Organization Model List of Essential Medicines [3]. Nevertheless, prescribing HCQ and CQ for the prophylaxis or treatment of COVID-19, is considered off-label.

So far, data to support the use of HCQ and CQ for COVID-19 are inconclusive [4 - 8]. In many of the ongoing studies, proposed treatment dosing exceeded the recommended maximum daily dose for these drugs considered safe for long-term therapy. Researchers are giving, typically, up to a 10-day course of 200 mg HCQ, three times daily and these high doses have caused concerns about possible retinal damage [5, 9, 10]. Currently, the American Academy of Ophthalmology(AAO), recommends a maximum daily HCQ dose of 5 mg/kg of Actual Body Weight (ABW) [11]. Following the latest AAO guidelines, HCQ safe dosing should be based on ABW rather than Ideal Body Weight (IBW) [11]. This recommendation is a significant change in best practices for drug dosing that clinicians should be aware of.

HCQ ocular toxicity is well described in the literature, ranging from reversible Vortex Keratopathy (VK) of the cornea to a potentially blinding retinopathy associated with different doses of HCQ [12, 13].

VK of the cornea is completely reversible after discontinuation of HCQ therapy [14], and its incidence, in patients taking 800 mg/day of HCQ, was reported to be 6% within 6 months and 32% by 12 months [15]. The incidence of VK was reduced to 0–5% in patients taking 400 mg/day of HCQ [16, 17].

On the other hand, HCQ retinopathy is irreversible and can progress for many years, even after therapy cessation [18, 19]. The overall prevalence of HCQ retinopathy is estimated to be 7.5% (for those taking 4.0–5.0 mg/kg ABW/day), rising to around 20% after 20 years of therapy [20]. Although the exact mechanism of HCQ toxicity has not been clarified, drug retention in melanin-containing tissues (melanin affinity) may explain its retinal toxicity properties. Prolonged exposure to the drug may result in ganglion cell degeneration and Retinal

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Pigmented Epithelial (RPE) atrophy. The clinical presentation of HCQ retinopathy varies from the classic "bull's eye" parafoveal pattern, to more peripheral ellipsoid toxicity (pericentral pattern), which is most prevalent among Asian patients, even in the earlier stages of disease [21, 22].

There are several recognized risk factors for retinal toxicity, which include the duration of HCQ use, associated tamoxifen therapy, cumulative and weight-adjusted daily HCQ dose, as well as presence of concomitant kidney or liver disease [20]. More recently, hydroxychloroquinemia has been reported as a risk factor for retinopathy [23]. Normally, HCQ is metabolized by the liver or eliminated from the body by renal excretion. Given its prolonged half-life of 40 to 50 days [24], any change in the liver and renal function might increase drug toxicity, if doses are unadjusted. Pre-existing macular disease is considered either a contraindication to HCQ treatment [25] or a risk factor for the subsequent development of HCQ retinal pathology [11]. There is a lack of evidence to support that pre-existing macular disorders either increase susceptibility to HCQ retinopathy or interfere with future screening tests. Nevertheless, AAO guidelines, updated in 2016, advise that macular disorders should be detected and appropriately documented by Ophthalmologists within the first year of treatment [11].

HCQ retinopathy is a recognized potential side effect of long-term HCQ therapy. In a large retrospective study, the risk of retinal toxicity was less than 1% at 5 years and less than 2% up to 10 years [11]. Similar results were also found by a recent prospective cohort study that included patients with SLE enrolled from the Hopkins Lupus Cohort [23].

On the other hand, the risk of HCQ-related irreversible retinopathy at high doses for short periods of treatment is unknown. Limited data shows that HCQ retinal toxicity can appear as early as 2 months after starting treatment [26, 27]. Early HCQ retinal toxicity may also be triggered by the combined use of high dose nabumetone and ibuprofen [28]. In rheumatology care, retinopathy associated with the use of HCQ, for less than 1 month has not been reported. Existing reports in the rheumatology literature show that the use of a HCQ loading dose(~1,000 mg/day), for a short period(~3 months) should be reasonably safe [29]. Nevertheless, in a small series of oncology patients, exposed to very high doses of HCQ(1,000 mg/day) for ≥6 months, two of seven patients developed HCQ retinopathy at 11 months and 17 months, respectively [30]. This could be suggestive of possibly reduced HCQ safety when used at very high doses for a moderately prolonged period.

In a recent, uncontrolled, non-comparative, observational study of 80 mildly infected COVID-19 patients who were treated with HCQ (600 mg/day) in combination with azithromycin, one patient

developed blurred vision after five days of treatment. Further details of this adverse event were not provided by the researchers, while concerns were raised due to HCQ's association with retinopathy [9]. Nevertheless, a recent editorial in the American Journal of Ophthalmology(AJO), written by Marmor MF [31], argues in support of the conclusion that antimalarials do not pose a great risk for the development of retinal damage when used at high doses, for less than 2 weeks and, therefore, ophthalmic screening is not recommended for COVID-19 patients under that treatment regimen. On the other hand, in the AAO website, "Important coronavirus updates for ophthalmologists," it is stated that "The American Academy of Ophthalmology has no opinion on the use of chloroquine or hydroxychloroquine in COVID-19 patients" [32].

In view of the evolving situation of COVID-19, HCQ is being increasingly used and finding new indications. Current data suggest that higher HCQ doses of up to 800 mg b.i.d., could be most efficacious for viral suppression, while suboptimal dosing can result in wasted time and resources [33]. Nevertheless, there is limited safety information for these high doses. We therefore believe, globally expanding the use of HCQ in hundreds of thousands of COVID-19 patients at significantly higher than the recommended dosage over a short period of time, requires monitoring and screening. Since retinopathy is the only absolute contraindication for HCQ use [25], screening recommendations for detection and prevention of retinopathy have become more important than ever. Nevertheless, the value of screening testing is unknown in cases with high doses over a relatively short duration. Additionally, performing screening in a busy hospital setting, during the coronavirus outbreak, besides being impractical, carries an unnecessary risk of virus transmission. Other potential drawbacks of screening include adding to the cost of healthcare and causing anxiety and stress to patient groups potentially at risk of retinopathy.

In general, there is a twofold purpose of screening patients for HCQ retinopathy: (1) to detect overdosing, which can be corrected and (2) to detect the rare occurrence of retinopathy among properly dosed patients. The findings of a recent study provide reassurance that the incidence of HCQ-induced retinal toxicity is rare when safe daily dosing is not exceeded [34]. So far, the literature is inconsistent on the issue of a gold standard screening test for defining HCQ retinopathy. As the indications of HCQ increase, the availability of improved modalities, such as multi-modal imaging, particularly Swept Source Optical Coherence Tomography (SS-OCT) and ultra-widefield imaging for the identification of peripheral retinal disease, as well as multifocal ERG (mfERG) to confirm the diagnosis of HCQ toxicity if the results of primary screening techniques are borderline [11], will become more important in early detection as well as timely and safe management of drug-induced retinal toxicity.

We therefore believe the following set of clinical recommendations could be used in a health care setting, during this time of ongoing public health crisis. (1) Initially, COVID-19 patients should be informed, before starting therapy, of the potential for uncommon but serious macular HCQ toxicity. (2) The screening physician or ophthalmologist should first focus on making sure that HCQ dosing is correct based on ABW. (3) Recording concomitant medications known to have an additive deleterious effect is also important. (4) Full medical history-taking should include the past medical history of maculopathy as well as renal and/or liver disease. Baseline

renal and liver function should also be established [35]. (5) We also recommend the use of the Threshold Amsler grid (TAG) as a screening tool for high risk groups as well as treated patients with visual symptoms. TAG test was initially advocated by the joint guidelines of the Royal College of Ophthalmologists, as an effective screening method to detect HCQ retinopathy [35, 36]. Nevertheless, the updated guidelines no longer recommend its use as a screening tool [11, 37]. TAG test was first suggested for retinopathy screening by Carr et al. [38], in 1966. A literature review revealed a specificity range of 85–100% [36, 39, 40], a sensitivity at best 69% [41 - 43] and a Negative Predictive Value(NPV) range of 98.4–100% [44], regardless of the prevalence assumed. Given the special circumstances attributed to the ongoing pandemic, the use of this low cost, easy to perform and quick test could practically serve the patients in a busy setting and keep the healthcare settings, medical personnel and patients from being overwhelmed by impractical, counterproductive and expensive eye tests. (6) Multimodal imaging, particularly SS-OCT and wide-field fundus autofluorescence imaging, should be reserved for patients with an abnormal TAG test result to confirm the presence of HCQ retinopathy. In cases of borderline results from multimodal imaging, mfERG could be additionally used to confirm the diagnosis of HCQ toxicity. An interesting option during this viral pandemic could also be the use of virtual clinics focused on HCQ retinopathy screening services [45]. Finally, we, as ophthalmologists, need to ensure people are fully informed of the small but real risk of irreversible damage to the vision from incorrect or improper use of HCQ. Health misinformation through the media in the uncertain times of pandemic, could possibly result in confusing people and causing permanent eye damage.

CONCLUSION

In conclusion, HCQ retinal toxicity is irreversible and can continue to progress even after cessation of treatment. The extensive use of HCQ by large populations at higher than recommended

doses may cause an increased risk of retinal toxicity. Currently, there is insufficient scientific evidence available on HCQ retinal toxicity associated with the current treatment regimen and dosing for COVID-19 patients. Therefore, decisions should be made on an individual basis, taking into consideration any pre-existing liver and kidney disease as well as macular pathology. Our recommendations aim to reduce the probability of unfavorable HCQ treatment outcomes and therefore emphasize the importance of monitoring and early detection for HCQ retinopathy by simple means and the need for correlating clinical observations with multimodal imaging.

AUTHORSHIP

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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