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American Academy of Ophthalmology Statement

Recommendations on Screening for Chloroquine and Hydroxychloroquine Retinopathy (2016 Revision)

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Background: The American Academy of Ophthalmology recommendations on screening for chloroquine (CQ) and hydroxychloroquine (HCQ) retinopathy are revised in light of new information about the prevalence of toxicity, risk factors, fundus distribution, and effectiveness of screening tools.

Pattern of Retinopathy: Although the locus of toxic damage is parafoveal in many eyes, Asian patients often show an extramacular pattern of damage.

Dose: We recommend a maximum daily HCQ use of $\leq$5.0 mg/kg real weight, which correlates better with risk than ideal weight. There are no similar demographic data for CQ, but dose comparisons in older literature suggest using $\leq$2.3 mg/kg real weight.

Risk of Toxicity: The risk of toxicity is dependent on daily dose and duration of use. At recommended doses, the risk of toxicity up to 5 years is under 1% and up to 10 years is under 2%, but it rises to almost 20% after 20 years. However, even after 20 years, a patient without toxicity has only a 4% risk of converting in the subsequent year.

Major Risk Factors: High dose and long duration of use are the most significant risks. Other major factors are concomitant renal disease, or use of tamoxifen.

Screening Schedule: A baseline fundus examination should be performed to rule out preexisting maculopathy. Begin annual screening after 5 years for patients on acceptable doses and without major risk factors.

Screening Tests: The primary screening tests are automated visual fields plus spectral-domain optical coherence tomography (SD OCT). These should look beyond the central macula in Asian patients. The multifocal electroretinogram (mfERG) can provide objective corroboration for visual fields, and fundus autofluorescence (FAF) can show damage topographically. Modern screening should detect retinopathy before it is visible in the fundus.

Toxicity: Retinopathy is not reversible, and there is no present therapy. Recognition at an early stage (before any RPE loss) is important to prevent central visual loss. However, questionable test results should be repeated or validated with additional procedures to avoid unnecessary cessation of valuable medication.

Counseling: Patients (and prescribing physicians) should be informed about risk of toxicity, proper dose levels, and the importance of regular annual screening. *Ophthalmology 2016;■:1–9 © 2016 by the American Academy of Ophthalmology.*

Retinal toxicity from chloroquine (CQ) and its analogue hydroxychloroquine (HCQ) has been recognized for many years. Chloroquine toxicity remains a problem in many parts of the world, but is seen less frequently in the United States where the drug largely has been replaced by HCQ. Hydroxychloroquine is used widely for the treatment of systemic lupus erythematosus (SLE), rheumatoid arthritis, and related inflammatory and dermatologic conditions. It is now being considered for new applications in diabetes mellitus, heart disease, and adjunct cancer therapy. Thus, it is important for ophthalmologists and other physicians to understand the prevalence and risk factors for retinopathy.

The American Academy of Ophthalmology recommendations for screening that were published in 2011[1] are revised in this article to account for new scientific data. The recent publication of a large demographic study has shown that toxicity is not rare among long-term users of the drug, and the risk is highly dependent on the daily dose by weight.[2] These data showed that real weight was better than ideal weight for calculating dose, and lower risk was achieved with doses $\leq$5 mg/kg real weight. It also has been found that the classic "bull's-eye" distribution of toxicity is infrequent in patients of Asian heritage,[3,4] who typically show early damage in a more peripheral pattern.

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Toxicity is of serious ophthalmologic concern because it is not treatable. Nonetheless, it has been demonstrated that central vision can be preserved if damage is recognized before there are changes in the retinal pigment epithelium (RPE).[5] With proper screening, bull's-eye retinopathy, as classically described with these drugs, no longer should be seen.

The goal of screening for retinopathy is not to stop valuable drugs at the first borderline abnormality, but to recognize definitive signs of toxicity at an early enough stage to prevent a loss of visual acuity. Ophthalmologists provide a valuable service not only by screening but also by advising medical colleagues and patients about risk, safe dosing, and appropriate screening procedures. Despite the existence of published guidelines, screening practices often have been inconsistent or deficient.[6,7] The recommendations in this revision are more concise and practical than the prior version, to encourage wider compliance.

Hydroxychloroquine and Chloroquine Toxicity

The mechanism of CQ and HCQ toxicity is not well understood. High experimental doses have acute effects on the metabolism of retinal cells, but it is not clear how these short-term metabolic effects relate to the slow and chronic damage that characterizes the clinical state of toxicity. Binding to melanin in the RPE may serve to concentrate the agents and contribute to, or prolong, their toxic effects. However, melanin binding also could serve as a mechanism for removing toxic agents from intracellular sites of damage. Inner and outer retina are damaged by CQ exposure in animal studies, but recent work suggests that inner retina is not damaged significantly as human HCQ toxicity develops.[8,9] In clinical practice, the primary damage is to the photoreceptors, and as the outer nuclear layer degenerates, there is secondarily disruption of the RPE.[10] No anatomic features of the retina and RPE are known to correlate specifically with the parafoveal or extramacular patterns of damage as CQ and HCQ toxicity develops. The macular localization of the disease suggests that light absorption or possibly cone metabolism may play a role, but that is speculation.

The clinical picture of HCQ and CQ toxicity had been characterized classically as a bilateral bull's-eye maculopathy, an appearance caused by a ring of parafoveal RPE depigmentation that spares a foveal island. However, this "textbook" pattern should no longer be seen, because recommended screening tests will detect HCQ toxicity long before RPE damage is visible by imaging or fundus examination. Although most patients of European descent show initial photoreceptor damage in the classic parafoveal distribution (Fig 1), most patients of Asian descent will show initial damage in a more peripheral extramacular distribution near the arcades (Fig 2).[3,4] African-Americans and Hispanics in that study[3] showed predominately a parafoveal pattern of damage as in European subjects, but possibly a greater tendency toward extramacular involvement. The numbers of patients of other races were too small to draw conclusions.

Visual acuity usually is excellent with either pattern until severe stages of damage, and most patients who develop HCQ toxicity have no visual symptoms at all. A few perceptive patients may notice paracentral scotomas while reading. If drug exposure continues, the area of functional disturbance expands, the RPE becomes involved, and the maculopathy can encroach on the foveal center with eventual loss of visual acuity (Fig 3).[2,10] Cystoid macular edema sometimes may develop,[11] and advanced cases show widespread RPE and retinal atrophy with loss of visual acuity, peripheral vision, and night vision.

Hydroxychloroquine and CQ retinopathy can progress even after the drugs are stopped, although the amount of progression and the risk to vision are functions of the severity of retinopathy at the time it is detected.[5,11] It seems doubtful that this late progression of damage after stopping the drug results from a continued reservoir of the drug, although clearance from the body does take many months. The late progression may represent a gradual decompensation of cells that were injured metabolically during the period of drug exposure.

Chloroquine, and less frequently HCQ, can cause whorl-like intraepithelial deposits (verticillata) in the cornea. These corneal changes are not a direct marker for retinal damage, are not associated with visual loss, and in contrast to retinopathy are usually reversible.

Statistical Risk of Toxicity

Earlier literature on the prevalence of CQ or HCQ retinopathy included few patients on long-term therapy and only recognized severe toxicity (bull's-eye changes). These reports have been superseded now by a large study of 2361 patients who used HCQ for more than 5 years and were evaluated with 10-2 visual fields or spectral-domain optical coherence tomography (SD OCT) so that toxicity could be recognized before there were any visible signs on fundus examination.[2] The overall prevalence of toxicity in this study population was 7.5%, although it varied greatly with the daily dose and duration of use. Daily dose (more properly, daily use, as measured by actual pharmacy dispensing) was the most critical determinant of risk, and the risk was more closely correlated with real weight than ideal weight. Very thin patients in particular are at increased risk when dose is calculated by ideal weight (as previously recommended). Patients in this new study[2] mostly had been prescribed routine doses of HCQ by prior standards, but the average use was approximately 5.0 mg/kg of real weight because of varying compliance and body habitus. Thus, 5.0 mg of HCQ/kg real weight corresponds with present medical prescription practices and should be therapeutically effective for most patients.

Population statistics from the new study showed that patients taking HCQ using 4.0 to 5.0 mg/kg real weight had markedly lower cumulative risk of toxicity than those using higher levels. Kaplan–Meier curves show that patients staying with $\leq$5.0 mg/kg have less than 1% risk in the first 5 years of therapy and less than 2% up to 10 years (Fig 4).