Hydroxychloroquine Screening Alert: Change is in the Wind

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Hydroxychloroquine (HCQ) retinopathy is an infrequent but unfortunate consequence of long usage of the drug at excessive dosage. The American Academy of Ophthalmology (AAO) published recommendations for screening in 20111 that reduced the risk of retinopathy, and these have been widely followed and publicized, including a recent review in OSL Retina that showed classic field and optical coherence tomography (OCT) findings.2 However, recent papers have shown that those guidelines are no longer optimal, and that screening practices must be changed. Updated 2016 AAO recommendations3 incorporate the latest information, and if followed, will allow longer usage of HCQ with even less retinopathy. This brief note is an alert to give OSLI Retina readers the key information to meet current practice standards, minimize risk, and detect HCQ retinopathy before there is significant visual loss. A classic “bull’s eye” should never be seen again.

RECENT FINDINGS ABOUT HCQ RETINOPATHY

Dosage
A survey of nearly 2,500 patients on long-term HCQ showed that real weight was a better indicator of dosage and retinopathy risk than ideal weight.4 Old data suggesting that the drug fails to distribute in fat were experimental and flawed, using small numbers of animals with non-human fat distribution. Human data show clearly that the best balance of dose versus risk is obtained when HCQ users stay below 5 mg/kg real weight.4 The dose limit for chloroquine can only be estimated, and the suggested value is less than 2.3 mg/kg real weight. The biggest problem with the old ideal dosage guideline was that small women (a major part of the lupus population) were often overdosed, whereas less than 5 mg/kg real weight gives an accurate prediction of risk independent of body habitus. Because blood levels stabilize slowly, doses can be adjusted accurately by using one less tablet on certain days of the week.

Dose Versus Duration
The cumulative and annual risks of using HCQ depend upon a balance of daily dose and duration of use, and there is no magic number or cumulative dose that signifies retinopathy is imminent. HCQ can be continued, no matter how long it has been used, as long as the visual fields and spectral-domain OCT (SD-OCT) remain normal. Kaplan-Meier curves3,4 show that with proper dosage, the drug is remarkably safe for the first 10 years, but the risk rises with continued use. However, once a patient is found to be free of retinopathy, the incremental risk in the ensuing year is relatively low.

High-Risk Factors
Beyond dose and duration, the only major risk factors are preexisting maculopathy, renal disease, and use of tamoxifen. Older age, liver disease, and
obesity do not seem of major importance. Significant macular disease (more than just a few hard drusen) is a contraindication because it seems irrational to add a toxic drug to diseased tissue, and also because it may interfere with recognition of HCQ damage in visual fields or SD-OCT.

**Pattern of Fundus Damage**

Parafoveal scotomas and photoreceptor thinning have been considered the hallmark signs of toxicity, but the fact is that Asian patients will most often (but not always) show initial damage outside the central macula, near the arcades (Figure). This must be taken into account when planning field tests and imaging. One can cover all bases with Asian patients by testing both 10-2 and 24-2 using a rapid SITA-FAST protocol (takes no longer than a standard 10-2), and by getting wide-field fundus autofluorescence images or extrafoveal OCT scans. Note that HCQ damage most often begins inferiorly.

**Photoreceptor Damage**

Some papers have suggested that the inner retina might be involved in HCQ retinopathy, but more recent work has found no clinically relevant changes in the inner retina. For practical purposes, HCQ is a photoreceptor toxin, and even the outer retina will remain clinically normal until frank retinopathy develops.

**Sensitivity Versus Specificity**

Visual fields (and multifocal electroretinograms [mfERGs]) are functional tests, as well as the most sensitive screening procedures; they sometimes show scotomas before damage is visible in the SD-OCT. However, not all patients are good field-takers, and

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Figure. Fundus autofluorescence images showing racial differences in the pattern of damage from hydroxychloroquine retinopathy. (A) Normal eye. (B) Typical pattern in European patients (parafoveal bull’s eye). (C) Mixed damage in both parafovea and arcade regions. (D) Typical pattern in Asian patients (pericentral damage near arcades). From Melles and Marmor; used with permission.
SD-OCT is objective and more specific when characteristic changes are present. The best balance of sensitivity and specificity in screening is obtained by using both visual-field testing and SD-OCT. mERG and fundus autofluorescence can aid with uncertain findings.

**Prognosis for Vision**

HCQ retinopathy often progresses after the drug is stopped, but the rate depends on the initial extent of damage. Before the retinal pigment epithelium (RPE) becomes involved, progression rarely lasts beyond a year and is unlikely to threaten the fovea. But if screening has missed early signs, and RPE damage (bull’s eye) is already present, then progression may continue for years and eventually cause central vision loss. Therefore, recognition of toxicity at an early stage is very important.

**OLD VERSUS NEW AAO RECOMMENDATIONS: THE BOTTOM LINE**

The 2016 AAO recommendations utilize all this new information. Some old advice stands, such as ruling out maculopathy at baseline, deferring screening for 5 years at proper dosage (and no high-risk factors), annual screening thereafter, and awareness that fundus examination is not a screening test (for lack of sensitivity). However, there are four critical changes concerning dose, risk, and fundus appearance:

- The maximum recommended dose is now 5 mg/kg real weight.
- The site of early damage in Asian patients is often pericentral, near the arcades. Screening tests must be suitably adjusted.
- Maculopathy, renal disease, and tamoxifen are the major risk factors.
- Risk of retinopathy depends on both dose and duration, but there is no “maximum” exposure.

HCQ is a valuable medication for lupus or rheumatoid arthritis because of its low systemic toxicity, and it should not be stopped just because a field or SD-OCT seems borderline or suspicious. Toxicity develops slowly, and there is time to have the patient return within a few months for retesting and/or additional procedures that would confirm or negate the suspicion. If patients and prescribing physicians are given good advice about proper dosage and screening is effective, you can forget about bull’s eyes.

**REFERENCES**


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