In 2011, the American Academy of Ophthalmology published updated guidelines on screening for retinal toxicity from chloroquine and hydroxychloroquine. Although hydroxychloroquine has been in clinical use for decades, initially as an anti-malarial drug and then as an immunosuppressant for a number of autoimmune conditions, protocols to screen for retinal toxicity continue to evolve as our imaging technology advances.

Part of the challenge lies in the fact that there exists no single gold-standard objective test for toxicity; rather, clinicians must interpret clues from a number of imaging modalities. Early signs of toxicity can be subtle, but it is imperative to detect disease promptly, as the classic “bull’s-eye maculopathy” is a late finding. Late toxicity is devastating and typically associated with severe, bilateral, and irreversible vision loss.

In this installment of Practical Retina, Yasha S. Modi, MD, and Rishi P. Singh, MD, provide a welcome and well-illustrated guide to current screening guidelines, pearls for interpreting each screening modality, and insights into future research for earlier reliable detection.

Hydroxychloroquine: A Brief Review on Screening, Toxicity, and Progression

by Yasha S. Modi, MD; Rishi P. Singh, MD

The anti-malarial drugs chloroquine (CQ) and hydroxychloroquine (HCQ) are used to treat a variety of autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus.\(^1\,2\) HCQ, the hydroxylated form of chloroquine, has demonstrated a more favorable side effect profile with decreased ocular toxicity, although the risk for retinopathy is still present with rates varying between 1% to as high as 7.5% in patients with long-term exposure.\(^3\,9\)

Historically, HCQ retinal toxicity was identified by symptoms such as central visual loss, including difficulty reading, reduced color vision, and central scotoma. Funduscopic exam demonstrated signs ranging from fine pigmented stippling of the macula and loss of the foveal light reflex, referred to as premacularopathy, to the characteristic bilateral bull’s-eye maculopathy.\(^10\,11\) Given these irreversible late clinical findings, screening guidelines with the intended goal of detecting functional and anatomic abnormalities prior to symptom onset, have been implemented.

SCREENING GUIDELINES

In 2011, the American Academy of Ophthalmology (AAO) revised its 2002 guidelines for HCQ retinal toxicity screening.\(^12\) In contradistinction to the 2002 guidelines, the 2011 guidelines recommended subjective testing with a 10-2 Humphrey visual field that could no longer be substituted by the previously accepted Amsler grid test.\(^12\,14\) An alternatively accepted objective test in the 2011 guidelines includes a multifocal electroretinogram (mfERG). Additional recommended objective tests to detect...
anatomic change include spectral-domain optical coherence tomography (SD-OCT) and fundus autofluorescence (FAF). Acceptable pairs of screening tests include a HVF 10-2 (subjective test) with either a SD-OCT or FAF (objective tests). An alternatively accepted screening modality is an mfERG as a stand-alone test, given the test is both objective and conveys information on subtle retinal functional abnormalities.

The guidelines further reiterated specific risk factors associated with toxicity and made screening guidelines accordingly. The designation of high-risk included patients with: cumulative HCQ consumption greater than 1 kg, daily dosing greater than 6.5 mg/kg/day of ideal body weight, or concomitant renal or liver disease. Additional, albeit less definitive, risk factors included advanced age or comorbid retinal or macular disease. For those without high-risk characteristics, a baseline screening upon initiation of HCQ was recommended followed by a 5-year examination-free window. For patients with high-risk factors, annual screening was recommended.

DETECTING HCQ TOXICITY

There remains no established criterion for diagnosing HCQ toxicity and, as such, the physician must rely on a combination of characteristic functional and anatomic abnormalities to diagnose a patient with HCQ toxicity. An understanding of each screening modality and a keen eye to detect subtle abnormalities is critical to diagnosing early disease.

SD-OCT has emerged as a sensitive and reproducible screening modality to detect early HCQ screening. The earliest observable qualitative alterations include outer retinal changes, such as loss of the cone outer segment tip line and parafoveal loss of the ellipsoid zone, which advances to parafoveal thinning of the outer nuclear layer and subsequent damage of the retinal pigment epithelium. This later, classic stage is described as the “flying saucer” sign (Figures 1A-1C).

If the screening ophthalmologist detects any level of outer retinal atenuation or thinning in the parafoveal region, a high degree of suspicion for HCQ toxicity must be maintained and corroborated with other screening modalities.

FAF is a test that indirectly evaluates the functionality of the retinal pigment epithelium (RPE). Lipofuscin, which is stored in the RPE and has inherent autofluorescent properties, is detected by this screening modality. It is believed that hyperautofluorescence corresponds to a dysfunctional or “sick” RPE manifesting as an accumulation of lipofuscin, whereas hypoautofluorescence corresponds to the absence of the RPE. In the setting of HCQ toxicity, parafoveal changes of hyperautofluorescence precede the development of hypoautofluorescence. Figure 2A demonstrates a classic example of hyper- and hypoautofluorescence corresponding to RPE dysfunction and loss in a bull’s-eye pattern, whereas Figure 2B demonstrates a more subtle ab-
normality manifesting solely abnormal hyperautofluorescence. Of note, pathologic involvement of the RPE in HCQ toxicity has been demonstrated to be a later-stage finding than parafoveal outer retinal changes seen on OCT, and thus the authors believe FAF may be better used as a confirmatory screening test or test to follow patients with known toxicity.

Humphrey visual field 10-2 remains a gold standard in HCQ screening. Although earlier publications have espoused the use of a red stimulus, the 2011 AAO recommendations advocate the use of the white stimulus. When evaluating a reliable visual field result, any central or paracentral abnormalities, particularly if there are contiguous points of depression, should be taken as a potential sign of HCQ toxicity. Any abnormalities should be correlated with objective tests, including OCT and FAF, and the visual field should be repeated in a short time frame to corroborate the abnormal result. Figure 3 demonstrates a case of reproducible paracentral scotomas in a patient with HCQ toxicity but an otherwise seemingly normal SD-OCT and FAF. This example underlies the importance of this imaging modality, as it suggests that the earliest pathologic sign may manifest through a reliable HVF.

mFERG is a recent addition to the armamentarium of HCQ screening tools in HCQ. This test generates localized and topographic ERG responses across the posterior pole and can objectively and reproducibly detect paracentral ERG depression in HCQ toxicity. The characteristic waveform abnormalities seen include paracentral amplitude loss. A protracted implicit time, in conjunction with a paracentral decrease in retinal function, has demonstrated increased specificity in evaluating patients with HCQ toxicity. Although the test is highly sensitive in detecting macular dysfunction, the limited availability, longer testing time, and need for specialized expertise in interpretation limits its use. A recent study by Cukras et al. utilizing mFERG as a “gold standard” for identifying HCQ toxicity reported that SD-OCT retinal thickness and Humphrey visual field 10-2 mean deviation detected toxicity in all cases and the combination of these tests might serve as suitable and less-expensive surrogate markers of toxicity.

**PROGRESSION OF HCQ TOXICITY**

Once HCQ toxicity is diagnosed, it is critical to stop or change the medication while maintaining control of the patient’s underlying systemic disease. This oftentimes requires frequent communication between the ophthalmologist, rheumatologist, and patient to optimize both ocular and systemic health.

With the exception of stopping HCQ, there are no other treatment options for preventing further HCQ toxicity. Additionally, there are no established guidelines for following patients with toxicity. Retrospective reports have demonstrated that...
Figure 3. (A, B) A case of reproducible paracentral scotomas in a patient with hydroxychloroquine toxicity. The spectral-domain optical coherence tomography demonstrates a shaggy outer plexiform layer appearance but otherwise minimal outer-retinal parafoveal attenuation (C). The macular fundus autofluorescence pattern is otherwise unremarkable (D).
patients with HCQ may remain stable or continue to progress despite stopping the medication. Marmor et al., evaluating a small series of patients with toxicity, demonstrated that severe disease involving paracentral RPE loss is more likely to progress despite cessation of the medication, whereas early and moderate disease demonstrates greater anatomic and functional stability over time with progression confined mostly to the first year.

More recently, Mittelu et al. demonstrated subclinical regeneration of the ellipsoid zone for patients with an intact ELM at the time of diagnosis, suggesting there may be a threshold level that underlies the transition from stable or reversible toxicity to progressive toxicity.

CURRENT RESEARCH AND POTENTIAL APPLICATION TO CLINICAL CARE

Research in HCQ has consistently focused on elucidating pathophysiologic mechanisms of toxicity as well as detecting disease at incrementally earlier levels of toxicity. Although the pathophysiology of HCQ toxicity remains unknown, animal models of chloroquine toxicity have demonstrated inner-retinal changes (lysosomal damage in the ganglion and bipolar cells) as the first abnormality that ultimately progresses to lysosomal disruption in the photoreceptors or RPE. These inner-retinal abnormalities have been correlated in human studies in which OCT demonstrated relative thinning of the inner retina in HCQ toxicity relative to control. These findings, however, have not been uniformly substantiated, and controversy exists regarding the layers affected in HCQ toxicity, as well as which layers are first involved. Despite this controversy, this body of research has applied novel segmentation algorithms (Figure 4), which consistently demonstrate paracentral outer-retinal thinning in the setting of toxicity. This affords the clinical opportunity to follow patients longitudinally and rely on a quantitative rather than qualitative assessment to identify parafoveal outer retinal attenuation at an earlier stage.

CONCLUSION

Macular toxicity is a rare, but potentially devastating finding in patients exposed to long-term or high-dose HCQ use. The disease follows a predictable pattern that makes it amenable to screening. Although HVF 10-2 has remained a gold standard in HCQ screening, the addition of SD-OCT, FAF, and mfERG to the screening armamentarium allow for increasingly earlier detection of subtle toxicity. A keen recognition of subtle imaging abnormalities remains critical to making the diagnosis in the subclinical window.

REFERENCES