

Monitoring for Hydroxychloroquine Retinal Toxicity

Multifocal ERG is useful in detecting early maculopathy.

BY TODD KLESERT, MD, PHD

In this issue of Retina Today, Todd Klesert, MD, PhD, discusses practical approaches to monitoring retinal toxicity due to hydroxychloroquine therapy.

We extend an invitation to readers to submit pearls for publication in Retina Today. Please send submissions for consideration to Ingrid U. Scott, MD, MPH, (iscott@psu.edu); or Dean Elliott, MD (deliott@doheny.org). We look forward to hearing from you.



—Ingrid U. Scott, MD, MPH; and Dean Elliott, MD

Antimalarial drugs have been used as effective treatments for autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus for more than 50 years.¹ Retinal toxicity associated with these drugs was first recognized in patients on long-term chloroquine therapy for malaria.² Retinal toxicity has since been well documented as a risk for patients taking hydroxychloroquine (Plaquenil, Sanofi-Aventis).³⁻⁷ Although the incidence of hydroxychloroquine retinal toxicity is low, the impact of unrecognized toxicity can be devastating. Macular damage from hydroxychloroquine (Figure 1) appears to be permanent and may continue to progress even after discontinuation of the drug due to its slow clearance from the body; in fact, the drug may persist in patients' urine for years after discontinuation.⁸⁻¹⁰ Therefore, detection of toxicity at its earliest stages is critical.

INCIDENCE AND RISK FACTORS

The larger retrospective studies generally agree that the incidence of retinal toxicity is roughly 0.5% for all patients taking hydroxychloroquine.^{3,11,12} Most reported cases have occurred in patients taking daily doses greater than 6.5 mg/kg of ideal body weight¹¹ and/or on therapy for longer than 5 years.³ However, in the largest

study to date of patients taking hydroxychloroquine, Wolfe and Marmor¹² found no significant association between retinal toxicity and daily dose, weight, or age. The investigators found that the single most important risk factor is duration of therapy, with the incidence of toxicity rising significantly after 1,000 g of cumulative dose (approximately 7 years on the most common daily dose of 400 mg). The incidence of definite or probable retinal toxicity increased from less than 0.3% at 5 years to more than 2% at 15 years.

AAO MONITORING GUIDELINES

With an estimated 150,000 patients taking hydroxychloroquine at any one time in the United States,¹ the resource burden on the US health care system for routine retinal toxicity monitoring is potentially significant. In the package insert for the drug, the manufacturer recommends ophthalmologic examinations every 3 months for patients on long-term therapy. Recognizing that the overall incidence of retinal toxicity is very low, the American Academy of Ophthalmology (AAO) developed alternative, specific consensus recommendations in 2002 for toxicity monitoring,¹³ intended to maximize the cost:benefit ratio for the health care system and minimize the burden for patients and ophthalmologists.

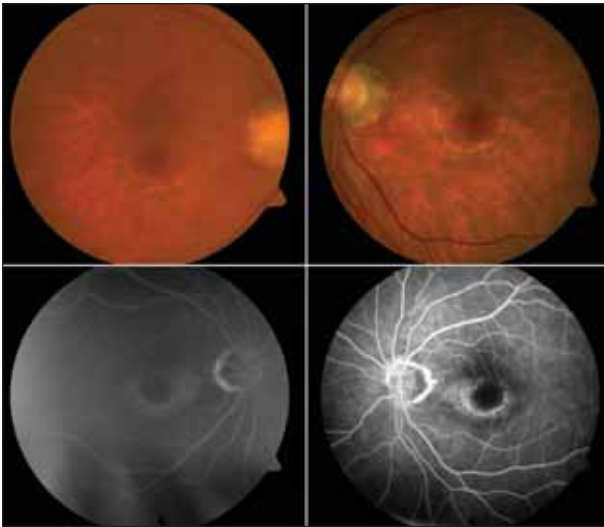


Figure 1. Color fundus and fluorescein angiogram photographs from a patient with advanced hydroxychloroquine maculopathy showing the characteristic bull's eye pattern of retinal pigment epithelial disturbance.

The AAO recommends that all patients beginning hydroxychloroquine therapy have a baseline evaluation, including a complete dilated examination and visual field test (Amsler grid or Humphrey 10-2 perimetry). Other testing, such as color vision and fundus photography, is optional. The AAO guidelines classify patients as either “low risk” or “higher risk.” Low-risk patients do not need further screening during the first 5 years of use except as part of the normal routine comprehensive examination schedule in the current Preferred Practice Pattern. Patients are told to return promptly for reevaluation if they notice any change in vision, Amsler grid appearance, color sensation, or dark adaptation.

Per the AAO guidelines, higher risk patients should be monitored annually with dilated examination and visual field testing. Additional testing is at the discretion of the ophthalmologist. Any one of the following criteria qualifies a patient as higher risk: treatment longer than 5 years, daily dose greater than 6.5 mg/kg, significant renal or liver disease, concomitant retinal disease, age older than 60 years, or obesity (unless the dose is appropriately low). Patients who have any visual symptoms or examination findings suggestive of toxicity should be evaluated further. If the findings are equivocal, the patient should be reevaluated in 3 months. If the patient is determined to have probable or definite toxicity, hydroxychloroquine treatment should be stopped immediately in consultation with the patient's rheumatologist.

PRACTICAL CONSIDERATIONS

For patients referred to me on hydroxychloroquine, I generally follow the AAO's monitoring guidelines. However, the commonly held notion that toxicity almost never occurs earlier than 5 years is not supported by the literature; Wolfe and Marmor¹² report a rate of 0.3% at 5 years. Therefore, I have a fairly low threshold for placing someone in the “higher risk” classification, thus requiring annual monitoring from the beginning.

One point on which I diverge from the AAO screening guidelines is in dosage calculation. Whereas the AAO dosage guidelines are based on actual body weight, I prefer to calculate the daily dose based on *ideal body weight*, which is the predicted healthy lean weight of an individual of a given height. Because very little hydroxychloroquine is distributed in the fat, an obese patient is effectively exposed to higher plasma concentrations of the drug than a lean patient of the equivalent weight. Therefore, use of actual body weight in calculating the daily dose underestimates the risk in patients who are above their ideal body weight (which is the majority of Americans).

For patients on the most common 400-mg daily dose, my definition of higher risk therefore includes not only anyone who weighs less than 135 lbs (> 6.5 mg/kg/day), but also anyone with an *ideal body weight* less than 135 lbs (ie, any woman under 5' 6" tall and any man under 5' 4", unless the patient has an exceptionally large frame). Keep in mind that there is no single standard ideal body weight chart, so these height cutoffs are open to individual interpretation.

At the initial examination and all subsequent follow-up visits, I check color vision with Ishihara plates and perform Amsler grid testing and Humphrey threshold perimetry. I also obtain fundus photographs on the initial visit. Recently, I have been using a central 5° Humphrey

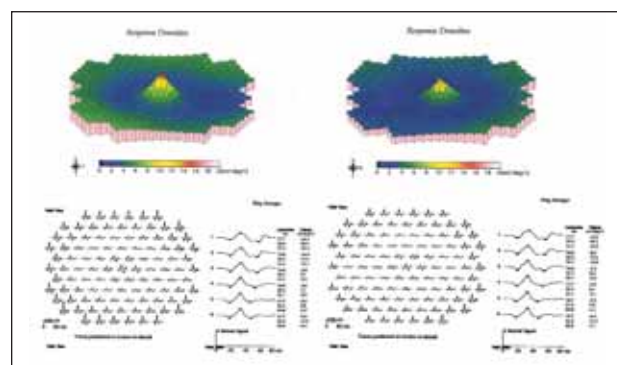


Figure 2. mERG from a patient with probable early hydroxychloroquine retinopathy. Diminished first-order response densities and flattened waveforms are apparent in a bull's eye distribution.

perimetry protocol with red stimulus because the testing is easier on the patient. Red stimulus has been shown to be more sensitive than white stimulus in detecting chloroquine retinopathy.¹⁵

When symptoms or routine monitoring tests raise concern for possible early toxicity, a more thorough evaluation is warranted. Fluorescein angiography may detect subtle macular window defects that are not apparent on clinical exam. High-resolution spectral domain optical coherence tomography may detect distinctive changes, from thinning to complete loss, at the inner and outer segment junction in the parafoveal region.¹⁶

MULTIFOCAL ERG TESTING

Several studies have examined the use of multifocal electroretinography (mERG) in detecting hydroxychloroquine maculopathy.¹⁷⁻²¹ mERG is probably more sensitive than other clinical tests in detecting early macular dysfunction and has the added advantage of being a largely objective test. mERG changes may predate any other detectable abnormality.^{13,22-25} I routinely obtain a baseline mERG in higher risk patients. In the absence of any significant abnormalities, I obtain follow-up mERG testing every few years.

Figure 2 shows the mERG results in a 53-year-old woman with rheumatoid arthritis, treated with 400 mg (8.9 mg/kg) of hydroxychloroquine daily for the previous 19 years. She had complaints only of mild difficulty matching colors with her clothes over the previous few years. Visual acuity was 20/20 in both eyes, and fundus examination and Amsler grids were normal. Color vision was 10 out of 14 in each eye by Ishihara plates, and Humphrey 10-2 perimetry suggested possible mild central depression. mERG revealed diminished first-order response densities in a bull's eye distribution, with relative sparing of the central foveal peak, consistent with hydroxychloroquine toxicity. Flattening of the first-order waveforms was also observed in the same distribution. The patient was diagnosed with probable hydroxychloroquine retinopathy, and immediate cessation of the drug was recommended. ■

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