

Hydroxychloroquine-Induced Retinal Toxicity

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Many systemic medications may cause retinal toxicity. One such commonly used medication for dermatologic and rheumatologic inflammatory conditions is hydroxychloroquine (Plaquenil), a chloroquine derivative. It is used to treat many diseases including malaria, rheumatoid arthritis and systemic lupus erythematosus.

Retinal toxicity from hydroxychloroquine is rare, but even if the medication is discontinued, vision loss may be irreversible and may continue to progress. It is imperative that patients and physicians are aware of and watch for this drug's ocular side effects. And before treatment is initiated with hydroxychloroquine, a complete ophthalmic examination should be performed to determine any baseline maculopathy.

Ophthalmologists should also follow the most current screening guidelines established by the Academy,¹ recently revised in light of new findings. (For a broader look at drugs with ocular side effects, see last month's Clinical Update, "Rx Side Effects: New Plaquenil Guidelines and More.")

Symptoms and Signs

Symptoms. Patients in earlier stages of hydroxychloroquine retinal toxicity usually do not experience symptoms, though the rare patient may note a paracentral scotoma that causes trouble with reading as well as diminished color vision. However, most patients



ADVANCED BULL'S-EYE RETINOPATHY. A 55-year-old female who had been taking hydroxychloroquine for 10 years before the onset of symptoms. Color fundus photos showing bull's-eye maculopathy (1). Fundus autofluorescence with central mottled hypoautofluorescence with surrounding rim of hyperautofluorescence (2). SD-OCT shows marked parafoveal thinning of the retina (arrows), especially of the outer photoreceptor layers (3).

usually notice symptoms only after scotomas have become severe. When allowed to advance, hydroxychloroquine retinal toxicity leads to loss of

up to three visual functions: acuity, peripheral vision and night vision.

Signs. On examination, a telltale sign of hydroxychloroquine toxicity

is a bilateral change in the retinal pigment epithelium of the macula that gives the commonly described appearance of a bull’s-eye (Fig. 1). This is a late finding, however, and too late for screening to be useful.

In early toxicity there are no visible signs, but field, OCT and mfERG changes can be detected. If abnormalities are present only unilaterally, investigate other causes besides hydroxychloroquine toxicity (see “Differential Diagnosis of Bull’s-Eye Maculopathy”).

Mechanism of Toxicity

The mechanism of hydroxychloroquine retinal toxicity has yet to be fully elucidated. Studies have shown that the drug affects the metabolism of retinal cells and also binds to melanin in the RPE, which could explain the persistent toxicity after discontinuation of the medication. However, these findings do not explain the clinical pigmentary changes causing a bull’s-eye maculopathy.

Medication Dosage

Several factors have been associated with the risk of developing hydroxychloroquine retinopathy. One of the most important appears to be dosage—with debate over whether daily intake vs. cumulative dosage is most significant. Recent studies indicate that cumulative dosage may be a more important consideration than daily dosage.² However, since higher daily dosage will obviously lead to the toxic cumulative dose more rapidly, daily dosage is still important to consider. Higher daily dosage also leads to higher concentration of the drug in the RPE, which could lead to more aggressive tissue damage. Previous reports indicate that toxicity is rare if dosing is less than 6.5 mg/kg/day.² To avoid overdosage, especially in obese patients or those of short stature, dose should be based on height, which allows for an estimation of ideal body weight. (The drug clears slowly from the blood, so basing dosage on weight puts obese patients at risk.) The typical daily dos-

Systemic Medications That Can Cause Retinal Toxicity

Canthaxanthine	Isotretinoin
Chlorpromazine	Methoxyflurane
Deferoxamine	Rifabutin
Digoxin	Sildenafil
Ethambutol	Tamoxifen
Ethylene glycol	Thioridazine

age for most indications is 200 mg to 400 mg per day. Daily dosage is recommended not to exceed 400 mg.

Risk for Toxicity

Although it is not possible to predict which patients will develop retinal toxicity, high-risk characteristics include the following:

- daily dose greater than 400 mg (or, in people of short stature, a daily dosage over 6.5 mg/kg ideal body weight) or total cumulative dose of more than 1,000 g
- medication use longer than five years
- concomitant renal or liver disease (because the drug is cleared by both routes)
- underlying retinal disease or maculopathy
- age greater than 60 years.

Watching for Plaquenil Toxicity

BASELINE EXAM

- Ocular exam
- Automated visual fields with white 10-2 protocol
- One or more of these objective tests:
FAF
mfERG
SD-OCT

Optional: Fundus photography

— *NORMAL* —>

ABNORMAL

ANNUALLY AFTER 5 YEARS

- Ocular exam
- Automated visual fields with white 10-2 protocol
- One or more of these objective tests:
FAF
mfERG
SD-OCT

TOXICITY SUSPECTED

- Repeat visual fields
- Perform more of the objective tests above
- Perform more frequent exams

TOXICITY CONFIRMED

- Refer to prescribing physician
- Discontinue medication
- Examine at 3 months, then annually until stable

Monitoring Guidelines

Guidelines on screening for retinopathy associated with hydroxychloroquine toxicity were initially published by the Academy in 2002. These guidelines were updated in February of this year, given the emergence of more sensitive diagnostic techniques and the recognition that risk of toxicity from years of hydroxychloroquine use is greater than previously believed.

The updated guidelines state that due to sensitivity, specificity and reliability issues, it is not recommended that Amsler grid testing, color vision testing, fundus examination and full-field electroretinogram or electrooculogram be used for toxicity screening. Fluorescein angiography may assist in visualizing early subtle changes in the RPE, but it is not considered a screen-

Differential Diagnosis of Bull's-Eye Maculopathy

Age-related macular degeneration
Benign concentric annular dystrophy
Central areolar choroidal dystrophy
Chloroquine/hydroxychloroquine retinal toxicity
Chronic macular hole
Cone and cone-rod dystrophies
Stargardt disease

ing tool for retinal toxicity.

It is critical to counsel patients about the benefits and limitations of screening, underscoring that it can catch toxicity at early stages and minimize vision loss but cannot necessarily prevent all toxicity and vision loss.

Baseline examination. At the initiation of treatment with hydroxychloroquine, the prescribing physician should refer the patient to an ophthalmologist. During the initial examination, it is recommended that the patient receive:

- 1) a thorough ocular examination documenting any preexisting conditions,
- 2) a Humphrey visual field central 10-2 white-on-white pattern, and
- 3) at least one of the following objective tests, if available:
 - fundus autofluorescence (FAF)
 - multifocal electroretinogram (mfERG) or
 - spectral domain OCT (SD-OCT).

In fact, mfERG—a test that is typically available in large clinical centers—objectively evaluates function and can be used in place of visual fields. It's also worth considering the use of color fundus photographs to assist in documenting changes over time, especially if there is preexisting retinal pathology. However, the dilated fundus exam should not be considered a screening tool, as it only picks up relatively late toxic changes.

Ongoing monitoring. Encourage the patient to obtain an annual ophthalmic examination as part of the screening process. Since toxicity is rare within the first five years of treatment, ancillary testing is not necessary unless

abnormalities are noted on baseline examination. However, earlier, more frequent screening may be prudent for those at higher risk for toxicity. After five years of treatment, perform annual screenings, including an ocular examination, 10-2 threshold field testing, and one of the objective tests. In practical terms, SD-OCT is most widely available, and is very sensitive, so practitioners should look for subtle parafoveal abnormalities.

Toxicity: suspected and confirmed. Whenever you note abnormalities, obtain additional testing. Repeat visual fields promptly if you see central or parafoveal changes, even if these appear to be nonspecific. If these findings are reproducible, follow up with objective testing. If toxicity is suspected, perform more frequent and detailed examinations. Once toxicity is confirmed, the prescribing physician should be notified and hydroxychloroquine discontinued unless it is medically critical and the patient has been informed of the visual risk. Before discontinuation, inform the patient that the drug clears slowly from the body and therefore visual function may continue to slowly deteriorate.

Conclusion

Patients and their physicians prescribing hydroxychloroquine need to be keenly aware of retinal toxicity risks and the importance of regular screening, and ophthalmologists who see these patients should keep retinal toxicity in the front of their minds. Adhering to the Academy's guidelines will help achieve the goal of identifying abnormalities with screenings and examination prior to the patient's visual complaints.

1 Marmor, M. F. et al. *Ophthalmology* 2011; 118:415–422.

2 Mieler, W. F. New Monitoring Guidelines for Hydroxychloroquine. Presented at Retina Subspecialty Day, Oct. 16, 2010, Chicago.

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