In the United States, hydroxychloroquine and chloroquine are used to treat inflammatory disorders such as systemic lupus erythematosus (SLE; most common use), rheumatoid arthritis, Sjögren syndrome, and post-Lyme disease arthritis. This class of drugs, however, has been associated with an increased risk of retinotoxicity. Although the reported incidence is relatively low, hydroxychloroquine/chloroquine retinotoxicity represents an underappreciated condition that is modifiable—but not reversible or stoppable—if detected early in development.

Toxicity from hydroxychloroquine may be seen in the cornea and the macula. Corneal findings may include a vortex keratopathy characterized by whorl-like epithelial deposits; however, these changes are considered relatively benign. The macular changes associated with this toxicity are potentially serious and are related to dosage and duration. Studies have suggested that the risk rises to 1% after 5 to 7 years of use, and that a cumulative dose of 1,000 g is sufficient for developing toxicity.

An additional consideration for eye care specialists is that preexisting liver and/or kidney disease may accelerate the development of retinotoxicity. Patients with these known risk factors require increased monitoring to stave off the potential visual consequences of retinotoxicity associated with this class of drugs.

THE MECHANISM OF RETINOTOXICITY

The recommended dosage is no more than 6.5 mg/kg per day, using the standard known as ideal weight. These drugs, however, have a half-life of 1 to 2 months, implying that effects can still be noted even after discontinuation of use. As well, discontinuation does not ensure halting progression. Both the liver and the kidney clear chloroquine and hydroxychloroquine, and any compromise of these organs may reduce the dosage needed to evoke retinotoxicity. Concomitant medical conditions in patients on these drugs may be important. Although reports vary, patients affected by SLE often have altered liver function.7 As a result, patients with SLE should have liver function tests performed and drugs that further aggravate liver function should be avoided.8 Additionally, more than 50% of patients with SLE have renal function abnormalities resulting in glomerular damage.9 It has been suggested that dosages of hydroxychloroquine should be lowered in patients with preexisting liver or kidney disease, with the corollary that standard dosing may induce toxicity sooner.10-17

The exact mechanism of retinotoxicity is arguable, but it is known that the drug binds to melanin in the retinal pigment epithelium (RPE), which may concentrate the agent.18 Chloroquine is known to affect perifoveal cells19 by disrupting lysosomal RPE function, which then precipitates the deposition of lipofuscin.20,21 The degradation also occurs in cone photoreceptors.21 Animal studies suggest that photoreceptors are affected with reversible inner retinal lipidosis and irreversible photoreceptor degeneration.22,23 It has also...
been reported in an animal study that inner and outer retinal changes were observed, first in the ganglion cell layer with accumulation of cytoplasmic bodies and subsequently with photoreceptor and RPE degeneration. This degeneration may be attributable to an alteration of protein synthesis and lipid peroxidation. Hallberg et al suggested that the ganglion cells are affected early in the course by alteration of phospholipid metabolism, which is followed by retinal nerve fiber layer death. The effect on ganglion cells, with subsequent retinal nerve fiber layer thinning and photoreceptor damage, has been corroborated in other reports. A recent report suggests that significant retinal thinning occurs 1 mm from the foveal center in patients with early and late toxicity and that measuring thickness at 1 mm from the fovea may help screen for early toxicity.

**RETINAL MANIFESTATION OF CHLOROQUINE AND HYDROXYCHLOROQUINE TOXICITY**

The classic definition of chloroquine toxicity is characterized by bilateral pigmentary change of the macula which spares the fovea—or bull’s-eye maculopathy. The peripheral retina is infrequently involved. There is one report of progressive hydroxychloroquine toxicity mimicking low-tension glaucoma after discontinuation in a patient with a cumulative dose of 2,200,000 mg.

Visual complaints are primarily associated with central vision loss and visual field or color vision anomalies. It is also reported that a diminished electroretinogram (ERG) is associated with hydroxychloroquine toxicity. Other reports address the fact that there is discontinuity of the perifoveal photoreceptor inner segment/outer segment junction (photoreceptor integrity line [PIL]) and thinning of the outer nuclear layer that precedes loss on 10-2 visual field testing.

In 2009, Kellner et al reported that multifocal electroretinography (mfERG), melanin-related near-infrared fundus autofluorescence, lipofuscin-related fundus autofluorescence, and SD-OCT are all able to detect early stages of chloroquine toxicity. This group also reported that the loss of outer nuclear layer thickness is the earliest indicator, and that this process may initiate after the drug is supplied to retinal ganglion cells via the vascular system. Other reports corroborate the importance of SD-OCT testing and mfERG as sensitive tools in the early detection of retinotoxicity.
Figures 1 through 5 illustrate the application of current diagnostic technology on a relatively young patient with SLE after a cumulative dosage of more than 1 million mg.

CONCLUSIONS AND RECOMMENDATIONS

The relative availability of diagnostic technology affords an opportunity for a more sophisticated approach to managing patients taking chloroquine or hydroxychloroquine, including earlier detection to facilitate prevention of visual compromise. Guidelines for managing these patients were highlighted in a recent report by Marmor et al.18

Step 1. The first step in the process should be educating the patient regarding potential issues associated with the medication. The discussion should be documented in the patient’s chart.

Step 2. The updated guidelines also suggest an examination prior to the initiation of hydroxychloroquine. The patient’s liver and kidney function should also be determined prior to the initiation of treatment.

Step 3. Assess the patient and carefully chart:
- any visual complaints;
- a thorough medical history with emphasis on liver and kidney disorders;
- the duration and dosage of hydroxychloroquine;
- BCVAs;
- vortex deposits on corneal epithelium as a possible harbinger of retinal toxicity, as assessed by biomicroscopic evaluation;
- pigmentary abnormalities in the macula and periphery, and retinal vasculature as noted dilated on ocular examination; and
- visual field evaluation with 10-2 or another test of equal resolution (2° test spread).

Step 4. Apply at least 1 of the following specialized tests or obtain a consult to do so:
- SD-OCT to assess inner and outer retinal thickness and inner/outer segment (PIL) juncture in the perifoveal region with emphasis on the 1- to 1.5-mm zone from the fovea;
- fundus autofluorescence imaging to reveal subtle RPE defects and early photoreceptor damage; and/or
- mfERG to measure for localized paracentral depression.

Note that the following are no longer recommended for early detection of hydroxychloroquine and chloroquine retinotoxicity: fundus photography, time-domain OCT, fluorescein angiography, full-field ERG, electro-oculogram, color vision testing, Amsler grid, and 24-2 visual field testing.

Step 5. After establishing a baseline, screening for toxicity on an annual basis should be continued no later than 5 years after starting the medication.11 This step is a minimal recommendation, and annual examinations after baseline determination would be

“Should early toxicity be detected and the drug discontinued, it is important to remember that, even with discontinuation, the condition has the potential to progress, and appropriate follow-up is indicated.”

Figure 4. While the PIL is ultimately affected in retinotoxicity, this retinal cross-section shows no demonstrable effect on the PIL.

Figure 5. The 10-2 visual field demonstrates no defect.
judicious. Attention must also be paid to existing liver and renal function, as this could affect the relative dosage actually being delivered. Should early toxicity be detected and the drug discontinued, it is important to remember that, even with discontinuation, the condition has the potential to progress, and appropriate follow-up is indicated. It would likewise be judicious to communicate all findings and recommendations in writing to the primary care physician with a copy to the dispensing pharmacist.

Larry J. Alexander, OD, is a consultant to industry after having served in the US Navy, a professor at the University of Alabama at Birmingham School of Optometry, and practicing within a referral center in Louisville, Kentucky. He is the president of the Otopometric Retina Society and the senior director of clinical education for Optovue, Inc. Dr. Alexander may be reached at larryalexander.txrr.com.

Dwayne Yeager, OD, is an adjunct professor at the University of Houston College of Optometry and practices primary care optometry in West Monroe, Texas.


28. Hallberg A, Naejer F, Andersson A. Effects of long-term chloroquine exposure on the phospholipid metabo-

38. Kellner S, Kellner U. Chloroquine retinopathy. Lupusis and melanin-related fundus autofluores-


Would you like to comment on an author's article?
Do you have an article topic to suggest?
Do you wish to tell us how valuable Advanced Ocular Care is to your practice?
We would love to hear from you.
Please e-mail us at letters@hmctoday.com with any thoughts, feelings, or questions you have regarding this publication.