

RETINA SCREENING

Rx Side Effects: New Plaquenil Guidelines and More

BY MIRIAM KARMEL, CONTRIBUTING WRITER

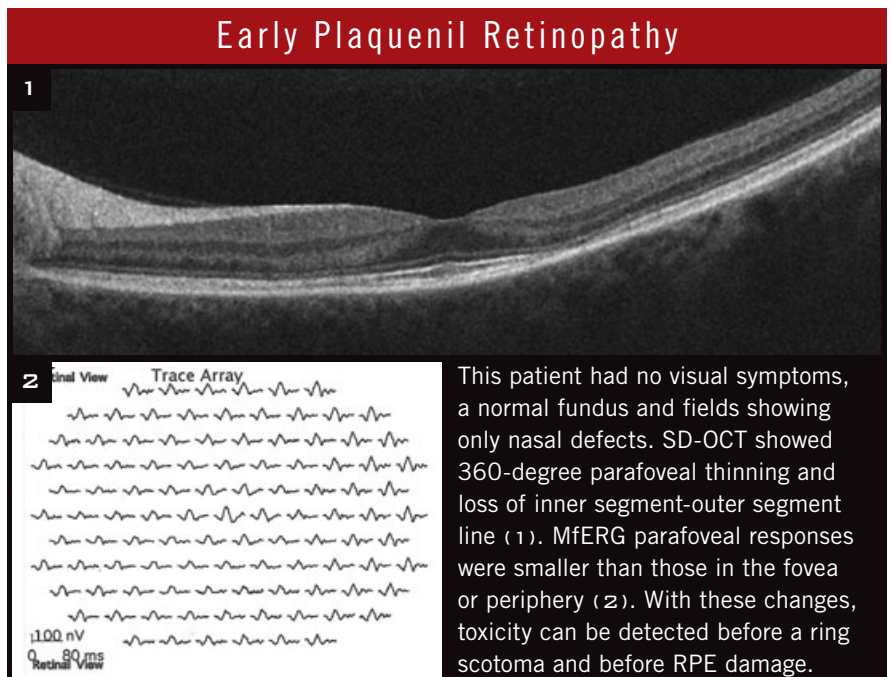
INTERVIEWING FREDERICK W. FRAUNFELDER, MD, ANNE E. FUNG, MD, AND MICHAEL F. MARMOR, MD

Drug-induced ocular side effects are back in the spotlight, thanks to the Academy's revision of its recommendations on screening for retinal toxicity from chloroquine and its analogue hydroxychloroquine (Plaquenil).¹

There are hundreds of drugs with potential retinal toxicity—so many that the National Registry of Drug-Induced Ocular Side Effects doesn't stratify them by incidence or effect, said Frederick W. "Rick" Fraunfelder, MD, director of the Registry and associate professor of ophthalmology at Oregon Health & Science University in Portland. "Plaquenil toxicity isn't even in the top 10, or the top 100" if you're looking at incidence, he said. "It's a pretty rare thing." Nevertheless, he urged doctors to master the Academy's new guidelines, because the effects from chloroquine and hydroxychloroquine, when they do occur, are severe and often irreversible. (Note that chloroquine is not used frequently in the United States and has been replaced by the use of hydroxychloroquine because the latter has fewer side effects.) Also, watch for June's Ophthalmic Pearls for more on spotting and treating Plaquenil toxicity.

The Plaquenil Problem

"Plaquenil toxicity is very distinctive," said Michael F. Marmor, MD, professor of ophthalmology at Stanford University. Dr. Marmor, who chaired the Academy's screening guidelines



This patient had no visual symptoms, a normal fundus and fields showing only nasal defects. SD-OCT showed 360-degree parafoveal thinning and loss of inner segment-outer segment line (1). MfERG parafoveal responses were smaller than those in the fovea or periphery (2). With these changes, toxicity can be detected before a ring scotoma and before RPE damage.

committee, said the goal in Plaquenil screening is to catch changes at a very early stage when there's just a minimal amount of loss of vision. "Then, when you stop the drug, the damage won't progress enough to cross the fovea and affect reading vision."

Plaquenil, widely used to treat lupus, rheumatoid arthritis and other inflammatory and dermatologic conditions, is very effective, and "the risk of toxicity in the first five years for someone without special risk factors is very low," Dr. Marmor said. However, risk increases with duration of use, and the guidelines call for annual screening after five years, or sooner if there are "unusual risk factors or a suspicion

of early toxicity."

Anne E. Fung, MD, a retina specialist at Pacific Eye Associates in San Francisco, averages one Plaquenil screening a week, due to her close affiliation with the medical center's rheumatology and dermatology clinics. Still, in 10 years of practice, she's seen just one case of toxicity. Dr. Marmor, on the other hand, has seen at least 10 cases in the past year.

Dr. Fung's case involved a 48-year-old woman with lupus. Nine years after discontinuing medical therapy, the patient had new scotomas, difficulty reading and progression of bull's-eye maculopathy. Plaquenil's long half-life in the body can cause irreversible and

progressive damage, Dr. Fung said.

Similarly, one study reported that 16 women who'd taken hydroxychloroquine or chloroquine, or a combination of the agents, showed no improvement seven years after stopping drug therapy, and progression occurred in six of the cases.²

The Revised Guidelines

The Academy's new guidelines represent "a paradigm shift from subjective to objective measures," said Dr. Fung. "It's a new algorithm, very much a new concept in Plaquenil screening." Some points to consider:

Preferred screening methods. 10-2 visual fields, but not Amsler grids, are still acceptable for screening if read with caution. Dr. Marmor said, "We also recommend use of objective tests such as spectral domain OCT, multifocal ERG and fundus autofluorescence." He added that older time domain OCT units lack enough sensitivity for Plaquenil toxicity.

Go by ideal, not real, weight. Dr. Marmor stressed the importance of not overdosing, which greatly accentuates the risk of toxicity. Therefore, the new guidelines suggest using a person's height as a dosing factor. By the old standards, obese people, if dosed by their actual weight, could be over-medicated, Dr. Marmor said. If you're short, the standard prescription of 200 mg of Plaquenil, twice daily, is too much, he said.

The recommended dosage is no more than 6.5 mg/kg/day, using the standard known as "ideal weight," which factors in height. Dr. Marmor suggested calculating this as follows:

- For women, the ideal weight is 100 lbs for 5 feet, plus five lbs per extra inch of height.
- For men, the ideal weight is 110 lbs for 5 feet, plus five lbs per extra inch of height.

What if the ideal dose is 300 mg/day? Both Drs. Marmor and Fung suggested alternate-day dosing. "It's possible to average a dose over the course of two or three days," Dr. Fung said. "Take two one day and one the next."

Unfortunately, prescribing doctors

Share Your Data

The National Registry of Drug-Induced Ocular Side Effects was founded in 1976 by Dr. Fritz Fraunfelder as a place where doctors could solicit information about and contribute reports of suspected drug toxicities.

How does it work? If you suspect that an ocular condition is drug-related, the Registry, a nonprofit organization, may help confirm that suspicion. For example, you may have a patient with eye inflammation who recently was vaccinated for hepatitis B. Is there a connection, as was reported last year?¹

"Doctors can call us and we can search" for similar cases, said Dr. Rick Fraunfelder. Patient information is protected, so access is restricted. "We'll give the physician available literature and all the current spontaneous reports." (The Registry includes data from the FDA and the World Health Organization's spontaneous database.) Dr. Fraunfelder also encourages doctors to enter their spontaneous reports into the database. For example, if a patient on a statin experiences double vision, you can submit that information to the Registry. At some point, if enough spontaneous reports are submitted, the computer issues a signal that further investigation may be warranted, Dr. Fraunfelder said.

To access the Registry, go to www.eyedrugregistry.com. The service is free, although Academy membership is required for entry.

1 Fraunfelder, F. W. et al. *Cutan Ocul Toxicol* 2010;29:26-29.

often don't consider the ocular threshold, said Dr. Fung. "I have had many patients on doses above the safe ocular threshold. So ophthalmologists are doing our patients a disservice if we are not vigilant."

Medicolegal concerns. Ophthalmologists also do themselves a disservice by not knowing the guidelines. "One of the top five reasons ophthalmologists go to court is from an adverse drug reaction," Dr. Fraunfelder said. "If the Academy is taking a position on Plaquenil, then ophthalmologists are held to that standard. We'd better be sure we're aware of it." Beyond Plaquenil, he said, it's essential to "be aware of local or systemic toxicities from topical ocular medications—and ocular toxicities from systemic medications."

With regard to Plaquenil, Dr. Marmor said, "The best hope is that patients and their rheumatologists know this drug is toxic and tell the ophthalmologist about it. Then the ophthalmologist needs to know what to do and to do it well." He expressed the concern that a doctor who continues to screen for hydroxychloroquine toxicity with Amsler grid alone could face potential liability if a patient has an adverse event.

Beyond Plaquenil: Other Drugs, Other Problems

If you're looking for a comprehensive assessment of drug reactions that relate to the eye, Dr. Fraunfelder and his father, Frederick T. "Fritz" Fraunfelder, MD, along with Wiley A. Chambers, MD, literally wrote the book.³

"So many drugs can cause ocular side effects that if you're trying to make a point about which drugs to watch out for, you can't really pick [just] one," Dr. Fraunfelder said. However, he has narrowed the list for a course he teaches at the Academy's Annual Meeting and for a published review of adverse ocular drug reactions.⁴

Here are some drugs to watch out for, based on recent reports.

- **Bisphosphonates** are used to manage osteoporosis and other conditions that involve loss of bone mass. Multiple clinical concerns include blurred vision, anterior uveitis and episcleritis.
- **Cetirizine** (Zyrtec and others), an antihistamine, can cause pupillary changes, blurred vision and keratoconjunctivitis sicca. Of nine cases reported to the Registry, eight involved children.
- **Erectile dysfunction drugs** cause a range of side effects that are common, dosage-dependent and, thus far, fully reversible. They include changes in

color and light perception, blurred vision, conjunctival hyperemia, ocular pain and photophobia.

- **Ethambutol** (Myambutol), used to treat pulmonary tuberculosis, has generated over 800 reports to the Registry. Ethambutol is associated with optic or retrobulbar neuritis, affecting one or both eyes. An unusual form of the toxicity causes peripheral constriction of the visual field. Monthly ophthalmic exams are recommended for doses of ethambutol exceeding 15 mg/kg/day.
- **Fluoroquinolones** are associated with side effects not seen in other classes of antibiotics. Topical administration may cause precipitates in the cornea and, possibly, uveitis.
- **Hepatitis B vaccine** may have an association with uveitis.
- **Herbal medicines and nutritional supplements** generated \$60 billion in sales worldwide in 2004, according to the World Health Organization.⁵ WHO has published guidelines on the use of herbal medicine, and the Registry lists common supplements and their visual symptom reactions.
- **Retinoids**, used to treat severe, recalcitrant acne and psoriasis and to induce remission of leukemia, have been linked to intracranial hypertension and papilledema when used in prescribed therapeutic doses.
- **Tamsulosin** (Flomax), used to treat benign prostatic hyperplasia and hypertension, has been associated with intraoperative floppy iris syndrome.
- **Topiramate** (Topamax) is used to treat epilepsy and migraines. The drug also is used off-label for a number of concerns, including weight loss, bipolar disorder and depression. It has been associated with acute angle-closure glaucoma and transient myopia.
- **Statins** may be associated with diplopia, ptosis and ophthalmoplegia, and they may exacerbate myasthenia gravis and cataracts.

Final Thoughts: Quick Tips

Some quick tips to consider when you are diagnosing and managing ocular toxicity:

Dr. Fraunfelder: "One of the main rules, but not a hard rule, is if it's a

drug toxicity, it usually is bilateral."

Dr. Fung: "I'm always concerned that the prescribing doctors are not completely aware of the dose-related toxicity of chloroquine and hydroxychloroquine. So I always check and calculate the dose. Also, communication with the prescribing doctor is very important. I have a form letter where I fill in the current dose, weight and goals."

Dr. Marmor: "Stop the drug [Plaquenil] if you detect parafoveal thinning. But you do have to discuss this with the patient and his or her rheumatologist to be sure you're not affecting the medical care. I've had a few patients continue because they think the drug is so critical for their quality of life. But the vast majority is happy stopping. There are alternatives."

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

2 Michaelides, M. et al. *Arch Ophthalmol* 2011;129:30-39.

3 *Clinical Ocular Toxicity* (Philadelphia: W. B. Saunders, 2008).

4 Fraunfelder, F. W. and F. T. Fraunfelder. *Ophthalmology* 2004;111:1275-1279.

5 *National Policy on Traditional Medicine and Regulation of Herbal Medicines—Report of a WHO Global Survey* (Geneva: WHO, 2005).

Learn More in Orlando

At this October's Annual Meeting in Orlando, Dr. Fraunfelder will teach a one-hour-long Instruction Course titled "**Drug-Related Adverse Effects of Clinical Importance to the Ophthalmologist.**" It will provide a detailed review of clinical concerns and management guidelines. Problems with drug toxicity that emerge during the next few months will be included.

More information on this Instruction Course will be posted online on June 1—go to www.aaopt.org/2011 and search the Online Program for "Fraunfelder."



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