Drug Toxicity to the Retina and Optic Nerve: Are You Missing It?

We live in an era in which science and technology are advancing in leaps and bounds," said David Sarraf, MD, at the Stein Eye Institute, University of California, Los Angeles. In this environment, he said, "Many new classes of drugs are being developed, and we have powerful advanced retinal imaging systems to identify many new manifestations of drug toxicity."

With these advances, ophthalmologists need to maintain a keen awareness of toxicities, said Gaurav K. Shah, MD, at The Retina Institute in St. Louis. "If you can't explain why vision is worsening, always consider medications."

William F. Mieler, MD, agreed, "If you don't take a thorough medication history or aren't aware of a medication's manifestations, you can easily miss drug toxicity."

And spotting it as early as possible is critical. "In most cases, it isn't possible to reverse retinal abnormalities, but you can prevent or limit progression of changes by stopping the medications," Dr. Mieler said. He is at the University of Illinois College of Medicine in Chicago.

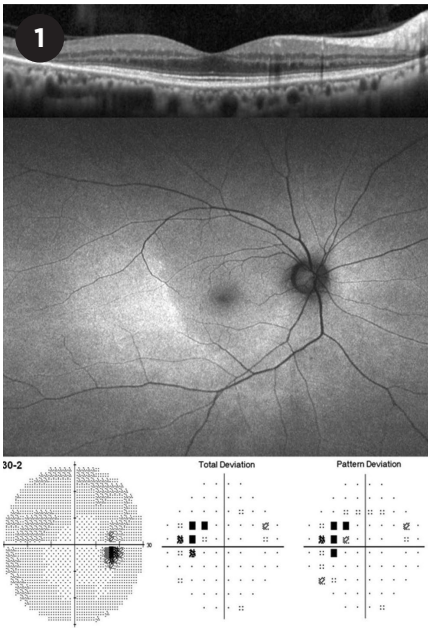
Several systemic drugs, including hydroxychloroquine, ethambutol, pentosan, thioridazine, and various cancer drugs, are known to cause toxicity to the posterior segment of the eye. Keeping them in mind can help preserve a patient's vision.

Hydroxychloroquine Toxicity: Screening Is Key

Hydroxychloroquine (Plaquenil) is a disease-modifying antirheumatic drug that is commonly used to reduce arthritic pain and swelling.

Signs and symptoms. "The association of Plaquenil therapy with macular toxicity is well established," said Michael F. Marmor, MD, at the Byers Eye Institute at Stanford University. He noted that the initial changes appear as subtle photoreceptor loss with damage to the ellipsoid zone. Dr. Sarraf added that ellipsoid loss has a parafoveal distribution, and the inferotemporal sector is typically affected first. The classic bull's-eye pattern of retinal pigment epithelium (RPE) loss occurs later in the disease process, said Dr. Mieler. He further noted that "although the toxicity is parafoveal in Caucasians, it is more peripheral in a pericentral distribution in Asians." (See Fig. 1.) For the most part, Hispanic and African American patients exhibit parafoveal distribution, though there may be a slightly greater likelihood of extramacular distribution among these patients compared with Caucasians.[1]

Higher-risk patients. The risk of Plaquenil maculopathy is markedly increased in patients who are also receiving tamoxifen (Nolvadex), a nonsteroidal antiestrogen agent used for long-term treatment of breast cancer and glioblastoma, said Dr. Mieler.



PERICENTRAL PRESENTATION (ASIAN EYE). *(Top) Horizontal spectral-domain optical coherence tomography, showing temporal loss of the outer retina (ellipsoid zone and interdigitation zone). (Middle) Wide-field fundus autofluorescence showing a broad area of hyperfluorescence extending beyond the outer edge of the inferotemporal macula. (Bottom) 30-2 visual field (VF) with superonasal scotoma corresponding to the retinal changes. A 10-2 VF test showed normal results.*

Patients are also at higher risk if they have a renal condition, which impairs clearance of Plaquenil and can lead to unpredictably high blood levels.[1]

Potential contraindication. Dr. Sarraf considers preexisting age-related macular degeneration (AMD) a relative

BY ANNIE STUART, INTERVIEWING **MICHAEL F. MARMOR, MD, WILLIAM F. MIELER, MD, DAVID SARRAF, MD,** AND **GAURAV K. SHAH, MD.**

contraindication against the use of Plaquenil. That's because Plaquenil toxicity can mimic AMD, making it more challenging to identify patients who develop the drug-related condition. "Anecdotally, I have also seen cases of more rapid progression of AMD features in patients being treated with Plaquenil," he said, adding that the same may be true for conditions such as retinitis pigmentosa.

Dose and duration. Both the daily and total cumulative dose can increase the risk of Plaquenil toxicity. "To minimize this, the dose should be maintained at less than 5.0 mg/kg per day for real body weight, rather than ideal weight," said Dr. Mieler.

The 400-mg dosage has traditionally been very popular, said Dr. Sarraf. "But due to better education of rheumatologists and retina specialists," he said, "physicians are moving away from this dosage and using a safer level of 200 to 300 mg."

Toxicity also increases the longer a patient takes the medication, said Dr. Shah. At five years of exposure, toxicity occurs in less than 1% of patients receiving Plaquenil therapy. "But at 20 years, it occurs in close to 20% of patients." Dr. Marmor pointed out that these percentages apply to an unscreened population. For a patient who has taken the drug for 20 years but shows no sign of damage now, the risk of developing toxicity in the ensuing year is only 4%, he said.

EHR alert. It can be easy to overlook that a patient is taking Plaquenil, especially if he or she is using multiple drugs, said Dr. Shah. "But when an electronic health record (EHR) alert comes up for Plaquenil, you know to at least initiate a conversation about screening with the patient."

Screening guidelines. In 2016, an Academy task force published new monitoring guidelines for Plaquenil.[1] These recommendations call for baseline ophthalmologic exam, inclusive of fundus examination, within the first year of starting long-term Plaquenil treatment to check for underlying disease, fundus appearance, and function.

Annual screening. In patients who aren't considered high risk, annual screening can be deferred until the five-year mark. At this point, the task force guidelines recommend 10-2 Humphrey visual field in all patients, adding 24-2 or 30-2 for Asian patients. Spectral-domain optical coherence tomography (SD-OCT) of the macula—and, for Asian patients, wider-angle scans across the vascular arcade—are also important.[1]

"Toxicity cannot be prevented by screening, so the goal is early detection of changes in visual field or spotting parafoveal thinning on OCT before changes to the retinal pigment epithelium appear," Dr. Marmor said. "If the drug is stopped before there is RPE damage, progression and central visual loss can be prevented," he said.

Try multifocal ERG first? Dr. Shah recommends using multifocal electroretinography (mfERG). Dr. Marmor noted that "the test is not widely available, and the approved standard systems can be tricky to use. It is a great corroborative test for ambiguous field loss, but rarely definitive when used alone."

Confirm a constellation of changes. Don't rely on just one test, said Dr. Shah. "You need to analyze a constellation of findings." Dr. Marmor agreed, noting that "mfERG and FAF can help to confirm borderline abnormalities. And since toxicity evolves slowly, there is always time to bring a patient back for re-testing or to refer for additional tests. Hydroxychloroquine is an excellent drug with low systemic toxicity and should not be stopped without firm evidence of retinal damage."

Communication key. "If I see a patient with evidence of Plaquenil toxicity," said Dr. Mieler, "I telephone the referring doctor—usually a rheumatologist—in front of the patient and ask, 'Can you stop the medication?'" This type of toxicity is not reversible, and no therapy is available. Spotting it prior to RPE loss can minimize or prevent central visual loss.[1]

"Whether you discontinue the medication or reduce the dosage, you need a continuous line of communication with the rheumatologist and the patient to ensure you optimize the patient's retinal status without adversely affecting his or her systemic status," said Dr. Sarraf.

Ethambutol: A Toxic Optic Neuropathy

Ethambutol toxicity can also be easily missed. Pulmonary specialists use this medication as a first line of defense against tuberculosis (TB) and *Mycobacterium avium* complex (MAC). Ethambutol is typically one of three drugs used for MAC, said Dr. Shah. The other two are a macrolide such as azithromycin and a rifamycin such as rifabutin. "I've probably seen three or four cases already this year of previously undiagnosed ethambutol toxicity," he said.

Signs and symptoms. Sometimes mistaken for a retina problem, ethambutol toxicity causes painless loss of central or paracentral vision when the drug damages the optic nerve, which can lead to an optic neuropathy that is symmetric and usually bilateral, said Dr. Shah. Other symptoms may include photophobia or poor dark adaptation.

Testing. Because this type of toxicity can cause changes in color vision, said Dr. Shah, it's helpful to test color vision before the patient starts the medication.

No symptoms. Patients who are taking ethambutol and are asymptomatic should receive monthly screenings, including visual acuity and color vision testing, he said.

Toxicity suspected. When you suspect ethambutol toxicity, check for changes in visual acuity and visual fields, in addition to color vision, said Dr. Shah. "Patients may have a relative afferent pupillary defect, but only when one eye is affected—not when

Stay Informed

Supported by the Academy and the Casey Eye Institute at Oregon Health & Science University, the **National Registry of Drug-Induced Ocular Side Effects** (www.eyedrugregistry.com) allows users to submit case reports and inquire about adverse events, and it points to links where the book *Drug-Induced Ocular Side Effects* can be purchased.

both eyes are affected." OCT analysis to assess for retinal nerve fiber layer loss, and visual evoked potential (VEP) testing, can also help to make the diagnosis of ethambutol toxicity, he said.

Dose related. With TB or MAC regimens, ethambutol toxicity is dose related, said Dr. Shah. "If the dose is less than 30 mg/kg per day, patients are typically safe," he said. "But a higher dose can become problematic. This is another drug that is cleared by the kidney, so it can be more of a problem in patients with renal dysfunction."

Reversible. The big take-home message? This toxicity is reversible if it's identified and the drug is stopped early enough, said Dr. Shah. "After stopping the drug, the patient's vision might improve, making it important to catch this before it's too late."

Pentosan Toxicity: Hiding in Plain Sight?

Pentosan polysulfate sodium (PPS) is a drug used for chronic interstitial cystitis, a bladder condition that is more common in women than in men, said Dr. Sarraf.

Signs and symptoms. A recent Emory University report showed that patients taking this drug may develop a pigmentary maculopathy that is centrally located in the macula of both eyes, said Dr. Sarraf. Patients reported having difficulty reading and prolonged dark adaptation even though visual acuity was generally intact and funduscopic findings were subtle.[2]

"Additional reports have shown that changes at the severe end of the spectrum may also include macular atrophy or even geographic atrophy," he said, adding that this toxicity may be more common than previously realized.

Another AMD masquerader. Dr. Shah said that one of his fellows just presented at the meeting of the American Society of Retina Specialists (ASRS) on their experience with this drug.[3] "He assessed nearly 55 patients on pentosan," said Dr. Shah. All had diagnoses of dry AMD and/or nonspecific RPE abnormalities, but at least three or four of those patients were described as having a pigmentary retinopathy, most likely related to the drug."

AMD patients in their 40s or 50s, in particular, should be checked for potential pentosan toxicity, said Dr. Shah. EHR records can confirm whether the patient is on the drug.

In fact, any time you see a pigmentary retinopathy in the macula of both eyes, added Dr. Shah, always have drug toxicity or interactions in the back of your mind. "With the exception of ethambutol, the RPE is where most drugs affect the eye."

"Although pentosan toxicity is commonly mistaken for AMD," said Dr. Sarraf, "it is associated with a very characteristic pattern on FAF, making it possible to distinguish the two disorders."

At present, the full extent of risk factors for development of pentosan-related retinal abnormalities, is not known, said Dr. Mieler. Further study is needed.

Thioridazine: Possible Progression After Discontinuation

This antipsychotic medication—brand name Mellaril—is the only drug in its class that causes significant retinal toxicity, usually occurring with dosages in excess of 1,000 mg a day, said Dr. Mieler.

"Like hydroxychloroquine, it causes disruption of the RPE," he said, "but the effect is much more diffuse, appearing not only in the macular region but also throughout the posterior pole and extending into the periphery." An initial salt-and-pepper appearance may be identified, but this may progress to severe toxicity that includes nummular atrophy of the RPE and choriocapillaris, he said. Because the drug is stored indefinitely in the RPE, retinal alterations may continue to progress even after discontinuation of the medication.[4]

Cancer Treatment: New Drugs May Bring New Risks

Toxicity in patients on cancer drugs may be detected relatively early because the ophthalmologist is more likely to be aware that a patient has cancer than other conditions, such as a bladder problem or lung infection, said Dr. Shah.

Ask about it. It's important to ask about all cancer medications the patient is currently taking—or has used in the past, said Dr. Mieler. For example, tamoxifen can cause intraretinal crystalline deposits in the eye, leading to early symptoms of mild decreased vision and dyschromatopsia.[4] Taxols, used to treat metastatic breast cancer, can cause nonleaking cystoid macular edema. But this toxicity is frequently overlooked because the etiologies of macular edema are so broad and diverse, said Dr. Mieler.

> Any time you see a pigmentary retinopathy in the macula of both eyes, always have drug toxicity or interactions in the back of your mind. —*Dr. Shah*

Two newer classes of cancer therapeutics with the potential for toxicity include MEK (mitogen-activated protein kinase kinase) inhibitors and immune checkpoint inhibitors.

MEK inhibitors. This new class of drug treats a variety of cancer subtypes, said Dr. Sarraf. It can disrupt the outer blood-ocular barrier and lead to the accumulation of fluid in the subretinal space in various patterns that include very shallow and bullous forms of exudative retinal detachment.

Dr. Sarraf noted that the fluid associated with MEK inhibitors can be confused with central serous chorioretinopathy (CSCR), but unlike CSCR, there is no evidence of pigment epithelial detachment or leakage on dye-based angiography. He said, "If you stop the MEK inhibitor, the fluid usually resolves." However, Dr. Mieler added, "It is important to keep in mind that these drugs are being employed for life-threatening conditions, so stopping them may not always be an option."

Immune checkpoint inhibitors. These drugs target the tumor by enhancing T-cell function and immunoreactivity, said Dr. Sarraf. "They may also trigger uveitis or Vogt-Koyanagi-Haradi (VKH)-like syndromes, causing subretinal fluid or macular detachment or even bullous areas of detachment in the peripheral retina." (See also "Checkpoint Inhibitors: Watch for AEs," page 21.)

1 Marmor MF et al. *Ophthalmology*. 2016;123(6):1386-1394.
2 Pearce WA et al. *Ophthalmology*. 2018;125(11):1793-1802.
3 Jain N et al. Expanded clinical spectrum of pentosan polysulfate sodium associated maculopathy. Presented at American Society of Retina Specialists; July 30, 2019; Chicago.
4 Andreoli MT, Mieler WF. What systemic medications require periodic fundus evaluation? What am I looking for and what tests do I do? In: Fekrat S, ed. *Curbside Consultation in Retina: 49 Clinical Questions.* 2nd ed. Slack Inc; 2019:167-171.

Dr. Marmor is professor of ophthalmology emeritus at Stanford University and a retina specialist at Byers Eye Institute in Palo Alto, Calif. *Relevant financial disclosures: None.*
Dr. Mieler is professor of ophthalmology, retina service; vice chair for education and director, ocular oncology clinic; and director, residency and vitreoretinal fellowship training, at the University of Illinois College of Medicine in Chicago. *Relevant financial disclosures: None.*
Dr. Shah is a partner at The Retina Institute in St. Louis, Mo. *Relevant financial disclosures: None.*
Dr. Sarraf is a retina specialist and clinical professor of ophthalmology at the Stein Eye Institute at the University of California, Los Angeles. *Relevant financial disclosures: Heidelberg Engineering: S; Optovue: C,S; Topcon: S.*
See disclosure key, page 10. **For full disclosures,** see this article at aao.org/eyenet.

SUBSPECIALTY DAY

AAO 2019 Inspire!

Be sure to attend Retina Subspecialty Day. Topics will span medical and surgical retina; pediatric retina, oncology, uveitis, and diabetes; imaging; and more. Also, be sure to attend both sessions about late-breaking developments, the pro-con debates on controversial topics, and discussion of complex cases.

When: *Friday, Oct. 11, 8:00 a.m.-5:28 p.m. and Saturday, Oct. 12, 8:00 a.m.-5:30 p.m.* ***Where:*** *Moscone West 3002.* ***Access:*** *Subspecialty Day registration (Friday, Saturday).*