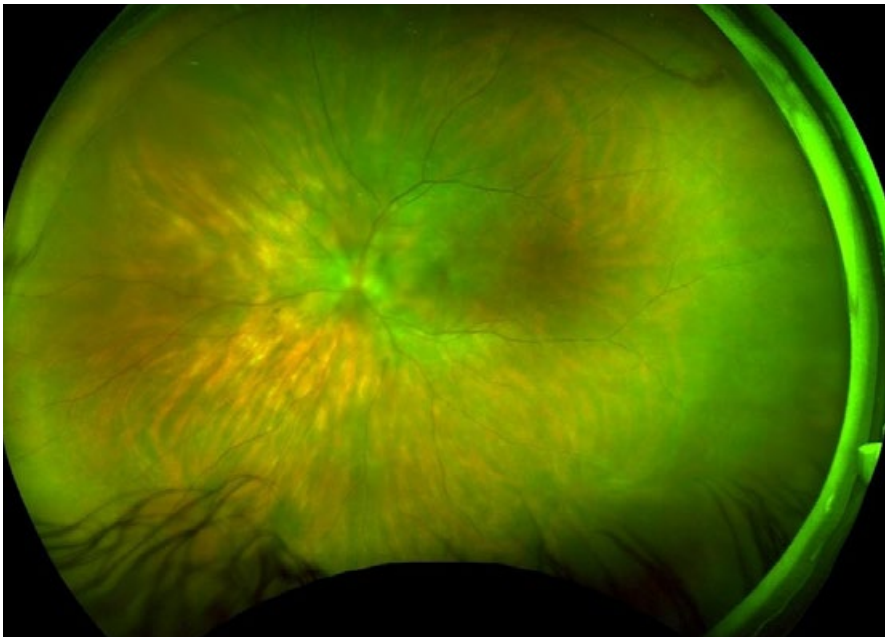
UVEITIS

Uveitis Guidelines: Immunomodulatory Therapy



INDIVIDUALIZED TX. *The guidelines provide recommendations by drug and disease. For instance, for birdshot chorioretinopathy (seen here), infliximab has a grade B recommendation, while intravenous immunoglobulins are grade C.*

SINCE GUIDELINES FOR SYSTEMIC treatment of noninfectious uveitis (NIU) were last published in 2000, treatment with biologic and other noncorticosteroid systemic immunomodulatory agents has become widespread. Now, an international, evidence-based consensus initiative has addressed the management of NIU in this new era of noncorticosteroid systemic immunomodulatory therapy (NCSIT).[1]

Rigorous methodology. Janet L. Davis, MD, MA, of the Bascom Palmer Eye Institute in Miami, emphasized the solid methodology behind the new recommendations. The group's steering committee identified clinical questions, conducted a systematic review, and circulated proposed guidelines among 130 international uveitis experts. Group members met in late 2016 to refine guidelines in a modified Delphi technique and assign Oxford levels of evidence.

Areas of clinical focus. The committee's final guidance statements addressed optimal timing for treatment escalation; transitioning among agents, including biologics; and multidisciplinary team collaboration and safety monitoring.

Key guidelines. Dr. Davis encouraged ophthalmologists who manage uveitis patients to read the consensus guidelines, and she highlighted the following recommendations:

- NCSIT for NIU may be introduced to control persistent or severe inflammation or to prevent ocular structural complications that pose a risk to visual function (see Table 1, online).
- Collection of historical, laboratory, and clinically relevant radiologic data should take place before initiation of NCSIT. These data document baseline organ functions and test for active or latent infectious diseases.
- Although there is considerable heterogeneity in the criteria used to judge disease activity—cell counts; flare; haze; deterioration (or lack of response) in visual function; and retinal, choroidal, or optic nerve lesions—they can be influential in decisions to modify therapy.
- Before changing a therapy because of ineffectiveness, consider the following: treatment nonadherence, infections, and masquerade syndromes.
- If NCSIT is not adequately effective, escalation to the maximally tolerated dose may be considered before introducing an alternative medication, including a biologic agent (see Table 2, online). Choices for therapy must be individualized based on multiple factors, including the patient's history, underlying cause of uveitis, and any systemic diseases.
- Withdrawal of NCSIT should be individualized based on tolerance of the current treatment, duration of disease control, and the specific cause of uveitis.
- Effective NCSIT drugs for NIU include mycophenolate mofetil (grade C recommendation), tacrolimus (grade B), cyclosporine (grade B), azathioprine (grade B), and methotrexate (grade B).
- Use of biologic agents for the treatment of NIU is supported for adalimumab (grade A recommendation), infliximab (grade B/C), and interferon alpha-2a (grade B).

• Communication across medical specialties, particularly between ophthalmologists and rheumatologists, fosters optimal therapy with safe prescribing and monitoring of NCSIT.

—*Gabrielle Weiner*

1 Dick AD et al., for the Fundamentals of Care for Uveitis International Consensus Group. *Ophthalmology*. Published online Jan. 6, 2018.

Relevant financial disclosures: Dr. Davis—AbbVie: C; Allergan: C.

EXTRA **MORE ONLINE.** For Tables 1 and 2, see this article at aao.org/eyenet.

ONCOLOGY

Novel Method Detects Intraocular Lymphoma

A STUDY BY INVESTIGATORS AT THE Proctor Foundation and the University of California San Francisco (UCSF) shows that metagenomic deep sequencing (MDS) holds promise as a future diagnostic tool for uveitic masqueraders, including primary vitreoretinal lymphoma (PVRL).[1]

"The gold standard for diagnosing PVRL is by identifying lymphomatous cells classically via cytopathology," said lead author John Gonzales, MD, at Proctor. "Other ancillary tests include flow cytometry, *IgH* gene rearrangement, and a newer test that identifies a common mutation in the *MYD88* gene."

"In this study, we described 2 patients with presumed infectious uveitis, [who were] later determined to have intraocular lymphoma by MDS and confirmed with conventional diagnostics," said coauthor Thuy Doan, MD, PhD, at UCSF.

How does MDS work? MDS is a high-throughput sequencing approach that can interrogate all of the genomic information in a clinical sample. "We theoretically can pick up any mutations a patient has, in addition to any non-host genomes, such as bacteria and viruses," Dr. Doan said. "MDS is so sensitive, we can use as little as 20 to 50 microliters of intraocular fluid, and this amount can be obtained routinely with an anterior chamber paracentesis performed in the clinic."

Surprising results. Drs. Doan and Gonzales outlined the study patients and results:

Patient 1 had B-cell vitreal lymphoma. Routine testing with pathogen-directed PCR analysis of ocular fluid after paracentesis was negative for herpes simplex virus (HSV), varicella zoster virus (VZV), and cytomegalovirus (CMV). MDS found both Epstein-Barr virus and human herpesvirus 8 present in the patient sample. Coinfection with these viruses is known to drive lymphoproliferation.

Patient 2 had intraocular B-cell lymphoma. Routine testing with pathogen-directed PCR was negative for HSV, VZV, CMV, and *Toxoplasma gondii*. Cytopathology revealed large B-cell lymphoma. MDS confirmed the negative findings for infection but found a less common, known mutation in the *MYD88* gene associated with lymphomas. This patient also had more than 100 other mutations associated with lymphoproliferative disorders, also detected by MDS.

"What's interesting is that this patient didn't have the most common *MYD88* gene mutation, L265P," said Dr. Doan. "We found a different *MYD88* mutation associated with lymphoma, which would have been missed with routine PCR testing."

Diagnosis is critical, said Dr. Gonzales, because PVRL has poor outcomes and life expectancy. Both coauthors hope to see MDS in clinical use in 3 to 5 years. "We're cautiously optimistic

CATARACT

Femtosecond Laser for Eyes With AMD

FINDINGS FROM THE FIRST STUDY TO EXPLORE THE EFFECTS OF CONVEN- tional and femtosecond laser-assisted cataract surgery (FLACS) in patients with age-related macular degeneration (AMD) found mixed results. On one hand, FLACS proved beneficial to patients with wet AMD. But on the other, the choice of surgery did not affect the long-term postoperative course.[1]

Previous studies have suggested that FLACS dissects and liquefies tissue with higher precision, less collateral damage, and a complication rate comparable to conventional cataract surgery. With that in mind, the researchers had hoped that, compared with phacoemulsification, the laser-assisted surgical option might lead to a more beneficial course of postoperative wet AMD. It did not. In long-term follow-up, changes in macular parameters—central macular thickness, central macular volume, and corrected distance visual acuity (CDVA)—were similar between the groups.

What's more, the need for postoperative anti–vascular endothelial growth factor (VEGF) injections was the same over a mean follow-up of 619 days (2.67 injections with FLACS, vs. 2.71 with conventional surgery), indicating similar progression of AMD no matter which approach was used.

Long- and short-term outcomes. While the long-term postoperative outcomes were similar, in the short term, the laser-treated eyes had less subclinical macular edema. "Originally, we assumed that the increased prostaglandin levels found in FLACS might pose an increased risk to AMD patients," said study coauthor Lucas M. Bachmann, MD, PhD, at the University of Zurich in Switzerland. "That patients after FLACS had a lower macular postoperative thickness than patients undergoing conventional phacoemulsification came as a surprise."

Limitations. These findings need confirmation, Dr. Bachmann said, noting, "The small number of patients in the FLACS group led to imprecise estimates of the treatment effect." Only 17 of the 140 study eyes underwent FLACS with the Catalys system (AMO), while the majority (n = 123) had

and think this has tremendous potential," said Dr. Doan. —*Rebecca Taylor*

1 Gonzales J et al. *Br J Ophthalmol.* 2018;102(1):6-8.

Relevant financial disclosures: Dr. Doan—NEI: S; Research to Prevent Blindness: S; Silicon Valley Community/Huang Pacific Foundation: S; UCSF Resource Allocation Program: S. Dr. Gonzales—NEI: S.

RETINA

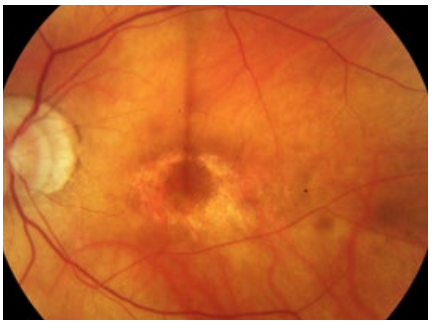
New App to Tackle Hydroxychloroquine Dosing Dilemma

HYDROXYCHLOROQUINE (HCQ; Plaquenil) is widely used for the treatment of rheumatoid arthritis and other connective tissue diseases. Excessive dosages of HCQ, however, can result in HCQ retinopathy, a potentially blinding disease. In an effort to minimize the risk and simplify the estimations of HCQ dosages in the clinic, a team of ophthalmologists created a free smartphone app for calculating optimal weekly dosages.[1] However, as initially described,[1] the app deviated from current screening recommendations,[2] thus leading to a revision.

How it works. The original DoseChecker app combined 2 approaches to HCQ dosing. The developers used both ideal and actual body weight as methods for determining the maximum dose. After a physician entered the patient's height and weight, the app selected the method that recommends the lower dose—under the assumption that the lowest dose is the safest dose to avoid any toxic effects. After making the calculation, the app then suggested a dosing schedule that divided the total weekly doses into a combination of 400- and 200-mg daily doses of hydroxychloroquine.

The developers advised that physicians will need to take other risk factors into consideration when using the app, including systemic disease, concomitant retinal disease, and tamoxifen usage.[1]

Potential problems. Such an app would be very helpful, said Michael F. Marmor, MD, of Stanford University in Palo Alto, California, and the lead author of the Academy's guidelines. However, the original DoseChecker's use of both actual and ideal body weight contradicts the Academy's guidelines[2] for calculating optimal daily dosage. "On the basis of a recent study of 2,361 long-term HCQ users,[3] the Academy now recommends that all patients using HCQ keep daily dosage less than 5.0 mg/kg actual body weight—not ideal body weight," said Dr. Marmor. "Older recommendations once advised calculating dosage as 6.5 mg/kg ideal body weight, but that conclusion was based on 50-year-old studies about HCQ and fat-using animals. We really should follow the most current human data."



TOXICITY. *A case of HCQ retinopathy in a 68-year-old woman with a 15-year history of HCQ use.*

Ideal body weight formulas tend to overdose slight individuals, especially women, Dr. Marmor added, whereas real weight predicts risk accurately and evenly across all body types.[3] As initially constructed, "the DoseChecker app selects actual body weight for thin individuals but switches to ideal body weight for heavier individuals, as it calculates a lower dose. However, 'lowest is safest' is only true for drugs that are equally effective at both doses, and there is no evidence to date that low HCQ doses are still therapeutic for heavy patients, or why physicians should give one group of patients a different dose than another," he said.

But there is good news, Dr. Marmor said. "As we speak, the developers are changing the app to use the Academy's dosing recommendations. When this revised app is available, it can be heartily recommended to simplify the calculation of daily dose and of the schedule of tablets needed to provide a proper weekly dose." He concluded, "This device has promise to aid rheumatologists as well as ophthalmologists in providing the latest and safest guidelines for prescribing HCQ."

—*Mike Mott*

1 Perlman EM et al. *JAMA Ophthalmol.* 2018;136(2):218-219.
2 Marmor MF et al. *Ophthalmology.* 2016;123(6):1386-1394.
3 Melles RB, Marmor MF. *JAMA Ophthalmol.* 2014;132(12):1453-1460.

Relevant financial disclosures: Dr. Marmor—None.

conventional cataract surgery.

Looking ahead. FLACS does hold promise, the study suggests. A subanalysis involving eyes that were evaluated by optical coherence tomography within 2 weeks of surgery (n = 33) showed potential for FLACS as a treatment option.

While only 4 eyes in this subgroup underwent FLACS, they did have a significantly lower central macular volume.

This short-term effect, in a real-life setting, indicates that patients with high macular vulnerability, including those with wet AMD, diabetic retinopathy, and retinal vein occlusion might benefit from FLACS, Dr. Bachmann said. "We are only starting to understand the possible benefits of FLACS. We presume that group differences may be even more pronounced in an adequately sized, controlled study."

—*Miriam Karmel*

1 Enz TJ et al. *J Cataract Refract Surg.* 2018;44(1):23-27.

Relevant financial disclosures: Dr. Bachmann—None.

See the financial disclosure key, page 8. **For full disclosures,** including category descriptions, view this News in Review at aao.org/eyenet.