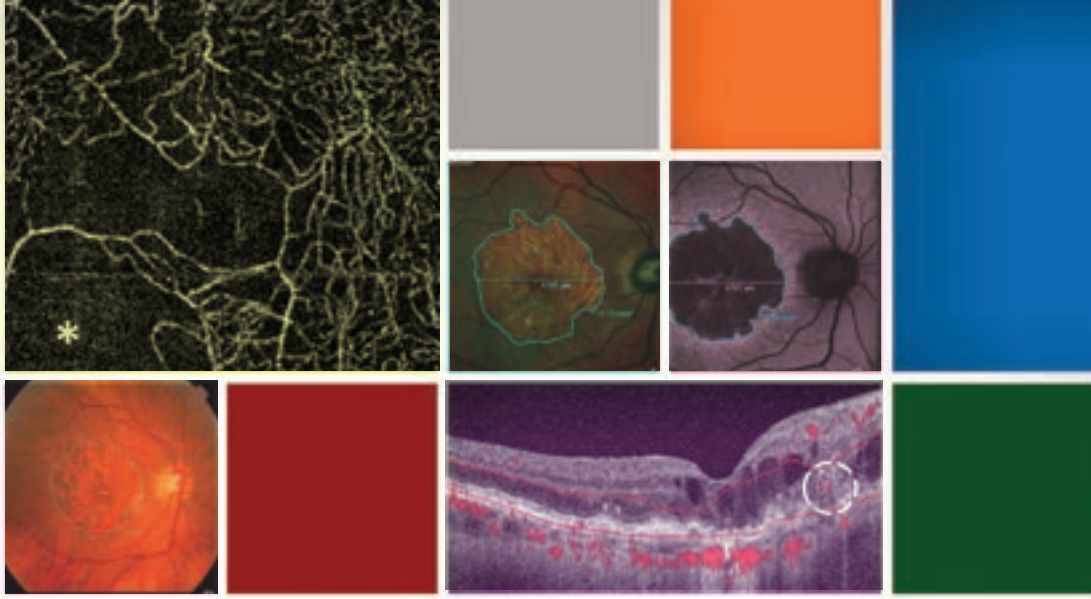
POWERED BY bmc

RT

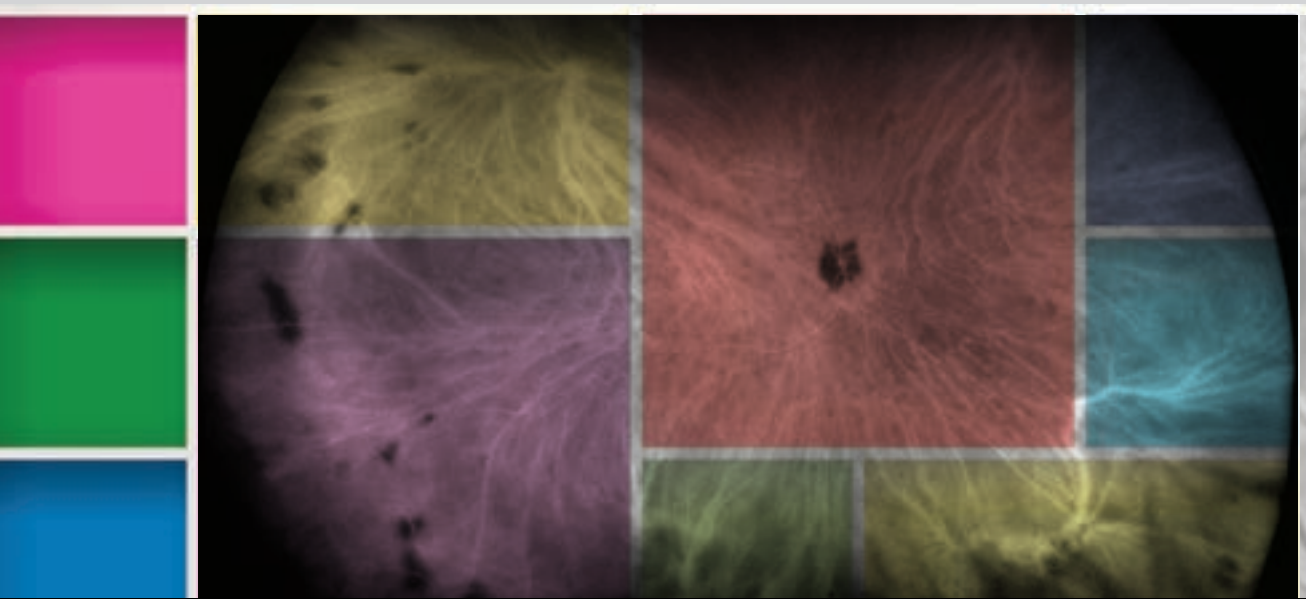
Retina Today

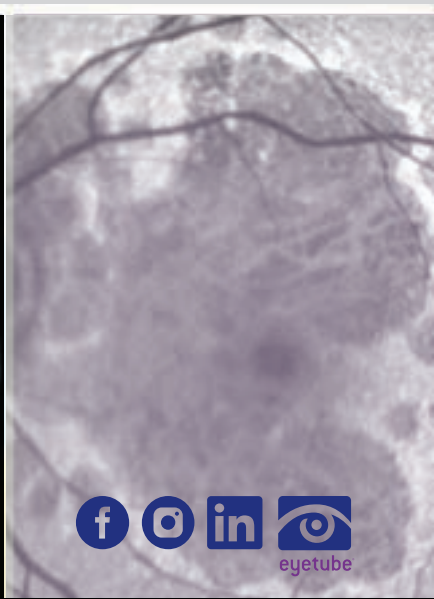
APRIL 2024 VOL. 19, NO. 3
RETINATODAY.COM



THE IMAGING ISSUE

The latest approaches to image capture and disease monitoring.





A REFERENCE GUIDE FOR OCT ANGIOGRAPHY | MULTIMODAL IMAGING IN UVEITIS | CAPTURING GEOGRAPHIC ATROPHY

INDICATION

IZERVAY™ (avacincaptad pegol intravitreal solution) is indicated for the treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD)

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

IZERVAY is contraindicated in patients with ocular or periocular infections and in patients with active intraocular inflammation.

WARNINGS AND PRECAUTIONS

Endophthalmitis and Retinal Detachments

- Intravitreal injections, including those with IZERVAY, may be associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering IZERVAY in order to minimize the risk of endophthalmitis. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately.

A moment worth protecting

Every moment is precious for your patients with geographic atrophy. Help protect their moments from the start with IZERVAY™.

Learn more at
IZERVAYecp.com

izervay™
(avacincaptad pegol intravitreal solution) 2 mg

Neovascular AMD

- In clinical trials, use of IZERVAY was associated with increased rates of neovascular (wet) AMD or choroidal neovascularization (7% when administered monthly and 4% in the sham group) by Month 12. Patients receiving IZERVAY should be monitored for signs of neovascular AMD.

Increase in Intraocular Pressure

- Transient increases in intraocular pressure (IOP) may occur after any intravitreal injection, including with IZERVAY. Perfusion of the optic nerve head should be monitored following the injection and managed appropriately.

ADVERSE REACTIONS

Most common adverse reactions (incidence ≥5%) reported in patients receiving IZERVAY were conjunctival hemorrhage, increased IOP, blurred vision, and neovascular age-related macular degeneration.

Please see Brief Summary of Prescribing Information for IZERVAY on the following page.

astellas

IZERVAY™ (avacincaptad pegol intravitreal solution)
Rx only

Brief Summary: This information is not comprehensive. Visit IZERVAYecp.com to obtain the FDA-approved product labeling or call 609-474-6755.

1 INDICATIONS AND USAGE
IZERVAY is indicated for the treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD).

2 DOSAGE AND ADMINISTRATION
2.1 General Dosing Information
IZERVAY must be administered by a qualified physician.

2.2 Recommended Dosage
The recommended dose for IZERVAY is 2 mg (0.1 mL of 20 mg/mL solution) administered by intravitreal injection to each affected eye once monthly (approximately every 28 ± 7 days) for up to 12 months.

2.4 Injection Procedure
Only 0.1 mL (2 mg) should be administered to deliver a single dose. Any excess volume should be disposed.

Prior to the intravitreal injection, patients should be monitored for elevated intraocular pressure (IOP) using tonometry. If necessary, ocular hypotensive medication can be given to lower the IOP.

The intravitreal injection procedure must be carried out under controlled aseptic conditions, which includes the use of surgical hand disinfection, sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent). Adequate anesthesia and a broad-spectrum topical microbicide should be given prior to the injection.

Inject slowly until the rubber stopper reaches the end of the syringe to deliver the volume of 0.1 mL. Confirm delivery of the full dose by checking that the rubber stopper has reached the end of the syringe barrel.

Immediately following the intravitreal injection, patients should be monitored for elevation in intraocular pressure (IOP). Appropriate monitoring may consist of a check for perfusion of the optic nerve head or tonometry.

Following intravitreal injection, patients should be instructed to report any symptoms suggestive of endophthalmitis (e.g., eye pain, redness of the eye, photophobia, blurring of vision) without delay.

Each vial and syringe should only be used for the treatment of a single eye. If the contralateral eye requires treatment, a new vial and syringe should be used and the sterile field, syringe, gloves, drapes, eyelid speculum, filter needle, and injection needle should be changed before IZERVAY is administered to the other eye. Repeat the same procedure steps as above.

Any unused medicinal product or waste material should be disposed of in accordance with local regulations.

3 DOSAGE FORMS AND STRENGTHS
Intravitreal solution: 20 mg/mL clear to slightly opalescent, colorless to slightly yellow solution in a single-dose vial.

4 CONTRAINDICATIONS
4.1 Ocular or Periocular Infections
IZERVAY is contraindicated in patients with ocular or periocular infections.

4.2 Active Intraocular Inflammation
IZERVAY is contraindicated in patients with active intraocular inflammation.

5 WARNINGS AND PRECAUTIONS
5.1 Endophthalmitis and Retinal Detachments
Intravitreal injections may be associated with endophthalmitis and retinal detachments. Proper aseptic injection techniques must always be used when administering IZERVAY in order to minimize the risk of endophthalmitis. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay, to permit prompt and appropriate management.

5.2 Neovascular AMD
In clinical trials, use of IZERVAY was associated with increased rates of neovascular (wet) AMD or choroidal neovascularization (7% when administered monthly and 4% in the sham group) by Month 12. Patients receiving IZERVAY should be monitored for signs of neovascular AMD.

5.3 Increase in Intraocular Pressure
Transient increases in intraocular pressure (IOP) have been observed after an intravitreal injection, including with IZERVAY. Perfusion of the optic nerve head should be monitored following the injection and managed as needed.

6 ADVERSE REACTIONS
The following potentially serious adverse reactions are described elsewhere in the labeling:

- Ocular and periocular infections
- Active intraocular inflammation
- Endophthalmitis and retinal detachments
- Neovascular AMD
- Increase in intraocular pressure

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of avacincaptad pegol was evaluated in 733 patients with AMD in two sham-controlled studies (GATHER1 and GATHER2). Of these patients, 292 were treated with intravitreal IZERVAY 2 mg (0.1 mL of 20 mg/mL solution). Three hundred thirty-two (332) patients were assigned to sham.

Adverse reactions reported in ≥2% of patients who received treatment with IZERVAY pooled across GATHER1 and GATHER2, are listed below in Table 1.

Table 1: Common Ocular Adverse Reactions (≥2%) and greater than Sham in Study Eye

Adverse Drug Reactions	IZERVAY N=292	Sham N=332
Conjunctival hemorrhage	13%	9%
Increased IOP	9%	1%
Choroidal neovascularization	7%	4%
Blurred Vision*	8%	5%
Eye pain	4%	3%
Vitreous floaters	2%	<1%
Blepharitis	2%	<1%

* Blurred vision includes visual impairment, vision blurred, visual acuity reduced, visual acuity reduced transiently.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
There are no adequate and well-controlled studies of IZERVAY administration in pregnant women. The use of IZERVAY may be considered following an assessment of the risks and benefits.

Administration of avacincaptad pegol to pregnant rats and rabbits throughout the period of organogenesis resulted in no evidence of adverse effects to the fetus or pregnant female at intravenous (IV) doses 5.1 times and 3.2 times the human exposure (based on AUC) at the maximum recommended human dose (MRHD) of 2 mg once monthly, respectively.

In the U.S. general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15%-20%, respectively.

Animal Data
An embryo fetal developmental toxicity study was conducted with pregnant rats. Pregnant rats received daily intravenous (IV) injections of avacincaptad pegol from day 6 to day 17 of gestation at 0.1, 0.4, 1.2 mg/kg/day. No maternal or embryofetal adverse effects were observed at any dose evaluated. An increase in the incidence of a non-adverse skeletal variation, described as short thoracolumbar (ossification site without distal cartilage) supernumerary ribs, was observed at all doses evaluated. The clinical relevance of this finding is unknown. Plasma exposures at the high dose were 5.1 times the MRHD, based on Area Under the Curve (AUC).

An embryo fetal developmental toxicity study was conducted with pregnant rabbits. Pregnant rabbits received daily IV injections of avacincaptad pegol from day 7 to day 19 of gestation at 0.12, 0.4, 1.2 mg/kg/day. No maternal or embryofetal adverse effects were observed at any dose evaluated. Plasma exposure in pregnant rabbits at the highest dose of 1.2 mg/kg/day was 3.2 times the human exposure at the MRHD, based on AUC.

8.2 Lactation
There is no information regarding the presence of avacincaptad pegol in human milk, the effects of the drug on the breastfed infant or on milk production.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for IZERVAY and any potential adverse effects on the breastfed infant from IZERVAY.

8.4 Pediatric Use
Safety and effectiveness of IZERVAY in pediatric patients have not been established.

8.5 Geriatric Use
Of the total number of patients who received IZERVAY in the two clinical trials, 90% (263/292) were ≥65 years and 61% (178/292) were ≥75 years of age. No significant differences in efficacy or safety of avacincaptad pegol were seen with increasing age in these studies. No dose adjustment is required in patients 65 years and above.

17 PATIENT COUNSELING INFORMATION
Advise patients that following IZERVAY administration, patients are at risk of developing neovascular AMD, endophthalmitis, elevated intraocular pressure and retinal detachments. If the eye becomes red, sensitive to light, painful, or if a patient develops a change in vision, instruct the patient to seek immediate care from an ophthalmologist.

Patients may experience temporary visual disturbances and blurring after an intravitreal injection with IZERVAY and the associated eye examinations. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

Manufactured by:
IVERIC bio, Inc., An Astellas Company. Parsippany, NJ 07054

Retina Today (ISSN 1942-1257) © 2024 Bryn Mawr Communications LLC is published January/February, March, April, May/June, July/August, September, October, and November/December by Bryn Mawr Communications LLC, 125 East Elm Street, Suite 400, Conshohocken, PA 19428. Subscription is free to all applicable US retina physicians. All others, applicable subscription charges apply. For subscription information call +1 800 492 1267 (US only) or e-mail retinatoday@bmctoday.com. Pending periodical postage paid at Wayne PA and additional entry offices. POSTMASTER Please send address changes to Bryn Mawr Communications LLC, 125 East Elm Street, Suite 400, Conshohocken, PA 19428. Bryn Mawr Communications LLC provides certain customer contact data, which may include customer names, addresses, phone numbers and e-mail addresses, to third parties for promotional and/or marketing purposes. If you do not wish Bryn Mawr Communications LLC to make your contact information available to third parties for any marketing purposes, please contact us at 800-492-1267 or e-mail us at retinatoday@bmctoday.com. This publication is intended for health care professionals and providers only. The information contained in this publication, including text, graphics and images, is for informational purposes only and is not intended to be a substitute for professional medical advice. Bryn Mawr Communications LLC, via its Editors and the Publisher, accepts no responsibility for any injury or damage to persons or property occasioned through the implementation of any ideas or use of any product described herein. While great care is taken by the Publisher and Editors to ensure that all information is accurate, it is recommended that readers seek independent verification of advice on drug or other product usage, surgical techniques and clinical processes prior to their use. The opinions expressed in this publication are those of the authors and are not attributable to the sponsors, the publication or the Editorial Board. References made in articles may indicate uses of medical equipment or drugs at dosages, for periods of time and in combinations not included in the current prescribing information. Inclusion of advertising material in this publication, or in supplements thereof, does not constitute any representation or guarantee by Bryn Mawr Communications LLC of the quality of such products or of the claims made by the manufacturers.

TABLE OF CONTENTS

©iStockphoto.com

FEATURED ARTICLES

26 **A Reference Guide for OCT Angiography**
By Ivy Zhu, MD; Nicole L. Decker, BS; and Amani A. Fawzi, MD

30 **The Utility of En Face OCT For Detecting Neovascularization in DR**
By Kotaro Tsuboi, MD, and Mizuki Hamada, MD

34 **Capturing Geographic Atrophy With Multimodal Imaging**
By Eric H. Souied, MD; Oudy Semoun, MD; and Vittorio Capuano, MD

38 **Multimodal Imaging in Uveitis**
By Eric Jung, MD, and Sumit Sharma, MD

42 **Adopting Remote Monitoring and AI: Lessons From Cardiology**
By Judy E. Kim, MD, FARVO, FASRS, and Jagmeet P. Singh, MD, ScM, PhD, FHRS, FACC

DEPARTMENTS

UP FRONT

8 **Guest Medical Editors' Page**
By Marion Munk, MD, and Justis P. Ehlers, MD

9 **Retina News**

MEETING MINUTES

13 **Retina Education on the Atlantic Coast**
By Jacques Bijon, MD, and Erin Flynn, MD

ONE TO WATCH

16 **Frank Brodie, MD, MBA**

CODING ADVISOR

17 **Determining When to Use Modifiers -58 and -78**
By Joy Woodke, COE, OCS, OCSR

MEDICAL RETINA

20 **Acute-Onset Vogt-Koyanagi-Harada Syndrome**
By Steven Scheidt, MS, and Heeral R. Shah, MD, FASRS

GLOBAL PERSPECTIVES

24 **Tailoring IVT Dosing With Vitreous Volume**
By Andreas F. Borkenstein, MD

FELLOWS' FOCUS

46 **Research Considerations During Retina Fellowship**
By Olufemi Adams, MD

RISING STARS IN RETINA

48 **Inês Laíns, MD, PhD**

SURGICAL PEARLS

49 **Managing Large Macular Holes: ILM Flap vs Peel**
By Kaitlyn Richards, BS, and Ankoor R. Shah, MD

OCULAR ONCOLOGY

52 **Ocular Effects of CAR-T Cell Therapy**
By Lars H. Andersen, MD; Jaskirat S. Takhar, MD; and Jose J. Echegaray, MD

IN THE BACK

56 **Ad Index**

VISUALLY SPEAKING

58 **Uveal Reactive Lymphoid Hyperplasia**
By Loka Thangamathesvaran, MD, and J. Fernando Arevalo, MD, PhD

WET AMD EYE

ANTI-VEGF

Therapy yields better long-term VA results when wet AMD detected with good VA[1]

FELLOW EYE

20/79 VA

Mean VA of fellow eyes at wet AMD diagnosis according to real-world data[1]

Over 60% of wet AMD "fellow eyes" lose too much vision[1]– even with frequent treatment visits

Detect Early. Treat Early.

ForeseeHome is a **remote monitoring** program for at-risk wet AMD fellow eyes that helps **detect conversion** at 20/40 or better in 83% of patients.[2]

- FDA Cleared
- Medicare Covered

ForeseeHOME™
AMD Monitoring Program

Introduce your patients to ForeseeHome during an injection visit and offer them an extra level of protection.

Our Monitoring Center works with your staff to easily implement an "inject and protect" protocol into your practice workflow that requires minimal effort or additional time.

The Key to Successful Home Monitoring

NOTAL VISION MONITORING CENTER

- Engagement & Education
- Benefits Verification & Authorization
- Continuous Monitoring

NOTAL VISION™
Monitoring Center

- Practice Workflow Implementation
- Remote Patient Management
- Vision Alert Management

References: 1. Ho AC, Kleinman DM, Lum FC, et al. Baseline Visual Acuity at Wet AMD Diagnosis Predicts Long-Term Vision Outcomes: An Analysis of the IRIS Registry. *Ophthalmic Surg Lasers Imaging Retina*. 2020;51:633-639. **2.** Real-World Performance of a Self-Operated Home Monitoring System for Early Detection of Neovascular AMD (ForeseeHome device), presented by Allen Ho, American Society of Retina Specialist Meeting 2020.

See website for FDA Indication for Use.

SM-125.3

GET STARTED TODAY

1-855-600-3112

Mon-Fri, 8 AM to 6 PM EST

notalvision.info/rettoday

PRACTICE MAKES PROGRESS


It's always fascinating when trendy technology seeps into health care. While working on this issue, our news feeds were overrun with stories of surgeons using Apple's new Vision Pro in the OR.[1] According to the press release, a nurse used the device to help with instrument selection, data visualization, and procedure monitoring.[1] Cool stuff, and even if you aren't an Apple aficionado, you have to admit this "spatial computer" is impressive.[2]

The news caught our eyes, but it didn't surprise us because the field of retina was way ahead of the curve with this technology. The first ophthalmic exoscope—the Beyeonics One visualization system—that integrates augmented reality into a surgical headset was installed into an ophthalmic surgical suite years ago.[3] Not only that, but the company recently announced the integration of intraoperative OCT into the headset, making it something of a spatial computer itself—for the surgeon.[4]

Retina has always been a field defined by technologic advancement, and our imaging tools are a great example. In an explosion of innovation in the early 2000s, we saw the advent of 3D visualization in the OR, intraoperative OCT, and OCT angiography (OCTA). Since then, it has been a slow march of improvement. For example, the January/February issue highlighted the addition of fluorescein angiography to surgical 3D heads-up displays. Other issues have touched on scanning laser ophthalmoscope-based multimodal fundus imaging and ultra-widefield technologies for the detection of diabetic eye disease. To catch up on these articles, see *Further Reading*. Some technology still in the pipeline may be poised to hit the clinic in the next few years; K. Bailey Freund, MD, and others have been lecturing on high-resolution OCT for a while now, with *Retina Today* following closely since its inaugural issue in 2006.[5]

While researchers work on fine-tuning the next generation, we asked experts to share their insights to help you perfect your skills with the imaging tools at your disposal. Two articles discuss why you should be using multimodal imaging for geographic atrophy and uveitis. We also have two articles detailing the benefits of OCTA for diabetic retinopathy, AMD, and other conditions. OCTA is the newest kid on the block, and although we have all played around with it, few of us are using it regularly in the clinic. We hope these articles help you gain enough confidence with your case selection and image interpretation to change that.

Lastly, Judy E. Kim, MD, FARVO, FASRS, partnered up with cardiologist Jagmeet P. Singh, MD, ScM, PhD, FHRS, FACC, to provide pearls for integrating home monitoring into the ophthalmology space—something cardiologists have been comfortable with for years. We can lean on the lessons learned with remote monitoring of implanted cardioverter-defibrillators and avoid many of the pitfalls, Drs. Kim and Singh share.

We are practicing in a high-tech world, and our clinics (and even some of our patients' homes) are chock-full of technology designed to help us document and monitor retinal changes like never before. And we bet the next decade will see yet another explosion of innovation. Who knows, we might one day see patients while wearing a headset rather than carting around a laptop, floating OCTs all over the place. ■

– Marion Munk, MD, and Justis P. Ehlers, MD

1. eXeX and Cromwell Hospital pioneer the first use of Apple Vision Pro in UK surgery [press release]. PRNewswire. March 12, 2024. Accessed March 14, 2024. www.prnewswire.com/news-releases/exex-and-cromwell-hospital-pioneer-the-first-use-of-apple-vision-pro-in-uk-surgery-302085906.html
2. Introducing Apple Vision Pro: Apple's first spatial computer [press release]. Apple. June 5, 2023. Accessed March 14, 2024. www.apple.com/newsroom/2023/06/introducing-apple-vision-pro
3. BVI Installs First Beyeonics One System [press release]. Eyewire+. August 18, 2022. Accessed March 14, 2024. eyewire.news/news/bvi-installs-first-beyeonics-one-system
4. Loewenstein A. Novel use of intra-op OCT integrated with exoscope. Presented at: FLORetina-ICOOR; Nov. 30-Dec. 3, 2023; Rome.
5. Duker JS. Advances in OCT improve understanding of disease states. *Retina Today*. 2006;1(1).

FURTHER READING

The Ins and Outs of Intraoperative FA
By Lukan Mishev, MD; Nassim A. Abreu-Arbaje, MD; Joaquín Sosa-Lockward, MD; Lauren Gibson, MD; Aly Nguyen, BS; and Alan J. Franklin, MD, PhD

3D Heads-Up Display: Pearls for New Users
By Reem Amine, MD; Leanne M. Clevenger, MD; and Justis P. Ehlers, MD

Diagnostic Yield in Non-Dilating Pupils
By Manish Nagpal, MBBS, MS, FRCS; Navneet Mehrotra, MBBS, DNB, FRF; Akansha Sharma, MBBS, MS; and Abhishek Verma, MBBS, DO

Assessing DR With Ultra-Widefield Imaging
By Harnaina K. Bains, BS; Venkatkrish M. Kasetty, MD; and Dennis M. Marcus, MD

OCT BIOMARKERS LINKED WITH INCREASED RISK OF AMD PROGRESSION

To better understand the relationship between structural biomarkers of intermediate AMD, as measured by OCT, and retinal sensitivity, researchers looked at the microperimetry findings of 45 eyes of 23 patients with intermediate AMD. They found that intraretinal hyperreflective foci (HRF), double-layer sign (DLS), and greater drusen volume increase the risk of progression and decrease retinal sensitivity.[1]

In the prospective, cross-sectional, observational study, published online in *Ophthalmology Retina*, patients underwent OCT and microperimetry. The team analyzed retinal sensitivity with a 33-point grid covering the macula, which was then superimposed on OCT, making it possible to determine the point-to-point location of any OCT risk factors. Univariable and multivariable linear mixed effects models were used for analysis.[1]

A total of 1,479 points of retinal sensitivity and the corresponding structural area on OCT were included. Retinal sensitivity was significantly decreased in the presence of OCT risk factors HRF, hyporeflectivity within drusenoid lesions, DLS, and greater drusen volume when analyzed with the univariable linear mixed effects model. The multivariable model showed a significant decrease in retinal sensitivity with HRF, DLS, and greater drusen volume.[1]

1. Thomsen AK, Gøttsche LF, Hinnerskov JMV, Falk MK, Sørensen TL. Microperimetry and structural risk factors on optical coherence tomography in intermediate age-related macular degeneration [published online ahead of print March 3, 2024]. *Ophthalmol Retina*.

GUT BACTERIA MAY CAUSE BLINDNESS IN INHERITED EYE DISEASE

A recent study reported that bacteria from the gut may be responsible for vision loss in certain inherited eye diseases. The researchers studied murine eyes with the Rd8 mutation of the *Crumbs homolog 1 (CRB1)* gene—implicated in Leber congenital amaurosis and retinitis pigmentosa—and found intestinal bacteria. The data suggest that the genetic mutation may relax the body's defenses and allow harmful bacteria to reach the eye and cause blindness.[1]

The *CRB1* gene, which is expressed in the retina and plays a crucial role in the blood-retina barrier, is also key to controlling the integrity of the lower gastrointestinal tract, where it combats pathogens and harmful bacteria by regulating what passes between the gut and the rest of the body. This study suggests that mutations in the *CRB1* gene permit translocation of bacteria from the gut to the eye, causing *CRB1*-associated retinal degeneration.[1]

Within the mouse study, the researchers were able to rescue retinal function by either depleting the bacteria systemically or reintroducing normal *CRB1* expression—offering a potential treatment pathway for patients with Rd8-mutation-associated retinal degeneration.[1]

1. Peng S, Li JJ, Song W, et al. CRB1-associated retinal degeneration is dependent on bacterial translocation from the gut. *Cell*. 2024;187(6):P1387-1401.E13.

REMOVING BARRIERS TO ROP SCREENING WITH AI

A recent study found that AI-based autonomous telemedicine may be an effective retinopathy of prematurity (ROP) screening approach to reducing outcome disparities between low- and high-income countries.[1]

The study evaluated the performance of an AI algorithm that was trained and calibrated using 2,530 examinations from 843 infants. For the study, the algorithm was tested using two external datasets: 6,245 examinations in the Stanford University Network for Diagnosis of ROP (SUNDROP) and 5,635 examinations in the Aravind Eye Care Systems (AECS) telemedicine programs.[1]

The AI platform revealed a prevalence of more-than-mild ROP and type 1 ROP of 5.9% and 1.2%, respectively, in the SUNDROP and 6.2% and 2.5%, respectively, in the AECS datasets. Examination-level areas under the receiver operating characteristics curve for more-than-mild ROP and type 1 ROP were 0.896 and 0.985, respectively, in the SUNDROP and 0.920 and 0.982, respectively, in the AECS datasets. At the cross-sectional examination level, more-than-mild ROP detection had high sensitivity. At the patient level, all infants who developed type 1 ROP screened positive prior to diagnosis.[1]

1. Corner AS, Murickan T, Oh MA, et al. Multinational external validation of autonomous retinopathy of prematurity screening [published online ahead of print March 7, 2024]. *JAMA Ophthalmol*.

FURTHER READING:

Worsening Vision From a Dislocated IOL

By Cristos Ifantides, MD, MBA; Sara Bozorg, MD; Brenton Finklea, MD; Beeran Meghpara, MD; and Tanya Trinh, MBBS, FRANZCO

In *CRST*, February 2024

OCT SHEDS LIGHT ON SCLERAL ABNORMALITIES IN HIGH MYOPIA

Hypothesizing that visualizing scleral fiber orientation may offer insights into the pathogenesis of pathologic myopia, researchers used polarization-sensitive OCT to find inner scleral fiber aggregation without outer scleral thickening at the site of dome-shaped maculopathy (DSM).[1]

The case series included 72 patients with 89 highly myopic eyes with and without DSM.[1] Of the total eyes, 41.6% had DSM. Among the 52 eyes without DSM, 13 eyes with simple high myopia had a visible inner sclera that displayed radially oriented fibers. In contrast, the entire thickness of the sclera was visible in the 39 eyes with pathologic myopia, and imaging showed vertically oriented fibers in the outer sclera. Eyes with both horizontal and bidirectional DSM had clusters of fibers with low birefringence at the site of DSM. Horizontally or obliquely oriented scleral fibers were aggregated in the inner layer of DSM. The vertical fibers located posterior to the inner fiber aggregation were not thickened and appeared thin compared with the surrounding areas.[1]

The researchers speculate that such findings could lead to targeted therapies that address scleral abnormalities and reduce the risk of damage to the overlying neural tissue.[1]

1. Ohno-Matsui K, Igarashi-Yokoi T, Azuma T, et al. Polarization-sensitive oct imaging of scleral abnormalities in eyes with high myopia and dome-shaped macula [published online ahead of print March 7, 2024]. *JAMA Ophthalmol*.

PREDICTORS OF WORSE OUTCOMES WITH AOFVD IDENTIFIED

A research team set out to identify clinical and OCT features of patients with adult-onset foveomacular vitelliform dystrophy (AOFVD) who are at a higher risk of worse visual acuity, choroidal neovascularization (CNV), and atrophy. They found that lesion size, vitreomacular traction (VMT), ellipsoid zone (EZ) attenuation, choroidal thickness, and hyperreflective foci were features that predicted worse outcomes in patients with AOFVD.[1]

The retrospective, observational cohort study included 101 eyes of 63 patients who had been diagnosed with AOFVD. Clinical and OCT features associated with progression to atrophy and CNV were determined using t-tests and chi-square analysis; linear regression was used to determine correlation with worse visual acuity.[1]

Statistically significant risk factors for worse final visual acuity were baseline presence of VMT, EZ attenuation, and increased lesion height and width. Risk factors for disease progression included diabetes, statin use, presence of hyperreflective foci, and increased lesion width and volume. Baseline VMT was a predictor for atrophy as well, in addition to decreased choroidal thickness and greater maximal height, width, and volume of the lesion; lower baseline visual acuity and increased lesion volume were associated with CNV.[1] ■

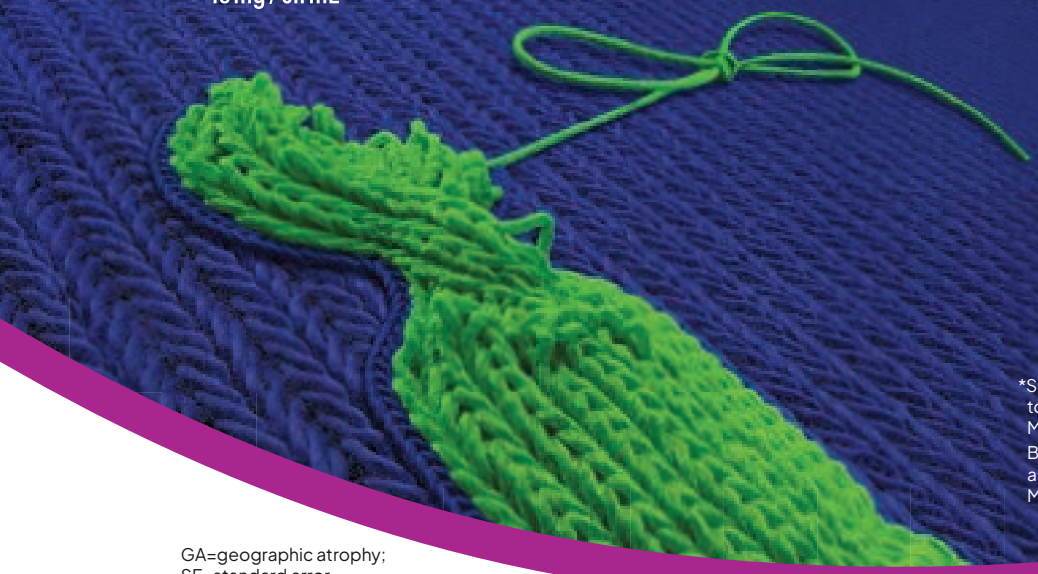
1. Nipp GE, Sarici K, Lee T, Hadziahmetovic M. Risk factors for worsening morphology and visual acuity in eyes with adult-onset foveomacular vitelliform dystrophy. *Ophthalmol Retina*. 2024;S2468-6530(24)00108-8.

Eyewire+ Pharma Update

- **Nanoscope Therapeutics** released positive topline results of its phase 2b RESTORE trial of **MCO-010**, a gene therapy for patients with advanced retinitis pigmentosa. The trial demonstrated a statistically significant improvement in BCVA at week 52 in both the high- and low-dose treatment groups compared with sham.
- **Iveric Bio/Astellas** announced that CMS has assigned a permanent J-code, J2782, for avacincaptad pegol (Izervay).
- **FYB201 (Ravegza, Formycon AG)** received marketing authorization from the Saudi Food & Drug Authority for the treatment of wet AMD and other retinal disease. This biosimilar is approved in the United States and parts of Europe as **Cimerli (Sandoz)**.
- **Exonate** announced positive phase 1b/2a data on **EXN407**, a drug candidate for diabetic retinopathy (DR) and diabetic macular edema (DME).
- **GenSight Biologics** announced results of a phase 3 meta-analysis of **lenadogene nolparvovec (GS010; Lumevoq)**, a gene therapy candidate to treat Leber hereditary optic neuropathy. The data showed a greater rate of visual recovery than was seen with untreated patients and those treated with idebenone.
- **Nesvategrast (OTT166, OcuTerra Therapeutics)**, a selective RGD integrin inhibitor eye drop for the treatment of DR, did not meet the primary efficacy endpoints of the phase 2 DR:EAM trial.
- **Sandoz** completed the acquisition of **ranibizumab-eqrn (Cimerli)** from Coherus BioSciences for a payment of $170 million plus inventory costs of Cimerli.
- The 1-year results of the phase 3 PULSAR and PHOTON trials of **8 mg aflibercept (Eylea HD, Regeneron)** for wet AMD and DME, respectively, were published in *Lancet*.

Want more retina news from *Eyewire+*?

SYFOVRE®
(pegcetacoplan injection)
15 mg / 0.1 mL



GA unravels so much SAVE RETINAL TISSUE BY SLOWING PROGRESSION[1-3]

SYFOVRE achieved continuous reductions in mean lesion growth rate* vs sham pooled from baseline to Month 24[1,4]

Monthly	Every Other Month (EOM)
OAKS trial (mm^2): (3.11 vs 3.98) **22%**	OAKS trial (mm^2): (3.26 vs 3.98) **18%**
DERBY trial (mm^2): (3.28 vs 4.00) **18%**	DERBY trial (mm^2): (3.31 vs 4.00) **17%**

SE in trials (monthly, EOM, sham pooled): OAKS: 0.15, 0.13, 0.14; DERBY: 0.13, 0.13, 0.17.

*Slope for baseline to Month 24 is an average of slope of baseline to Month 6, Month 6 to Month 12, Month 12 to Month 18, and Month 18 to Month 24.[1]

Based on a mixed effects model for repeated measures assuming a piecewise linear trend in time with knots at Month 6, Month 12, and Month 18.[1]

GA=geographic atrophy;
SE=standard error.

Explore the long-term data

The CMS-assigned permanent J-code for SYFOVRE is J2781—effective 10/1/23[1]

INDICATION

SYFOVRE® (pegcetacoplan injection) is indicated for the treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD).

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

- SYFOVRE is contraindicated in patients with ocular or periocular infections, and in patients with active intraocular inflammation

WARNINGS AND PRECAUTIONS

- **Endophthalmitis and Retinal Detachments**
  - Intravitreal injections, including those with SYFOVRE, may be associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering SYFOVRE to minimize the risk of endophthalmitis. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately.
- **Retinal Vasculitis and/or Retinal Vascular Occlusion**
  - Retinal vasculitis and/or retinal vascular occlusion, typically in the presence of intraocular inflammation, have been reported with the use of SYFOVRE. Cases may occur with the first dose of SYFOVRE and may result in severe vision loss. Discontinue treatment with SYFOVRE in patients who develop these events. Patients should be instructed to report any change in vision without delay.
- **Neovascular AMD**
  - In clinical trials, use of SYFOVRE was associated with increased rates of neovascular (wet) AMD or choroidal neovascularization (12% when administered monthly, 7% when administered every other month and 3% in the control group) by Month 24. Patients receiving SYFOVRE should be monitored for signs of neovascular AMD. In case anti-Vascular Endothelial Growth Factor (anti-VEGF) is required, it should be given separately from SYFOVRE administration.
- **Intraocular Inflammation**
  - In clinical trials, use of SYFOVRE was associated with episodes of intraocular inflammation including: vitritis, vitreal cells, iridocyclitis, uveitis, anterior chamber cells, iritis, and anterior chamber flare. After inflammation resolves, patients may resume treatment with SYFOVRE.
- **Increased Intraocular Pressure**
  - Acute increase in IOP may occur within minutes of any intravitreal injection, including with SYFOVRE. Perfusion of the optic nerve head should be monitored following the injection and managed as needed.

ADVERSE REACTIONS

- Most common adverse reactions (incidence ≥5%) are ocular discomfort, neovascular age-related macular degeneration, vitreous floaters, conjunctival hemorrhage.

Please see Brief Summary of Prescribing Information for SYFOVRE on the adjacent page.

Trial Design: SYFOVRE safety and efficacy were assessed in OAKS (N=637) and DERBY (N=621), multi-center, 24-month, Phase 3, randomized, double-masked trials. Patients with GA (atrophic nonexudative age-related macular degeneration), with or without subfoveal involvement, secondary to AMD were randomly assigned (2:2:1:1) to receive 15 mg/0.1 mL intravitreal SYFOVRE monthly, SYFOVRE EOM, sham monthly, or sham EOM for 24 months. Change from baseline in the total area of GA lesions in the study eye (mm^2) was measured by fundus autofluorescence (FAF).[1,4]

References: 1. SYFOVRE (pegcetacoplan injection) [package insert]. Waltham, MA: Apellis Pharmaceuticals, Inc.; 2023. **2.** Pfau M, von der Emde L, de Sisternes L, et al. Progression of photoreceptor degeneration in geographic atrophy secondary to age-related macular degeneration. *JAMA Ophthalmol*. 2020;138(10):1026-1034. **3.** Bird AC, Phillips RL, Hageman GS. Geographic atrophy: a histopathological assessment. *JAMA Ophthalmol*. 2014;132(3):338-345. **4.** Data on file. Apellis Pharmaceuticals, Inc.

Apellis

SYFOVRE® (pegcetacoplan injection), for intravitreal use
BRIEF SUMMARY OF PRESCRIBING INFORMATION
Please see SYFOVRE full Prescribing Information for details.

INDICATIONS AND USAGE

SYFOVRE is indicated for the treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD).

CONTRAINDICATIONS

Ocular or Periocular Infections
SYFOVRE is contraindicated in patients with ocular or periocular infections.
Active Intraocular Inflammation
SYFOVRE is contraindicated in patients with active intraocular inflammation.

WARNINGS AND PRECAUTIONS

Endophthalmitis and Retinal Detachments
Intravitreal injections, including those with SYFOVRE, may be associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering SYFOVRE in order to minimize the risk of endophthalmitis. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately.
Retinal Vasculitis and/or Retinal Vascular Occlusion
Retinal vasculitis and/or retinal vascular occlusion, typically in the presence of intraocular inflammation, have been reported with the use of SYFOVRE. Cases may occur with the first dose of SYFOVRE and may result in severe vision loss. Discontinue treatment with SYFOVRE in patients who develop these events. Patients should be instructed to report any change in vision without delay.
Neovascular AMD
In clinical trials, use of SYFOVRE was associated with increased rates of neovascular (wet) AMD or choroidal neovascularization (12% when administered monthly, 7% when administered every other month and 3% in the control group) by Month 24. Patients receiving SYFOVRE should be monitored for signs of neovascular AMD. In case anti-Vascular Endothelial Growth Factor (anti-VEGF) is required, it should be given separately from SYFOVRE administration.
Intraocular Inflammation
In clinical trials, use of SYFOVRE was associated with episodes of intraocular inflammation including: vitritis, vitreal cells, iridocyclitis, uveitis, anterior chamber cells, iritis, and anterior chamber flare. After inflammation resolves patients may resume treatment with SYFOVRE.
Increased Intraocular Pressure
Acute increase in IOP may occur within minutes of any intravitreal injection, including with SYFOVRE. Perfusion of the optic nerve head should be monitored following the injection and managed as needed.

ADVERSE REACTIONS

Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.
A total of 839 patients with GA in two Phase 3 studies (OAKS and DERBY) were treated with intravitreal SYFOVRE, 15 mg (0.1 mL of 150 mg/mL solution). Four hundred nineteen (419) of these patients were treated in the affected eye monthly and 420 were treated in the affected eye every other month. Four hundred seventeen (417) patients were assigned to sham.
The most common adverse reactions (≥5%) reported in patients receiving SYFOVRE were ocular discomfort, neovascular age-related macular degeneration, vitreous floaters, and conjunctival hemorrhage.

Table 1: Adverse Reactions in Study Eye Reported in ≥2% of Patients Treated with SYFOVRE Through Month 24 in Studies OAKS and DERBY

Adverse Reactions	PM (N = 419) %	PEOM (N = 420) %	Sham Pooled (N = 417) %
Ocular discomfort*	13	10	11
Neovascular age-related macular degeneration*	12	7	3
Vitreous floaters	10	7	1
Conjunctival hemorrhage	8	8	4
Vitreous detachment	4	6	3
Retinal hemorrhage	4	5	3
Punctate keratitis*	5	3	<1
Posterior capsule opacification	4	4	3
Intraocular inflammation*	4	2	<1
Intraocular pressure increased	2	3	<1

PM: SYFOVRE monthly; PEOM: SYFOVRE every other month
*The following reported terms were combined:
Ocular discomfort included: eye pain, eye irritation, foreign body sensation in eyes, ocular discomfort, abnormal sensation in eye
Neovascular age-related macular degeneration included: exudative age-related macular degeneration, choroidal neovascularization
Punctate keratitis included: punctate keratitis, keratitis
Intraocular inflammation included: vitritis, vitreal cells, iridocyclitis, uveitis, anterior chamber cells, iritis, anterior chamber flare

Endophthalmitis, retinal detachment, hyphema and retinal tears were reported in less than 1% of patients. Optic ischemic neuropathy was reported in 1.7% of patients treated monthly, 0.2% of patients treated every other month and 0.0% of patients assigned to sham. Deaths were reported in 6.7% of patients treated monthly, 3.6% of patients treated every other month and 3.8% of patients assigned to sham. The rates and causes of death were consistent with the elderly study population.

Postmarketing Experience
The following adverse reactions have been identified during postapproval use of SYFOVRE. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Eye disorders: retinal vasculitis with or without retinal vascular occlusion.

USE IN SPECIFIC POPULATIONS

Pregnancy
Risk Summary
There are no adequate and well-controlled studies of SYFOVRE administration in pregnant women to inform a drug-associated risk. The use of SYFOVRE may be considered following an assessment of the risks and benefits.
Systemic exposure of SYFOVRE following ocular administration is low. Subcutaneous administration of pegcetacoplan to pregnant monkeys from the mid gestation period through birth resulted in increased incidences of abortions and stillbirths at systemic exposures 1040-fold higher than that observed in humans at the maximum recommended human ophthalmic dose (MRHOD) of SYFOVRE (based on the area under the curve (AUC) systemically measured levels). No adverse maternal or fetal effects were observed in monkeys at systemic exposures approximately 470-fold higher than that observed in humans at the MRHOD.
In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.
Lactation
Risk Summary
It is not known whether intravitreal administered pegcetacoplan is secreted in human milk or whether there is potential for absorption and harm to the infant. Animal data suggest that the risk of clinically relevant exposure to the infant following maternal intravitreal treatment is minimal. Because many drugs are excreted in human milk, and because the potential for absorption and harm to infant growth and development exists, caution should be exercised when SYFOVRE is administered to a nursing woman.
Females and Males of Reproductive Potential
Contraception
Females: It is recommended that women of childbearing potential use effective contraception methods to prevent pregnancy during treatment with intravitreal pegcetacoplan. Advise female patients of reproductive potential to use effective contraception during treatment with SYFOVRE and for 40 days after the last dose. For women planning to become pregnant, the use of SYFOVRE may be considered following an assessment of the risks and benefits.
Pediatric Use
The safety and effectiveness of SYFOVRE in pediatric patients have not been established.
Geriatric Use
In clinical studies, approximately 97% (813/839) of patients randomized to treatment with SYFOVRE were ≥ 65 years of age and approximately 72% (607/839) were ≥ 75 years of age. No significant differences in efficacy or safety were seen with increasing age in these studies. No dosage regimen adjustment is recommended based on age.

PATIENT COUNSELING INFORMATION

Advise patients that following SYFOVRE administration, patients are at risk of developing endophthalmitis, retinal detachments, retinal vasculitis with or without retinal vascular occlusion and neovascular AMD. If the eye becomes red, sensitive to light, painful, or if a patient develops any change in vision such as flashing lights, blurred vision or metamorphopsia, instruct the patient to seek immediate care from an ophthalmologist. Patients may experience temporary visual disturbances associated either with the intravitreal injection with SYFOVRE or the eye examination. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

Manufactured for:
Apellis Pharmaceuticals, Inc.
100 Fifth Avenue
Waltham, MA 02451

SYF-PI-30NOV2023-2.0

12/23 US-PEGGA-2200163 v4.0

RETINA EDUCATION ON THE ATLANTIC COAST


The 2024 Atlantic Coast Retina Club and Macula Conference packed a punch with cases, lectures, and more.

BY JACQUES BIJON, MD, AND ERIN FLYNN, MD

The 48th Annual Atlantic Coast Retina Club (ACRC) and 24th Macula Conference, held on January 4-6, 2024, in New York City, was an exceptional 3-day meeting organized by K. Bailey Freund, MD. The first 2 days involved mystery cases presented by residents, fellows, and experts in the field of retina. The last day included an array of topics, such as surgical and medical management, uveitis, oncology, retinal imaging, and AI. The event was further enriched by the presentation of the Founder's Awards and a notable interview with Wiley A. Chambers, MD, former director of the Division of Ophthalmology at the FDA.

TRAINEE CASE PRESENTATIONS

The first day focused on cases presented by residents and fellows. These presentations featured mystery cases that were discussed with a panel of moderators. A few interesting highlights include the following:

- a case of pseudoxanthoma elasticum (by Suveera Dang, MD),
- choroidal metastasis from breast cancer treated with targeted immunotherapy (by Rolika Bansal, MD),
- idiopathic unilateral choroidals in a young hypertensive patient (by William Foulsham, MD, PhD), and
- an orbital perforation secondary to a MIRAgel scleral buckle (by Rusdeep S. Mundae, MD).

These cases stimulated a great deal of dialogue among the moderators and the audience, who discussed the differential diagnoses and various management approaches.

The day concluded with a moment of recognition for four exceptional presentations. Congratulations are extended to Eugene Kang, MD, for his compelling case on inherited optic neuropathy; Luis A. Martinez-Velazquez, MD, PhD, for an intriguing case of chorioretinitis with secondary multiple evanescent white-dot syndrome in the context of Lyme disease; Apoorv P. Chebolu, MD, for his presentation on ocular sarcoidosis; and Laura A. Jenny, AB, for her presentation on ocular enhanced S-cone syndrome (Figure 1).

FACULTY CASES

The second day featured cases presented by leading experts in medical retina, vitreoretinal surgery, tumors and oncology, uveitis, and inherited retinal diseases. The cases involved unique clinical manifestations of retinal pathologies and techniques in imaging and disease management that generated interesting discussions. Notable takeaways include:

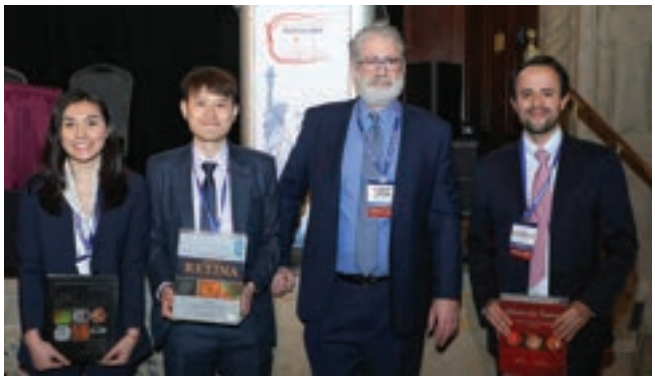
- the use of cell-free DNA to diagnose an amelanotic choroidal mass (by Jasmine H. Francis, MD, FACS),
- scleral glue adhesions for plaque radiotherapy in patients with a thin or weak sclera (by Carol L. Shields, MD),
- management of a tractional membrane secondary to Coats disease (by Yoshihiro Yonekawa, MD),
- thickened retinal nerve fiber layer to identify early preclinical vasculitis (by David M. Brown, MD, FACS), and
- the interpretation of hypointense bands in OCT angiography in the setting of retinal occlusive disease (by Diogo Cabral, MD).

MACULA 2024

The last day began with new findings in retinal histology and pathology and imaging innovations. Interesting topics included imaging mass spectrometry of subretinal drusenoid deposits (by Andreas Pollreisz, MD), mineral components in Bruch membrane in the setting of pseudoxanthoma elasticum (by Imre Lengyel, PhD), and a new understanding of lipofuscin and the implications for autofluorescence findings in the retinal pigment epithelium (by Christine A. Curcio, PhD). These talks provided a research perspective on retinal diseases that helps to inform diagnosis and treatment.

This session was followed by retinal imaging. Notable highlights include recognition of subclinical macular neovascularization via double-layer signs in AMD (by Amani A. Fawzi, MD) and the trizonal distribution of drusen and subretinal drusenoid deposits (by David Sarraf, MD), as revealed by en face OCT, corresponding to the density and types of photoreceptor cells.

ATLANTIC COAST RETINA/MACULA



Images courtesy Kevin Caldwell Photography

Figure 1. Four trainees were awarded for their top-notch case presentations. Pictured here (left to right) are Laura A. Jenny, AB; Eugene Kang, MD; K. Bailey Freund, MD; and Luis A. Martinez-Velazquez, MD, PhD. The final honoree not pictured here is Apoorv P. Chebolu, MD.

VITREORETINAL SURGERY PEARLS

Saturday also featured surgical panels that tackled difficult cases and various management techniques. Topics included epiretinal and internal limiting membrane peeling, diabetic tractional retinal detachments, and complex proliferative vitreoretinopathy. The panelists—Gaetano R. Barile, MD; Talia R. Kaden, MD; James Klancnik, MD; Kyle D. Kovacs, MD; and Kenneth J. Wald, MD—shared their surgical approaches and preferred instrumentation, dyes, and tamponades. This was moderated by Audina M. Berrocal, MD, who provided her own challenging cases for discussion.

RETINAL DISEASES, AMD, AND MANAGEMENT

A session on other macular diseases emphasized novel techniques, including new guidelines for central serous chorioretinopathy (by Camiel J.F. Boon, MD, PhD, FEBO) and an update on a ciliary neurotrophic factor implant for macular telangiectasia type 2 (by Emily Y. Chew, MD).

This led into a review of new anti-VEGF drugs and delivery methods, as well as a discussion on complement inhibitors for geographic atrophy. The latter discussion was structured around clinical cases, and panelists Irene A. Barbazetto, MD; Philip J. Ferrone, MD; Lee M. Jampol, MD; and Philip J. Rosenfeld, MD, PhD, shared whether they would treat each patient. Finally, Peter K. Kaiser, MD, gave a thorough and informed update on emerging treatments for dry AMD.

The afternoon included a session on AI and its role in the clinic. For example, SriniVas R. Sadda, MD, presented on the use of deep-learning approaches for the assessment of AMD biomarkers and how this can facilitate the identification of patients for trials. The day ended with engaging panels exploring the diagnosis and management of inherited retinal diseases, pediatric retinal diseases, and uveitis.

MEMORABLE MOMENTS

It was fitting that the last day of the conference involved emotional and touching tributes to leaders in retina. These individuals have not only pushed the field forward through research and clinical innovation, but also have inspired and supported colleagues and generations of students. In a personal interview conducted by Dr. Brown, Dr. Chambers shared professional and personal accomplishments over his long career (Figure 2). He discussed his own values and judgments regarding the clinical trials he had a hand in. Dr. Chambers concluded his remarks with the announcement that he would be stepping down as director of the Department of Ophthalmology at the FDA. While uncertain about his next steps, Dr. Chambers spoke of the future with excitement and optimism. This unapologetically honest and inspirational interview was met with a standing ovation.

Figure 2. Wiley A. Chambers, MD, (left) shared insights into his career with interviewer David M. Brown, MD, FACS, (right) during a surprisingly personal interview.

Figure 3. The Founder's Awards were presented to (left to right) Susan B. Bressler, MD; Alexander J. Brucker, MD; and Richard B. Rosen, MD.

Finally, this year's Founder's Awards were presented by Dr. Shields and Lawrence A. Yannuzzi, MD. The three recipients were Susan B. Bressler, MD; Alexander J. Brucker, MD; and Richard B. Rosen, MD (Figure 3). Dr. Yannuzzi closed with words of warmth and kindness to his colleague and son-in-law, Dr. Freund, who coordinated this year's meeting.

See you in Baltimore for the next ACRC and Macula meeting, planned for January 9-11, 2025! ■

JACQUES BIJON, MD
- International Fellow, Vitreous Retina Macula Consultants of New York, New York
- j.bijon@gmail.com
- Financial disclosure: None

ERIN FLYNN, MD
- Vitreoretinal Fellow, Columbia University Medical Center, New York, New York
- eef2122@gmail.com
- Financial disclosure: None

Delivering Innovations for Subretinal Injections

New Silicone-Free MicroDose™ SF Injection Kit

Our MicroDose™ products set the standard for reliability and control during high precision subretinal injections. With the launch of our new MicroDose™ SF, we have added critical features such as a silicone-free syringe, removable plunger rod and dead-space reduction stopper. Combine either MicroDose™ device with one of our market leading specialized cannulas and create the ideal system for your surgical needs.

Contact us today to find out more!

NEW!

3315 MicroDose™ SF Injection Kit

3275 MicroDose™ Injection Kit

Features

●	US FDA cleared for low-volume subretinal injections	●
●	Precise, pneumatically controlled injection using Alcon, DORC, or B+L vitrectomy consoles	●
●	1mL syringe ideal for low-volume injection	●
●	Luer lock syringe allows for a wide variety of subretinal cannula options	●
●	Syringe can be pneumatically filled	●
●	Syringe can be manually filled utilizing the removable plunger rod	
●	Silicone-free syringe eliminates risk of silicone droplets during injection	
●	Unique stopper design reduces dead-space to approximately 10 microliters	

MedOne®
www.medone.com

FRANK BRODIE, MD, MBA

WHERE IT ALL BEGAN

Coming from a family of doctors, I was eager to buck the tradition after studying political science and philosophy at Carleton College in rural Minnesota. I took a job in marketing at General Mills and was in charge of new product development for the Fruit Roll-Ups franchise. However, I realized that I didn't want my boss's job, so I began to evaluate other careers. Hearing my family talk about their job satisfaction in caring for patients and the intellectual challenge and stimulation of medicine drew me back into the family business. I completed a post-baccalaureate at Bryn Mawr College and then spent a year working in a pediatric obesity clinic at the University of California San Francisco (UCSF) while I applied for medical school—perhaps a redemption for my time selling all those fruit snacks.

I then attended the University of Pennsylvania for medical school and also completed an MBA at Wharton. I enjoyed the creative aspects of business and wanted to see if I could find training and a career in which I could still engage that creativity.

MY PATH TO RETINA

I very much remember the first time I looked through the microscope to see a retinal detachment repair during medical school. It was an incredible opening to a secret 3D world that required many instruments, techniques, and knowlege. I was hooked.

SUPPORT ALONG THE WAY

I am fortunate to have many wonderful mentors. First and foremost is my uncle, Dan Schwartz, MD, a retina specialist at UCSF who has been a model for my career with numerous, creative high-impact projects in retina and beyond. I now share an office with him at UCSF, so we frequently discuss science, patients, and San Francisco sports. Other wonderful mentors include Eugene De Juan, MD; Cynthia A. Toth, MD; and Mark S. Blumenkranz, MD, MMS, all of whom have been role models in their development of new technologies and outstanding academic careers. Each of these mentors has guided me, supported my research, and become a lifelong friend.

Dr. Brodie's advice: Time is by far the most valuable asset. Worry less about your salary and more about how you will spend your time. Make sure you have great partners; they will be the ones caring for your patients, teaching you, and supporting you. I couldn't ask for better partners, and it makes the job infinitely more fun and satisfying.

AN EXPERIENCE TO REMEMBER

Prior to vitreoretinal fellowship I took a postdoctoral year at Stanford in Ophthalmic Device Innovation. My team developed a new type of intraocular surgical device, and saw the project through from the earliest prototypes to 3D models and testing with ex vivo pig eyes. We patented the device, and a startup company licensed it. This past year, they conducted a clinical trial to implant the device in a patient for the very first time. It was incredibly exciting and rewarding to see what had started as a sketch come to life and be used to help a patient. ■

Frank Brodie, MD, MBA, is an assistant professor of Ophthalmology and Vitreoretinal Surgery at UCSF and a vitreoretinal surgeon at the San Francisco Veterans Affairs Hospital. He is a cofounder of the Loving Eyes Foundation (www.lovingeyesfoundation.org), a nonprofit organization that uses 3D printing technology to create eye wear solutions for children with craniofacial anomalies. He can be reached at **frank.brodie@ucsf.edu**.

CODING ADVISOR
A Collaboration Between *Retina Today* and AMERICAN ACADEMY OF OPHTHALMOLOGY

DETERMINING WHEN TO USE MODIFIERS -58 AND -78

Both are used in association with the original surgery, but ultimately serve different purposes.

BY JOY WOODKE, COE, OCS, OCSR

When retina procedures are performed during the global period of a surgery, an appropriate modifier must be appended to the CPT code for reimbursement. When an unrelated procedure is performed postoperatively in the fellow eye, for example, modifier -79 is used. However, when the surgery is related to the original procedure, either modifier -58 or -78 should be considered.

DEFINITIONS

When considering which modifier is appropriate for a related procedure, clinicians should carefully review the definitions of modifiers -58 and -78.

Modifier -58 is defined as a staged or related procedure or service by the same physician or other qualified health care professional during the postoperative period and has three definitions for use:

1. Planned or anticipated (staged)
2. More extensive than the original procedure
3. Therapy following a surgical procedure

Modifier -78 is used for a related but unanticipated return to the OR or office procedure room by the same physician or other qualified health care professional during the postoperative period of the initial procedure.

Reporting modifier -58 will initiate a new global period for the CPT code reported. Modifier -78, on the other hand, does not prompt a new postoperative period, and the original global period remains.

REIMBURSEMENT

Using modifier -58 will provide 100% reimbursement for the CPT code submitted. Modifier -78 provides a payment for the intraoperative component of the CPT code only, as a new global period is not initiated. The preoperative component of the global surgical package is always 10%, but the intraoperative component varies based on the global period for the surgery. For example, CPT code 67113 has a 90-day global period, and the global surgical package is assigned as:

- Preoperative 10%
- Intraoperative 70%
- Postoperative 20%

As a result, CPT code 67113 reported with modifier -78 would be paid at 70%.

With procedures with a 10-day global period, for example, CPT code 67228 would have a 10% preoperative, 80% intraoperative, and 10% postoperative reimbursement, ultimately resulting in an 80% payment when appended with modifier -78.

CASE EXAMPLES

Let's apply these principles to real-life case studies.

Retinal Detachment Repair

Case 1. During the global period of a pneumatic retinopexy, CPT code 67110, the retina becomes detached in the same eye, and additional surgery is performed, CPT code 67108.

REPORTING MODIFIER -58 WILL INITIATE A NEW GLOBAL PERIOD FOR THE CPT CODE REPORTED. MODIFIER -78, ON THE OTHER HAND, DOES NOT PROMPT A NEW POSTOPERATIVE PERIOD, AND THE ORIGINAL GLOBAL PERIOD REMAINS.

Result. Modifier -58 would be used because this is a lesser (pneumatic) to greater (repair of retinal detachment, vitrectomy) procedure.

Case 2. During the global period of the repair of a complex retinal detachment with proliferative vitreoretinopathy, CPT code 67113, the retina is still detached in the operative eye, and the patient is returned to the OR for additional complex repair of the retinal detachment, CPT code 67113.

Result. Modifier -78 is the correct modifier, as this is an unplanned return to the OR for the same procedure.

Removal of Silicone Oil

Case 1. A patient has no vision in the fellow eye, and the surgeon decides that instead of inserting a gas bubble that would obstruct the patient's vision for approximately 8 weeks, silicone oil should be used during retinal detachment repair, CPT code 67108. Removal of the silicone oil around 6 weeks is preplanned and documented, CPT code 67036.

Result. Because it is preplanned and documented to remove the silicone oil 6 weeks post-surgery, modifier -58 would be reported with the vitrectomy CPT code.

Case 2. During the global period of a retinal detachment repair, the patient has a complication related to the silicone oil, and the physician decides to return to the OR to remove it.

Result. As this is a complication requiring an unplanned return to the OR, modifier -78 would be used.

Intravitreal Injection

Case 1. During the global period of a vitrectomy with laser, CPT code 67040, for proliferative retinopathy with macular edema, the patient receives an intravitreal injection of anti-VEGF for diabetic macular edema.

Result. This intravitreal injection would be considered therapy following a related major surgery, modifier -58.

Case 2. A postoperative intravitreal injection of antibiotics is administered to treat endophthalmitis in the operative eye.

Result. Modifier -78 would be correct, as this is a complication and an unplanned procedure. ■

JOY WOODKE, COE, OCS, OCSR
- Director of Coding & Reimbursement, American Academy of Ophthalmology, San Francisco
- jwoodke@aao.org
- Financial disclosure: None

Check out other articles on modifiers in *Retina Today*:

How to Implement the -JZ Modifier

Mastering Modifier -24

CODING QUICK LINKS

AAO Retina Practice Management and Coding

***Retina Today* Coding Advisor Column**

NGENUITY®
DIGITALLY ASSISTED SURGERY

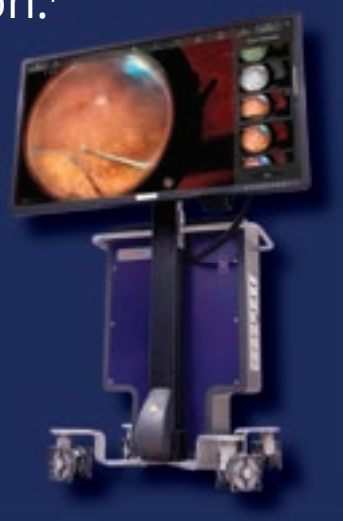
INTRODUCING NGENUITY 1.5

DIGITAL TO THE

Nth
DEGREE

It's time to experience the latest in digital visualization.[1]

Experience the digital revolution in surgical visualization systems! NGENUITY® 1.5 offers greater depth and detail with enhanced features like **Digital Image Guidance** and **Digital Detection**. Discover your new view with image modes like Tissue Detail, Capsule Clarity, and MIGS mode.[2]



ONLY NGENUITY® provides the most advanced visualization of your surgery with enhanced detail, magnification, and digital optimization to help achieve the best results.[1]

THAT'S DIGITAL TO THE NTH DEGREE.

Experience it for yourself. For more information or to request a demo, speak to your Alcon rep or visit NGENUITY.com

IMPORTANT PRODUCT INFORMATION
Caution: Federal (USA) law restricts this device to sale by, or on the order of, a physician. **Indication**: The NGENUITY™ 3D Visualization System consists of a 3D stereoscopic, high-definition digital video camera and workstation to provide magnified stereoscopic images of objects during micro-surgery. It acts as an adjunct to the surgical microscope during surgery displaying real-time images or images from recordings. **Warnings**: The system is not suitable for use in the presence of flammable anesthetics mixture with air or oxygen. There are no known contraindications for use of this device. **Precautions**: Do not touch any system component and the patient at the same time during a procedure to prevent electric shock. When operating in 3D, to ensure optimal image quality, use only approved passive-polarized glasses. Use of polarized prescription glasses will cause the 3D effect to be distorted. In case of emergency, keep the microscope oculars and mounting accessories in the cart top drawer. If there are any concerns regarding the continued safe use of the NGENUITY™ 3D Visualization System, consider returning to using the microscope oculars. **Attention**: Refer to the User Manual for a complete list of appropriate uses, warnings and precautions.

REFERENCES: **1**. Alcon Data on File, 2017. 2. NGENUITY® User Manual.

Alcon

ACUTE-ONSET VOGT-KOYANAGI-HARADA SYNDROME


This autoimmune condition may present with only ocular findings early in the disease course.

BY STEVEN SCHEIDT, BS, AND HEERAL SHAH, MD, FASRS

Vogt-Koyanagi-Harada (VKH) syndrome is a rare autoimmune and granulomatous inflammatory condition that affects the central nervous system. VKH has a vast range of presentations, which may involve cerebrospinal fluid, skin, hair, and eyes. VKH syndrome mainly occurs in adults, but there is a case report of a 3-year-old girl with VKH.[1]

VKH syndrome has an idiosyncratic phenotype and may present with early or late physical manifestations. Although the pathophysiology is not completely understood, VKH syndrome can be subdivided into a prodrome, an acute, and a chronic phase. The prodrome phase is characterized by nonspecific features such as fever, malaise, headache, and dizziness, which last for a few days. The acute phase lasts for a few weeks and is characterized by bilateral posterior uveitis and other ocular findings. In rare cases, the posterior uveitis may not occur at the same time in the contralateral eye but will have a short delay.[2]

The chronic stage can last a few months to years and involves depigmentation of the skin and uvea. At this point vitiligo is most often seen, commonly affecting the eyelashes, face, and trunk. Other symptoms such as alopecia may occur, and patients may present with changes in the color of the choroid to bright orange with a pale optic nerve.[3]

CASE PRESENTATION

A 26-year-old woman presented to the emergency department with an acute onset of progressive worsening bilateral eye pain and blurry vision. She denied any discharge from the eyes and stated that she had been having headaches, nausea, and fever for a few days. She was in good health before her vision problems, other than a history of chronic hair thinning that she shared with her mother and sister. She had no remarkable ocular history and denied orbital trauma. She had been seen at urgent care the previous week when her eye pain started, where she had been given prednisolone acetate drops and was instructed to follow up with an ophthalmologist. Her

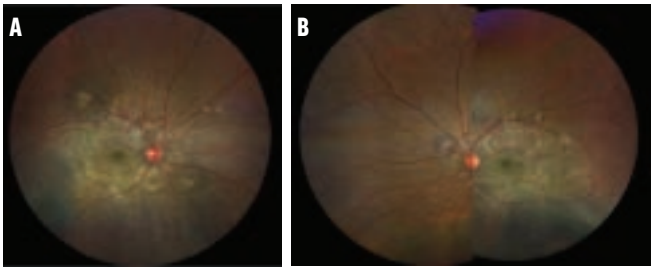


Figure 1. Fundus photos of the right (A) and left (B) eye at the first clinic visit showed 1+ vitreous haze and diffuse, bullous serous retinal detachments in the posterior pole and periphery.

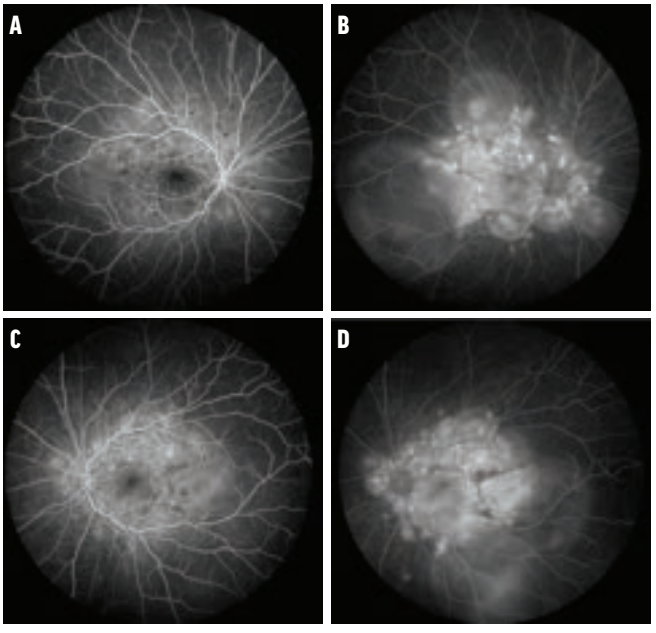


Figure 2. Fluorescein angiography of the right (A, B) and left (C, D) eye showed bilateral diffuse pinpoint leakage areas and late optic nerve leakage.

VA was 20/40 OD and 20/80 OS, and IOP was 16 mm Hg OD and 12 mm Hg OS. Her anterior segment examination was normal, except for a few keratic precipitates on each cornea. Dilated examination revealed 1+ vitreous

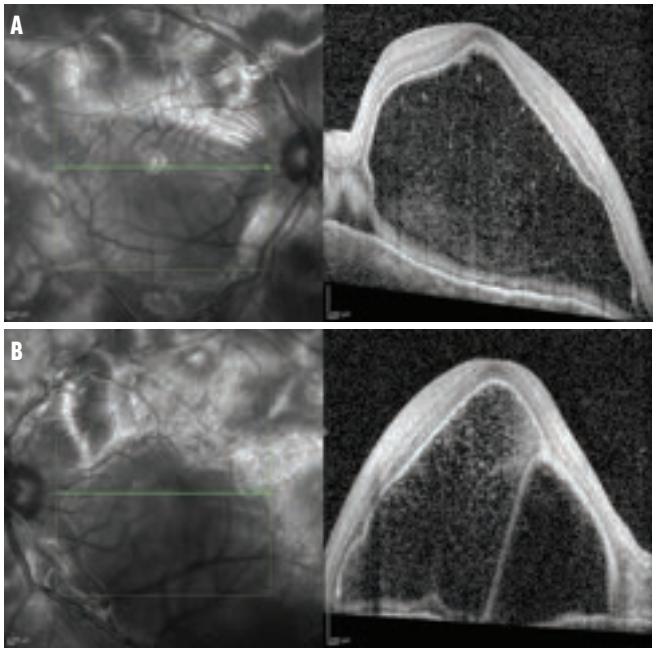


Figure 3. OCT macula of the right (A) and left (B) eye showed small, bilateral bullous retinal detachments.

haze and diffuse, bullous serous retinal detachments in the posterior pole and periphery of each eye (Figure 1). Fluorescein angiography showed bilateral diffuse pinpoint leakage and late optic nerve leakage (Figure 2). OCT revealed diffuse, small, bilateral bullous retinal detachments (Figure 3), and ultrasound revealed diffuse choroidal thickening (Figure 4).

Infectious labs, including human immunodeficiency virus, Bartonella titers, QuantiFERON gold, Lyme titers, and syphilis titers, had unremarkable results. We also ordered a complete blood count, basic metabolic panel, erythrocyte sedimentation rate, C-reactive protein, antinuclear antibody, angiotensin-converting enzyme, a rheumatoid factor, and a chest X-ray.

The patient continued topical prednisolone acetate in each eye four times daily. Over the next 3 days, she developed progressive changes in her mental status and a fever. She was taken to the emergency department for a further workup, was admitted as an inpatient, and neurology, infectious disease, and rheumatology were consulted. Workup as an inpatient consisted of a lumbar puncture, which showed 235 white blood cells (97% lymphocytes, 3% monocytes), 43 red blood cells, 48 glucose, and 153 total protein.

Management and Follow-up

The patient was ultimately diagnosed with VKH syndrome due to her ocular findings, hair loss, ethnicity (Bangladeshi), and findings of lymphocytic pleocytosis in her cerebrospinal fluid. She was treated with intravenous steroids for 3 days while in the hospital, discharged

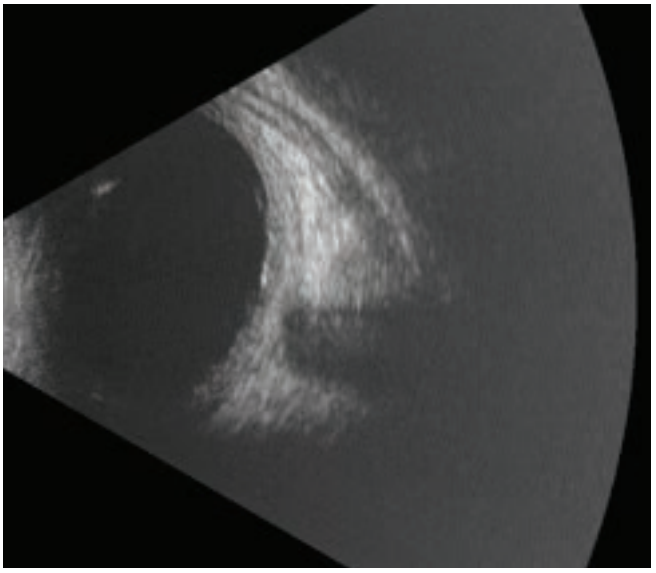


Figure 4. B-scan ultrasonography showed choroidal thickening in the right eye.

on 60 mg prednisone daily for 30 days, and instructed to follow up with her ophthalmologist in 1 week.

At the 1-week follow-up, she reported improvement of her eye pain and headaches and was afebrile. Although her vision was much better, she noted that it was still blurry and that lines looked wavy. Her fundoscopic examination showed that the retinal detachments had resolved (Figure 5). OCT of the macula showed mild subretinal fluid bilaterally that had dramatically improved since the last visit (Figure 6).

She was advised that her care would require a monthly taper of oral prednisone over 6 months with a possible transition to cyclosporine. She was also advised to continue following up with rheumatology and schedule annual ophthalmic examinations.

DISCUSSION

VKH is a noteworthy cause of noninfectious uveitis more common in people with pigmented skin. The incidence varies, with the highest incidence in Japan (7%), followed by the United States (1%–4%), and Brazil (3%). Women tend to be affected more often than men,[4] usually in the second to fifth decade of life.

Although our patient exhibited various findings that pointed to VKH syndrome, diseases such as sympathetic ophthalmia, Behçet syndrome, and other rare infectious etiologies can have a significant overlap of symptoms. Of note, one study found that the immunopathogenesis of Behçet syndrome involves CD4+ T cells, while VKH syndrome involves cytotoxic CD8+ T cells.[5] Although immunopathogenesis may not be entirely helpful on a clinical examination, it may help guide precise diagnostic approaches and treatment plans in the future. This is important given that the best treatment for VKH

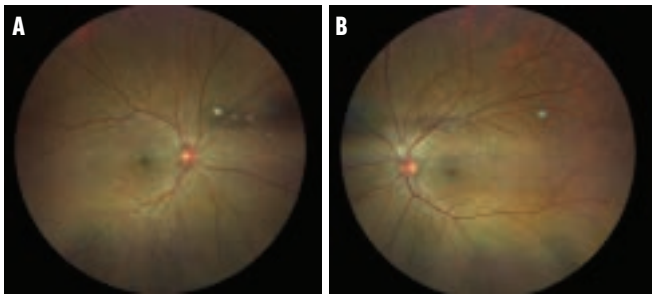


Figure 5. Fundus photos of the right (A) and left (B) eye showed improvement of the bullous serous detachments and vitreous haze after systemic corticosteroid treatment.

syndrome—corticosteroids versus immunosuppressants—is still controversial.

Since VKH syndrome is often a diagnosis of exclusion, having a broad differential and working step by step is crucial. It is common for VKH-related skin changes such as alopecia, poliosis, and vitiligo to appear later in the course of the disease, so patients may only present with a headache and bilateral optic disc swelling. This makes it easy to misdiagnose VKH syndrome as intracranial hypertension.[6] Furthermore, some patients may only present with ocular findings, and VKH may be misdiagnosed as an ocular condition.[6] There was a case of a 39-year-old woman who was originally diagnosed with uveitis and was referred to a neurologist, who diagnosed her with multiple sclerosis—only to discover years later that she actually had VKH syndrome.[7]

DIAGNOSTIC CRITERIA

Over the years, there have been several criteria proposed for the clinical diagnosis of VKH syndrome. One states that, to be diagnosed with VKH syndrome, a patient must have no evidence of ocular trauma and must meet at least three of the following criteria:

1. cutaneous findings, such as vitiligo, alopecia, or poliosis;
2. neurological findings, such as hearing loss, cranial nerve deficits, tinnitus, etc.;
3. bilateral choroidal iridocyclitis; and
4. posterior uveitis, which includes retinal pigmented detachments.[4]

While it is helpful to have a set of established findings to make a clinical diagnosis of VKH syndrome possible, these criteria fall short, considering patients can have symptoms that point to VKH syndrome but present with less than three of the four findings.[4] In addition, cutaneous and neurological findings are left up to the provider's interpretation and may consist of an array of different signs. The Revised Diagnostic Criteria Committee published an updated set of criteria in 2001, in which the most significant change was that VKH syndrome was now categorized into three categories: complete, incomplete, and probable.[8]

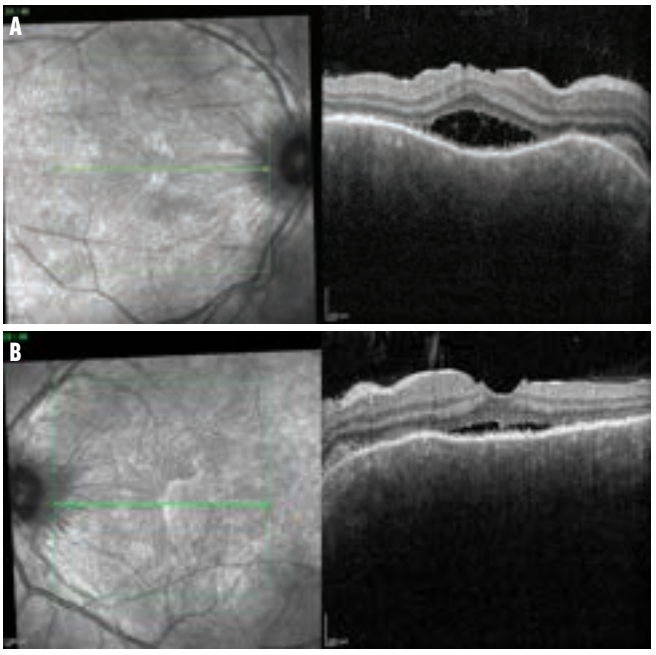


Figure 6. OCT imaging of the macula of the right (A) and left (B) eye showed improvement of the subretinal fluid.

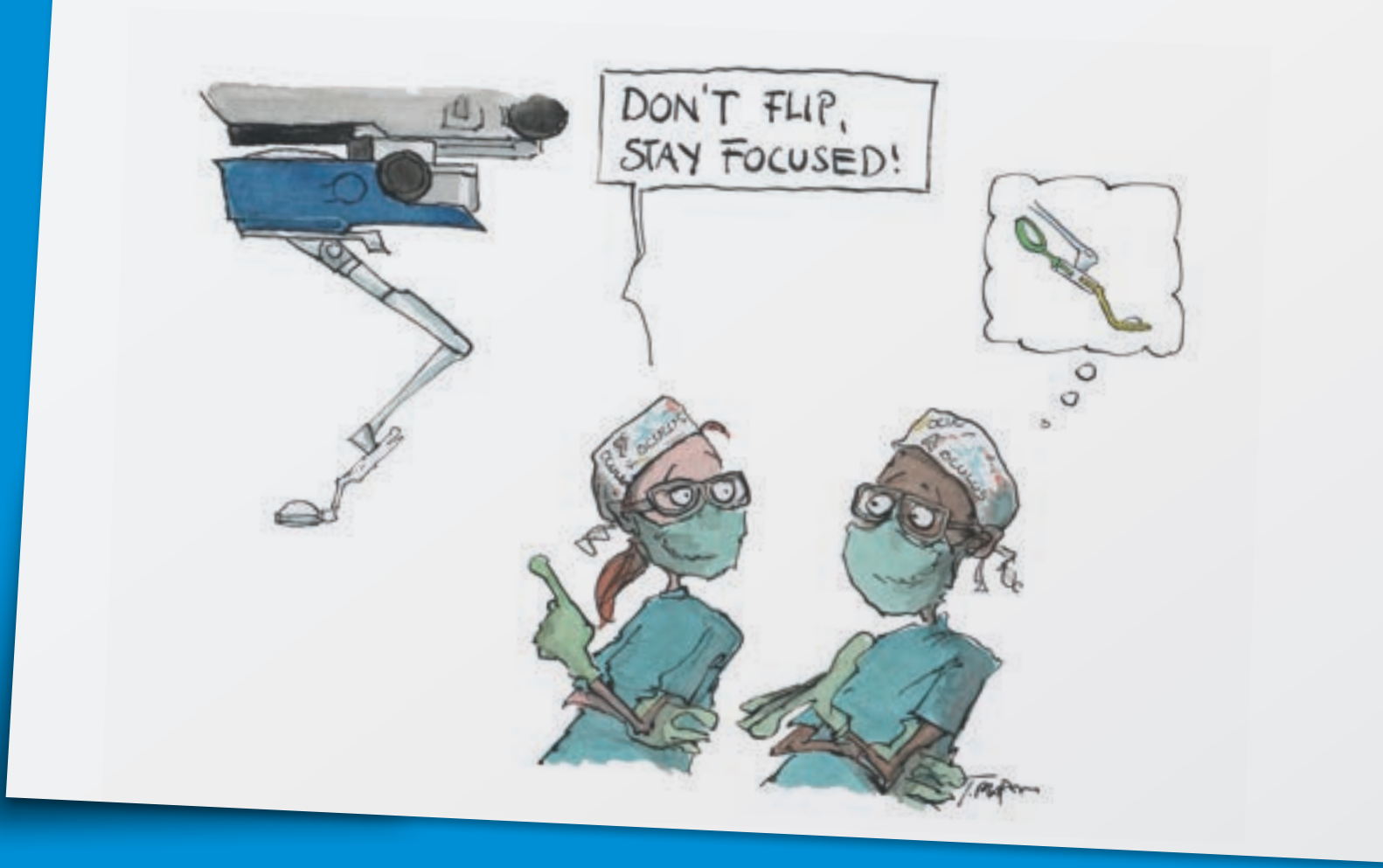
ONE STEP AT A TIME

Our patient was found to have VKH syndrome based on a diagnosis of exclusion, a lab workup, and her ocular findings. She responded well to systemic corticosteroid therapy and is continuing to follow up in the clinic. ■

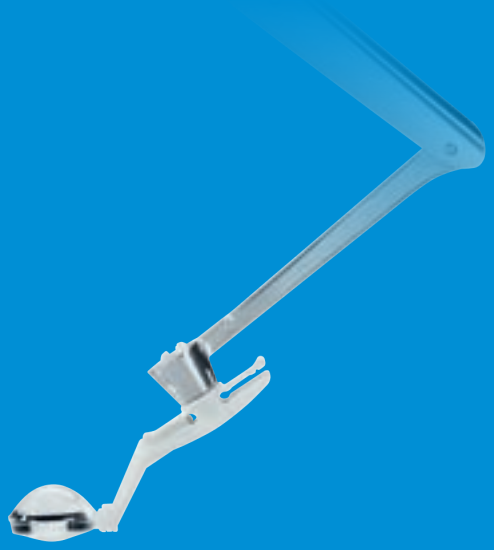
1. Patil YB, Garg R, Rajguru JP, et al. Vogt-Koyanagi-Harada (VKH) syndrome: a new perspective for healthcare professionals. *J Family Med Prim Care*. 2020;9(1):31-35.
2. Harris JP, Weisman MH. Head and Neck Manifestations of Systemic Disease Head and Neck Manifestations of Systemic Disease. CRC Press; 2007.
3. Wright KW, Strube YNJ. Pediatric Ophthalmology and Strabismus. 3rd ed. OUP: 2012.
4. Lavezzo MM, Sakata VM, Morita C, et al. Vogt-Koyanagi-Harada disease: review of a rare autoimmune disease targeting antigens of melanocytes. *Orphanet J Rare Dis*. 2016;11:29.
5. Kang H, Sun H, Yang Y, et al. Autoimmune uveitis in Behçet's disease and Vogt-Koyanagi-Harada disease differ in tissue immune infiltration and T cell clonality. *Clin Transl Immunology*. 2023;12(9):e1461.
6. Shoughy SS, Tabbara KF. Initial misdiagnosis of Vogt-Koyanagi-Harada disease. *Saudi J Ophthalmol*. 2019;33(1):52-55.
7. Algahtani H, Shirah B, Algahtani R, Alkahtani A, Alwadie S. Vogt Koyanagi Harada Syndrome mimicking multiple sclerosis: a case report and review of the literature. *Mult Scler Relat Disord*. 2017;12:44-48.
8. Read RW, Holland GN, Rao NA, et al. Revised diagnostic criteria for Vogt-Koyanagi-Harada disease: report of an international committee on nomenclature. *Am J Ophthalmol*. 2001;131(5):647-652.

STEVEN SCHEIDT, BS
- Medical Student, Kansas City University of Medicine and Biosciences, Kansas City, Missouri
- sscheidt02@gmail.com
- Financial disclosure: None

HEERAL SHAH, MD, FASRS
- Retina Specialist and Partner, Ramesh R. Shah MD PC, Joplin, Missouri
- Assistant Professor, Kansas City University of Medicine and Biosciences, Kansas City, Missouri
- heeralshahmd@gmail.com
- Financial disclosure: None



OCULUS HD Disposable LenZ –
For single-use on the ZEISS RESIGHT®



- **Perfect view in every case**
  Single-use means no scratches or opacities
- **Always sterile**
  Minimizes risk of infection and cross-contamination
- **Always available on the spot**
  Increase your O.R. capacity utilization

www.oculussurgical.com +49 641 2005-298 855-SDI-BIOM (Toll Free, US Only)

OCULUS® SURGICAL

TAILORING IVT DOSING WITH VITREOUS VOLUME

We have heard the adage, "As much as necessary, as little as possible," with regard to medication. Can we apply it to intravitreal therapy?

BY ANDREAS F. BORKENSTEIN, MD

The vitreous humor, which makes up approximately 80% of the eye, provides nutrients, maintains the eye's shape and structure, and helps to ensure clear vision.

The eyeball weighs approximately 6.5 g to 7.5 g, and an emmetropic adult has an average axial length (AL) of 23 mm to 24 mm. The literature tends to give only approximate volumes for the vitreous body of 4 mL to 5 mL, which is imprecise.

We conducted a study to analyze anatomical differences of the vitreous body between small/hypermetropic eyes and large/myopic eyes and use this information to create a formula for calculating precise, individual vitreous volume.

THE STUDY

The study included 72 eyes of patients who had undergone MRI of the orbit or skull in the last 12 months. The reasons for this imaging were diverse, including neurological disorders such as multiple sclerosis, chronic headache, migraine, follow-up on injury or tumors, and stroke or hemorrhage within the brain. Biometric data of the eye, including measurements of the anterior chamber and the AL of the eyeball, were also analyzed.

VIVEX: A Formula to Calculate Vitreous Volume

Based on the volume of a sphere with the diameter of the AL, which shows a volume of $AL^3 \times \pi/6$, a correction factor of 0.76 + 0.012 x (AL-24) was derived to account for the portion of the vitreous in the entire globe and the proportional increase of the vitreous for long (ie, myopic) eyes. This correction was developed based on the MRI analysis of emmetropic, myopic, and hypermetropic eyes (Figure 1).

With this newly developed formula, which we have coined *vitreous volume exact* (*VIVEX*), vitreous volume can be calculated using a known AL using the following formula:

$$V = \frac{AL^3 \cdot \pi}{6} \cdot (0.76 + 0.012 \cdot (AL - 24))$$

Using this formula, we calculated a wide range of volumes from 3 mL to 10 mL with differences between emmetropic, myopic, and hypermetropic eyes (Figure 2). We also created a VIVEX-correction table to easily obtain the individual vitreous volume knowing the AL.[1]

The following examples demonstrate the variety in vitreous volume:

- An emmetropic eye with an AL of 23.4 mm had a vitreous volume of 5.05 mL.
- A highly myopic eye with a refraction of -16.25/+1.00/120 had an AL of 30.5 mm and a vitreous volume of 12.45 mL.
- A hypermetropic eye with a refraction of +7.75/+1.00/120 had an AL of 20.6 mm and a vitreous volume of 3.29 mL.

Of note, the highly myopic eye had a vitreous volume that was nearly four-times as much as the volume of the hypermetropic eye.

Implications for Dosing

Intravitreal therapies for the treatment of retinal diseases have advanced significantly in recent decades. It has become a safe and effective option for treatment of macular degeneration, diabetic retinopathy, endophthalmitis, retinal vein occlusion, and other retinal diseases. Increases in ocular diseases, higher life expectancy, and development of novel drugs are likely to drive the global intravitreal injectable market at a rapid pace.[2]

Anti-VEGF therapy makes up the majority of intravitreal therapeutics in retina, and the standard dosing is one-size-fits-all; thus, the same amount of drug is administered to each patient, regardless of individual anatomy. The frequency and repetition of these injections are adjusted according to the follow-up control and the clinical findings on OCT. Currently, there are no recommendations for adjusting the dose according to the vitreous volume.

However, the application of a defined substance in a specific volume leads to a certain concentration. If the intravitreal medication is planned for the standard vitreous volume of 4 mL to 5 mL, it follows that, if the actual volume of the patient's eye is three-times that amount, the medication

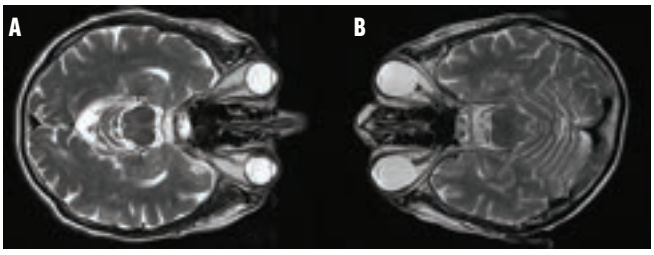


Figure 1. MRI shows the shapes of hyperopic (A) and myopic (B) eyes.

will dilute. Even assuming the active ingredient may still be available in sufficiently high quantities in a large vitreous volume, it remains that smaller eyes may then be overdosed. It is also well known that not all patients respond optimally and equally to the standard dose of a drug; this variability may be due to numerous individual factors.

POTENTIAL TO LOWER RISKS

Although intravitreal therapy is safe and effective, as with any procedure, there are associated risks and adverse effects. The risks of intravitreal injection include infection, endophthalmitis, uveitis, subconjunctival bleeding and vitreous hemorrhage, cataract formation, luxation of the human or intraocular lens, and increased IOP.[3] In addition to these local effects, systemic adverse effects, such as cardiovascular and renal complications, have been reported, highlighting the importance of cautious use.[4]

Currently, it remains uncertain whether the postoperative increase of IOP has a direct correlation to the volume. However, an exact systematic investigation of anatomical factors that may have an impact on IOP could be performed by measuring the volume preoperatively; it seems logical that the addition of a standard volume of a fluid into a small eye with a lower vitreous volume would lead to more pronounced effects on IOP than would be seen in a larger eye.

Drug packet inserts cannot provide dosing recommendations for all patient populations, but rather predominantly reflect the populations studied in the pivotal trials. However, throughout medicine, it is common to adjust drug dosages according to a mass or volume. For example, there are dosage recommendations for most drugs adapted to body weight, and drugs given to children have different maximum doses than those for adults. Spreadsheets and conversion formulas exist in many subspecialities in medicine, and calculation formulas are common in pharmacology, as well.

We believe that, if the vitreous volume can be measured easily and quickly preoperatively, then large-scale, multicentered studies should follow to determine whether there are any differences in the effectiveness or adverse effect based on vitreous volume. Studies should investigate the influence on IOP increases, iris lens diaphragm displacements, and effects associated with repeat injections.

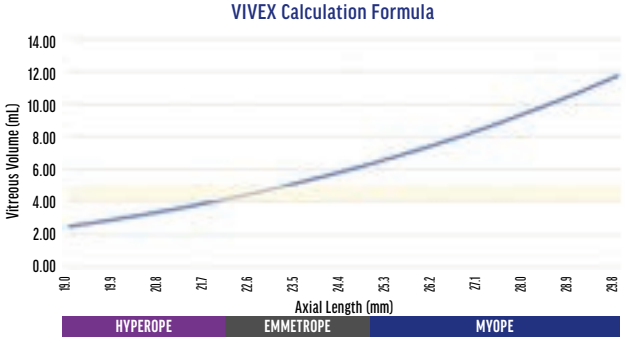


Figure 2. This diagram shows the differences in vitreous volume (range < 3 mL to > 10 mL) according to the AL of the eye calculated using the VIVEX formula.

LIMITATIONS

At this stage, our findings do not have a direct impact on clinical practice, as intravitreal therapy has proven to be safe and effective. However, this experimental analysis and the development of a new calculation formula should be the starting point for more systematic clinical investigations. Research on personalized intravitreal medications and the effect of the vitreous volume should be conducted.

Studies are also required to compare the performance of one-size-fits-all dosing with individually adjusted dosing. If no adverse effects of undertreatment are noticed, such customization could be a better choice for patients with lower vitreous volumes to avoid overloading the body with pharmacological agents. Other factors may play a role; in phakic or pseudophakic eyes, there will be slight deviations of minor impact, as a natural lens is around 4.0 mm thick, while an intraocular lens is around 1.0 mm thick.

The VIVEX formula could also be used to potentially increase safety when it comes to gas or silicone oil fill.

PRECISION MEDICINE IS THE FUTURE

We believe that with this newly developed formula, it will be easy to calculate the exact vitreous volume of each patient. Future research may reveal whether matching the dosage to the volume leads to any advantages in therapy or prevention of side effects, which may in turn affect the development of future intravitreal drug therapies and recommendations. ■

1. Borkenstein AF, Borkenstein EM, Langenbucher A. VIVEX: A formula for calculating individual vitreous volume: a new approach towards tailored patient dosing regime in intravitreal therapy. *Ophthalmol Ther*. 2024 ;13(1):205-219.
2. Intravitreal (IVT) injectible market. Persistence Market Outreach. Accessed March 19, 2024. bit.ly/3TQMDEB
3. Daka Q, Špegel N, Atanasovska Velkovska M, et al. Exploring the relationship between anti-VEGF therapy and glaucoma: implications for management strategies. *J Clin Med*. 2023;12(14):4674.
4. Fogli S, Del Re M, Rofi E, Posarelli C, Figus M, Danesi R. Clinical pharmacology of intravitreal anti-VEGF drugs. *Eye (Lond)*. 2018;32(6):1010-1020.

ANDREAS F. BORKENSTEIN, MD
■ Private practice, Borkenstein & Borkenstein, Privatklinik Kreuzschwestern, Graz, Austria
■ ordination@borkenstein.at
■ Financial disclosure: None

A REFERENCE GUIDE FOR OCT ANGIOGRAPHY

An illustrative overview of OCTA findings to help you implement this tool in common clinical scenarios.

By Ivy Zhu, MD; Nicole L. Decker, BS; and Amani A. Fawzi, MD



OCT angiography (OCTA) is a noninvasive imaging technique that uses the principles of motion detection to reveal depth-resolved images of the retinal and choroidal vasculature, down to the capillary level.[1] OCTA has several advantages over traditional imaging techniques, including being noninvasive (no dye injection), depth resolved, and rapid. A key benefit of OCTA is its ability to distinguish the various vascular networks without obscuration by leakage, making it very helpful for characterizing retinal neovascularization and nonperfusion with precision beyond dye-based angiography.

Here, we detail several clinical scenarios in which OCTA can be a useful diagnostic tool and illustrate key imaging features. In general, absence of flow (nonperfusion) is best appreciated with en face images. The presence of abnormal flow is most accurately detected using a combination of en face imaging assisted by the OCT B-scan with flow overlay to pinpoint abnormal flow related to structural pathological changes.

The OCT B-scan with flow overlay is particularly useful in situations where the quality of the en face image is equivocal. These tools are complementary and, together, can provide the clinician with a wealth of knowledge. Although beyond the scope of this discussion, it is also important to be cognizant of the artifactual errors that can occur and influence image interpretation.[2,3] Examples include segmentation errors with en face images and projection artifacts with both en face images and B-scan flow overlay.[2,3]

AT A GLANCE

- OCT angiography (OCTA) has several advantages over traditional imaging techniques, including being noninvasive, depth resolved, and rapid.
- OCTA can distinguish the various vascular networks without obscuration by leakage, making it helpful for characterizing neovascularization and nonperfusion.
- OCTA is particularly useful in cases of type 1 neovascularization, where sub-retinal pigment epithelium neovascularization can develop without active exudation.
- En face OCTA and OCT B-scans are complementary and, together, can provide the clinician with a wealth of knowledge.
- There are several conditions for which OCTA can provide detailed information that would otherwise be time-consuming or impossible to find with traditional techniques.

DIABETIC RETINOPATHY

OCTA can be useful in evaluating nonperfusion and neovascularization, giving the clinician insight into the degree of ischemia and severity of retinopathy. Nonperfusion is more easily detectable on the en face images than the cross-sectional OCT B-scan (Figures 1-3).

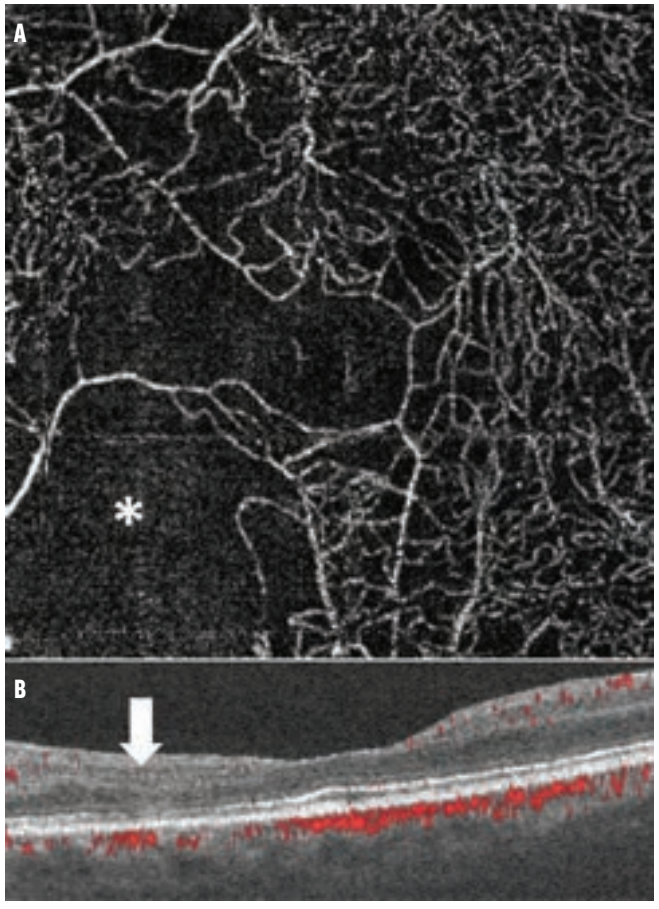


Figure 1. The en face OCTA deep capillary plexus slab of an eye of a 30-year-old woman with type 1 diabetes revealed significant areas of nonperfusion and capillary dropout (A, asterisk). The area of nonperfusion corresponds to a lack of flow seen on the OCT B-scan flow overlay (B, arrow). Note the asymmetry in flow between the temporal and nasal retina. There is also significant thinning of the fovea and temporal retina, including photoreceptor disruption, and disorganization of the retinal inner layers with distortion of the retinal layers on the OCT B-scan.

FURTHER READING

For more on using OCT angiography to capture retinal findings in diabetic retinopathy, see *The Utility of En Face OCT For Detecting Neovascularization in DR*, by Mizuki Hamada, MD, and Kotaro Tsuboi, MD, PhD.

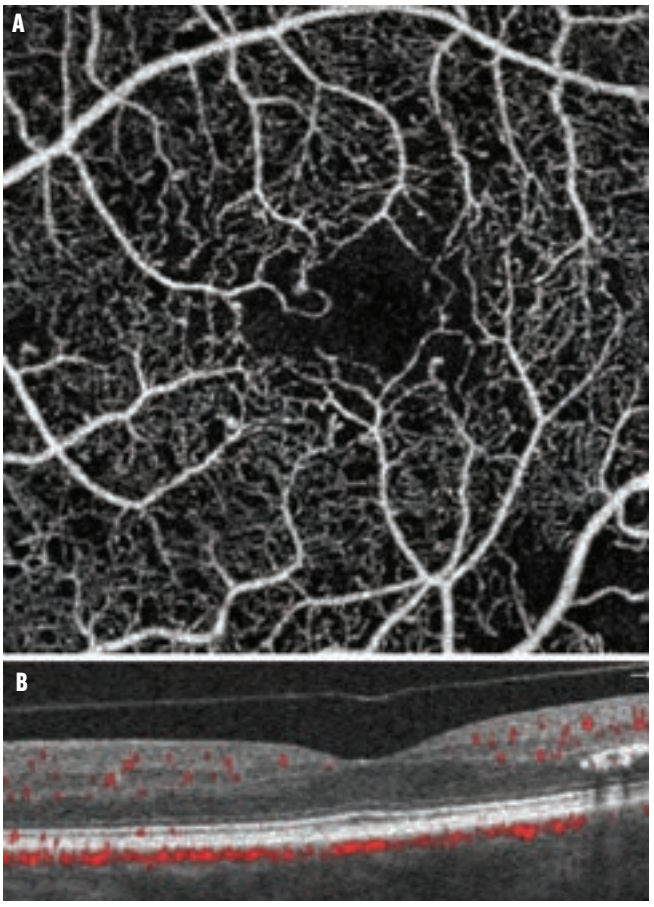


Figure 2. The full-thickness en face OCTA of the eye of a 36-year-old woman with type 1 diabetes showed an irregular, enlarged foveal avascular zone (FAZ) due to nonperfusion (A). Note the relatively normal retinal appearance on the OCT B-scan with flow overlay (B). In general, the full-thickness OCTA slab is the best approach for outlining the entire FAZ.

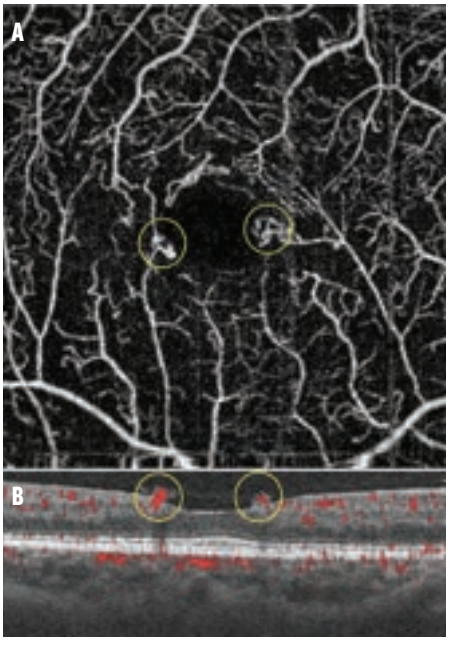


Figure 3. The en face superficial capillary plexus slab of an eye of a 48-year-old woman with type 2 diabetes illustrated abnormal blood vessels in the juxtafoveal region (A, circles). These abnormal vessels correspond to hyperreflective foci that project anterior to the internal limiting membrane on each side of the FAZ, with flow (B, circles, red overlay), consistent with neovascularization elsewhere, rather than intraretinal microvascular abnormalities.

AMD

OCTA is typically used in the setting of AMD to confirm the presence of neovascularization prior to treatment. It is particularly useful in cases of type 1 neovascularization, where sub-retinal pigment epithelium (RPE) neovascularization (also known as *subclinical* or *nonexudative* AMD) can develop without active exudation (Figure 4). OCTA can also be used to pinpoint the exact location of new blood vessel growth in cases of type 3 neovascularization (Figure 5).

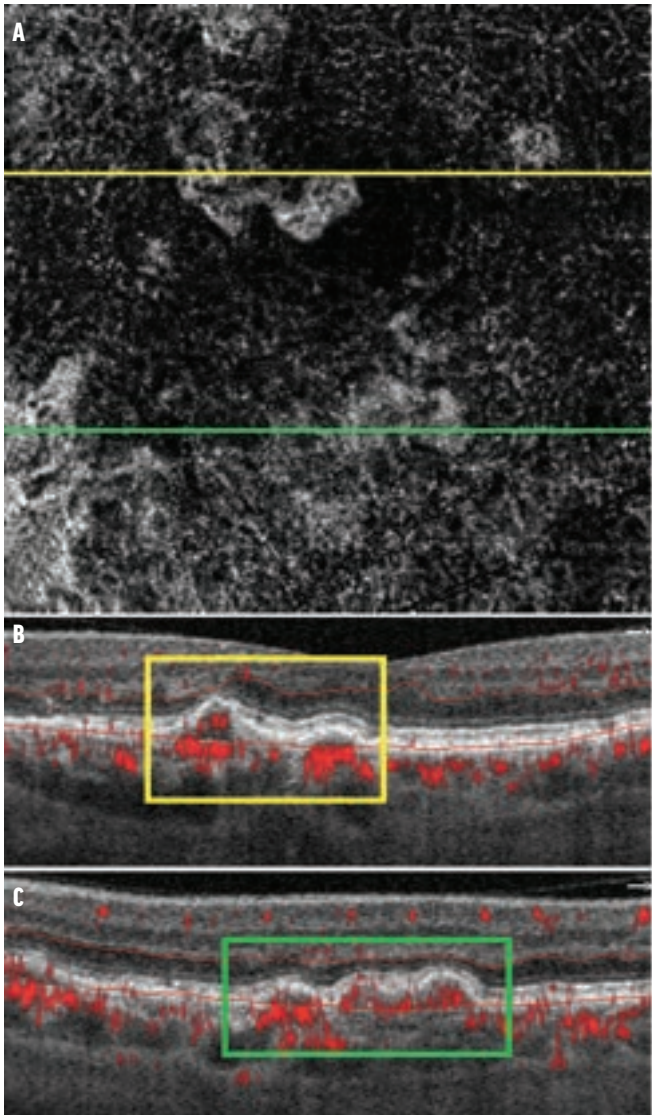


Figure 4. The en face outer retina slab of an eye of a 64-year-old woman with a history of nonexudative AMD showed several areas suspicious for neovascular networks (A). The colored lines correspond to the colored boxes in the OCT B-scans with flow overlay (B and C), where multiple areas of flow are present within the shallow pigment epithelial detachment and above Bruch membrane, consistent with a type 1 neovascular membrane. In these situations, the OCTA distinguishes drusen or drusenoid pigment epithelial detachments from subclinical neovascularization.

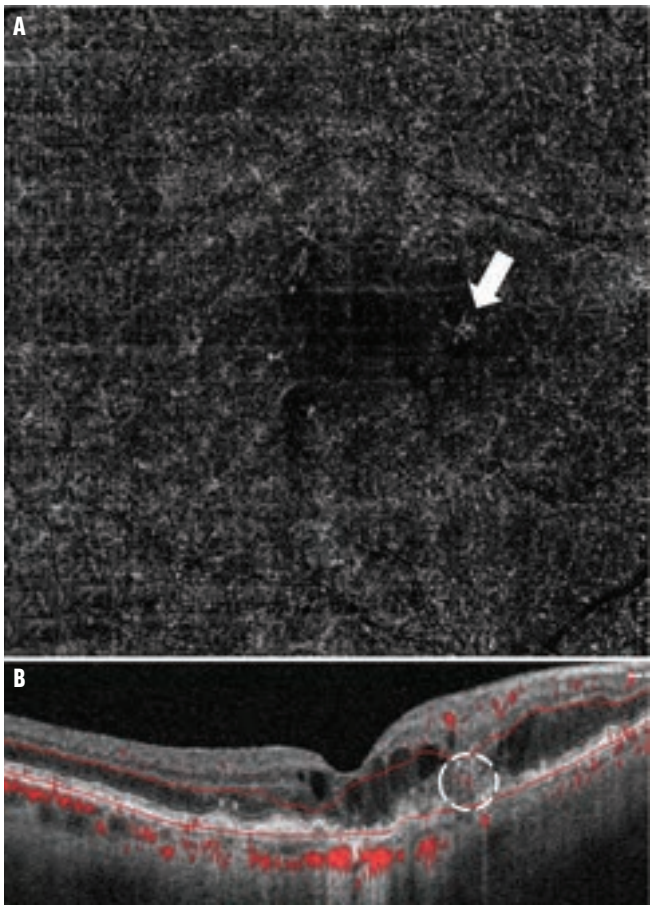


Figure 5. The en face deep capillary plexus slab of the eye of a 77-year-old man with AMD showed a subtle area of possible neovascularization in the outer retinal slab, consistent with possible type 3 neovascularization in AMD (A, arrow). By looking at the cross-section with flow overlay (B), an area of definite abnormal flow with surrounding outer retinal hyperreflectivity confirms the neovascular lesion (circle). The OCT B-scan with flow overlay was useful to confirm the presence of neovascularization due to the poor quality of the en face image. The B-scan can also be helpful in situations where the area of neovascularization may be too small or inconclusive on the en face slab.

OCTA IS A POWERFUL TOOL THAT CAN BE USED IN THE DIAGNOSIS AND SURVEILLANCE OF A VARIETY OF RETINAL CONDITIONS.

POLYPOIDAL CHOROIDAL VASCULOPATHY (PCV)

PCV is traditionally diagnosed via the identification of polyps or branching vascular networks using ICG angiography, which can be time-consuming and difficult to obtain.[4] However, OCTA in combination with structural OCT can be used to identify flow features consistent with PCV (Figure 6). In polyps, flow is present at the top of the pigment epithelial detachment and seen in the outer retina slabs, while branching vascular networks show flow between the RPE and Bruch membrane.[5] Cross-sectional OCTA may be sensitive in detecting polyps on en face segmentation.[6] Occasionally, the flow within a polyp may be too slow to detect using OCTA.

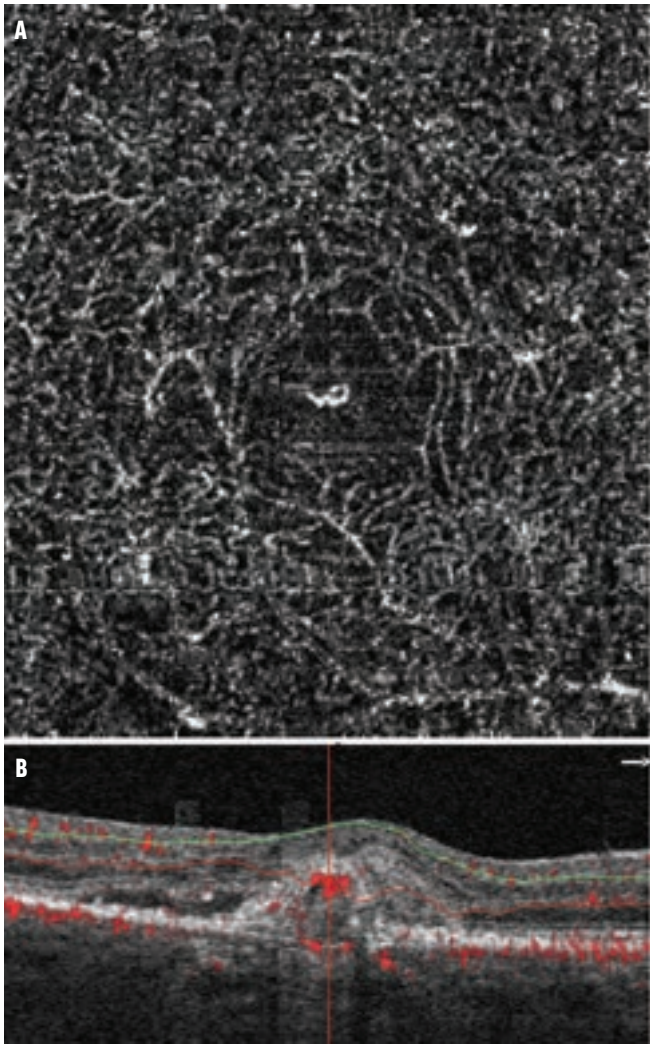


Figure 6. In the eye of a 67-year-old man with PCV, the en face deep capillary plexus slab showed the anterior projection of a central polyp within the FAZ (A). The OCT B-scan with flow overlay confirmed the presence of flow within a hyporeflective ring-like lesion between the RPE and Bruch membrane, consistent with a polyp (B).[6]

NEOVASCULARIZATION IN MULTIFOCAL CHOROIDITIS

The use of OCTA in inflammatory conditions, such as neovascularization in multifocal choroiditis or punctate inflammatory choroidopathy, can help clinicians distinguish choroidal neovascular membranes from inflammatory lesions (Figure 7).

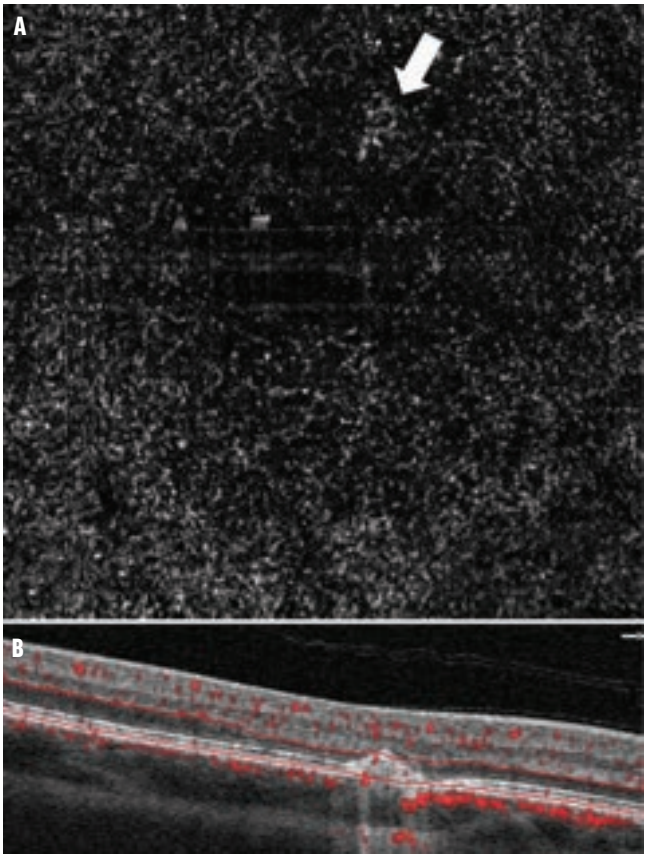


Figure 7. The en face OCTA outer retina slab of the eye of a 34-year-old woman with myopia and a history of multifocal choroiditis showed a neovascular network (A, arrow) that corresponds with several areas of flow under the RPE and above Bruch membrane on the OCT B-scan (B). In this case, OCTA was helpful in distinguishing choroidal neovascular membranes from a new inflammatory lesion, which ultimately favored treatment with injections of anti-VEGF over steroid. This patient responded well to a limited series of anti-VEGF injections.

PRACTICE MAKES PROGRESS

OCTA is a powerful tool that can be used in the diagnosis and surveillance of a variety of retinal conditions. However, it can be challenging for the inexperienced user to identify the appropriate clinical scenarios that would benefit from OCTA imaging and to interpret the results. Here, we illustrated several conditions for which OCTA provided detailed information that would otherwise have

(Continued on page 56)

THE UTILITY OF EN FACE OCT FOR DETECTING NEOVASCULARIZATION IN DR

We conducted a study of our own to better understand this association.

By Mizuki Hamada, MD, and Kotaro Tsuboi, MD, PhD


While OCT has enhanced the objective diagnosis of diabetic macular edema (DME), early detection of proliferative diabetic retinopathy (PDR) remains challenging for ophthalmologists and often requires a thorough dilated fundus examination or fluorescein angiography (FA).[1] Recent advances in OCT angiography (OCTA) not only enable the identification of retinal neovascularization (RNV) above the internal limiting membrane (ILM), but also offer a wider field of view, making OCTA a promising tool.[2-4] Additionally, structural OCT can be instrumental in detecting RNV, particularly in distinguishing it from intraretinal microvascular abnormalities (IRMA).[5,6] In a recent longitudinal study, we detailed the early stages of RNV using both en face OCT and en face OCTA in eyes with DR.[7,8]

PUTTING THE THEORY TO THE TEST

We conducted a cross-sectional study to analyze the sensitivity and specificity of en face OCT and en face OCTA for the detection of clinically occult RNV in nonproliferative DR (NPDR).[9] We obtained four high-resolution scans (600 x 600 sampling densities over

AT A GLANCE

- In a recent longitudinal study, the authors detailed the early stages of retinal neovascularization using both en face OCT and en face OCT angiography (OCTA) in eyes with diabetic retinopathy.
- OCTA's capacity to detect flow signals above the internal limiting membrane has provided a more reliable method to categorize lesions.
- By pinpointing neovascularization precursors instead of relying on indirect retinal features to forecast progression risk, we may be able to achieve greater precision in identifying eyes on the verge of developing proliferative diabetic retinopathy.

9 x 9 mm) and generated a 17 x 17 mm widefield OCTA scan. We created two different custom slabs for en face OCT and en face OCTA to optimize RNV detection (Figure 1). RNV lesions were identified using a combination of en face OCT, en face OCTA with custom vitreoretinal interface slab, and cross-sectional OCTA.

Of the 63 enrolled eyes, 27 (43%) had severe NPDR, 16 (25%) had moderate NPDR, and 20 (32%) had mild NPDR. Combining en face OCT, en face OCTA, and cross-sectional OCTA, the graders detected 42 RNV lesions in 12 (19%) eyes. Of these, eight (67%) were severe NPDR, two (17%) were moderate NPDR, and two (17%) were mild NPDR. The sensitivity of en face OCT alone for detecting eyes with RNV was similar to that of en face OCTA alone (100% vs 92%), whereas the specificity of en face OCT alone was significantly lower than that of en face OCTA alone (32% vs 73%). For detecting individual RNV lesions, en face OCT had a sensitivity of 100% compared with a sensitivity of 67% for en face OCTA. A combination of en face OCT and en face OCTA detected subclinical RNV in eyes with NPDR that was barely detectable on color fundus photography (Figure 2).

We also measured the RNV flow area captured by OCTA and the RNV membrane area captured by OCT (Figure 3). The mean membrane area of an RNV lesion on en face OCT was larger than the mean flow area on en face OCTA by a factor of 3.4 (standard deviation: 2.8). When comparing the area of RNV flow of the 14 RNV lesions that the graders missed with en face OCTA to grader-detected RNV, the area of missed RNV lesions was significantly smaller than that of manually detectable RNV.

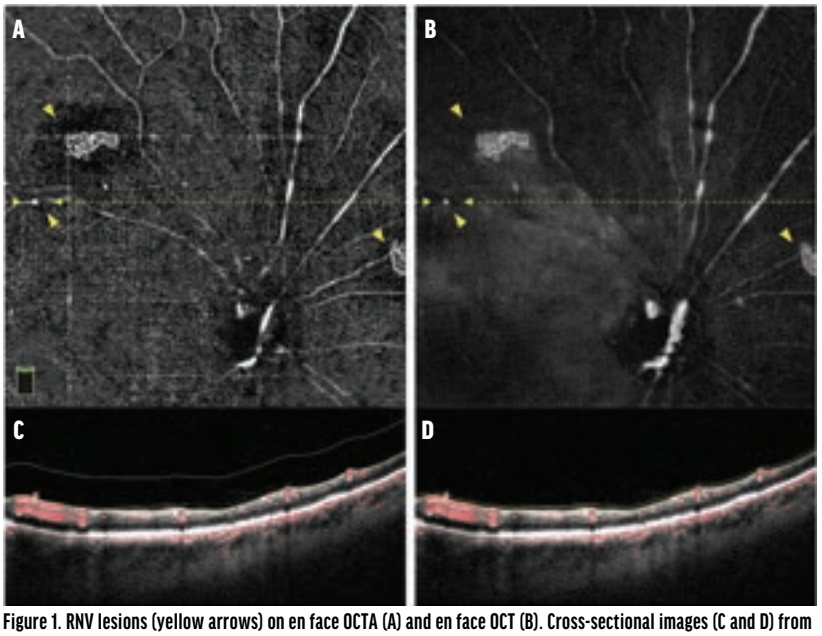


Figure 1. RNV lesions (yellow arrows) on en face OCTA (A) and en face OCT (B). Cross-sectional images (C and D) from the location of the dashed lines show a small RNV tuft.

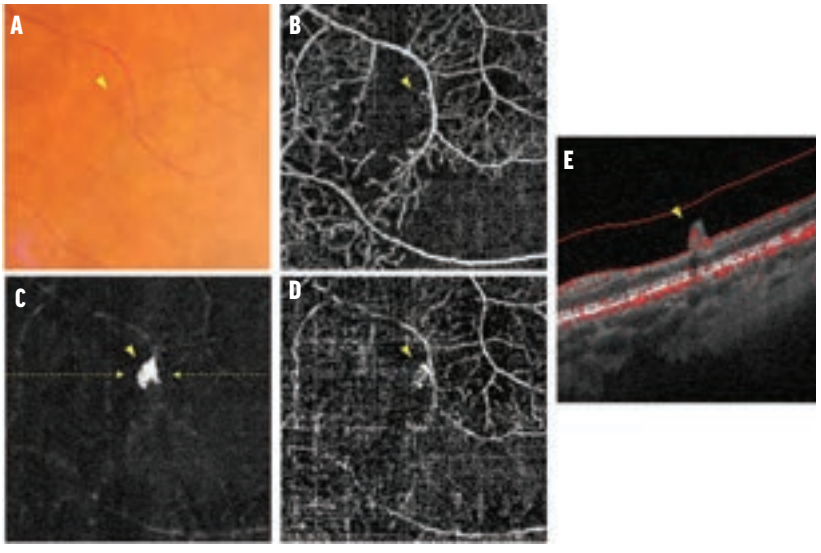


Figure 2. Multimodal imaging of subclinical RNV. Color fundus photography (A) and en face OCTA (B) of the whole retinal slab barely show RNV. However, en face OCT (C) and en face OCTA (D) with the vitreoretinal interface slab illustrate RNV. A cross-sectional OCTA (E) demonstrates a flow signal breaching the ILM, confirming RNV.

DECIPHERING THE RESULTS

The clinical significance of the small RNV lesions detected by en face OCT remains uncertain. It's also undetermined if their early detection and intervention could substantially mitigate the risk of vision impairment. However, prior longitudinal studies have shown that these small RNV lesions can grow.[7,8] Based on this, we postulate that if RNV initially progresses through a subclinical phase, as observed in our study, then identifying subclinical RNV could more accurately predict the imminent risk of advancing to overt PDR than photographic grading. By pinpointing RNV precursors instead of relying on indirect retinal features such as intraretinal hemorrhages to forecast progression risk, we may achieve greater precision in identifying eyes at risk of developing PDR.

It's important to emphasize that OCTA played a crucial role in verifying the nature of the epiretinal lesions in our study. Lee et al highlighted the value of structural OCT in differentiating between IRMA and neovascularization.[5] The study drew attention to the unique histological insights that OCT B-scan can provide, which FA might miss. It also featured cases that were clinically diagnosed as RNV on OCT but did not exhibit

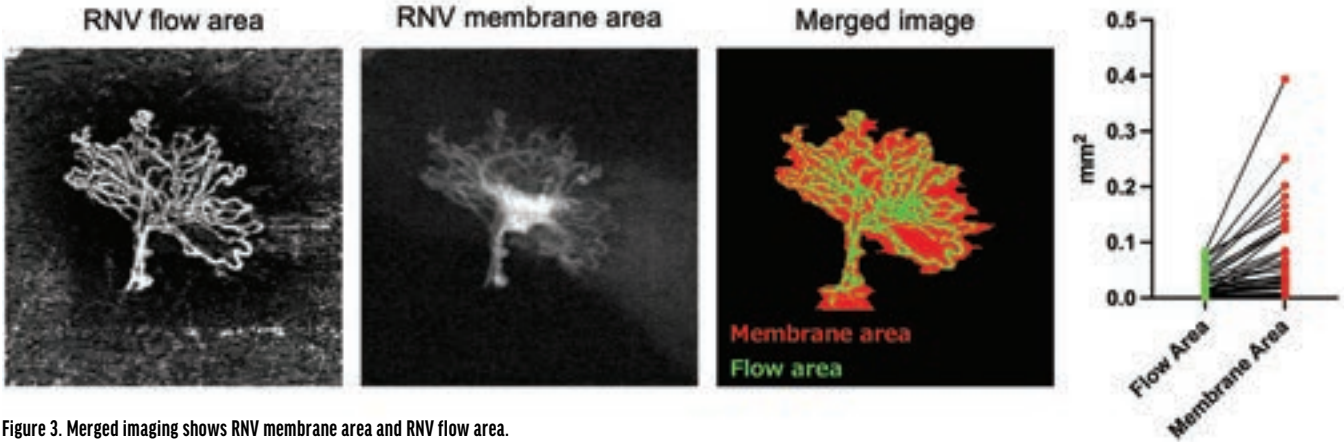


Figure 3. Merged imaging shows RNV membrane area and RNV flow area.

leakage on FA. The team posited that while FA is beneficial, it isn't the best tool for determining whether a lesion qualifies as neovascularization elsewhere. Moreover, they acknowledged instances where clinical examination and structural OCT findings diverged on classifying a lesion as either IRMA or RNV. Given the technology available when this study was conducted in 2015, there was no definitive means to ascertain the nature of such lesions. However, with the advent of OCTA, the capability to detect flow signals above the ILM has provided a more reliable method to categorize a lesion. This approach aligns more closely with histological findings as opposed to relying solely on clinical examination, FA, or structural OCT.

CAVEATS

One primary constraint of our study is the relatively limited field of view. Previous studies have shown a high sensitivity (ranging from 73% to 100%) for detecting eyes with RNV using OCTA. However, a single 12 x 12 mm OCTA and a 15 x 9 mm montaged OCTA are estimated to identify only about 40% of individual RNV lesions that ultra-widefield FA can detect. To expand the field of view without compromising the image resolution and quality, further imaging advances are necessary.

Another drawback is that neither en face OCT nor en face OCTA was highly specific for RNV detection when used individually. A common reason for false-positive RNV detection was vessel crossings in en face OCT. As a result, analyzing cross-sectional OCTA (superimposed on OCT) was essential to ascertain if the hyperreflective material on OCT or the flow signal on OCTA above the ILM represented RNV.

Additionally, widefield OCTA entails numerous B-scans—with this study using 2,400 for a 17 x 17 mm scan—making it cumbersome for routine use. Nonetheless, with enough training, an automated algorithm could discern false-positive lesions, enhancing the specificity of these imaging techniques for RNV detection.

KEY TAKEAWAY

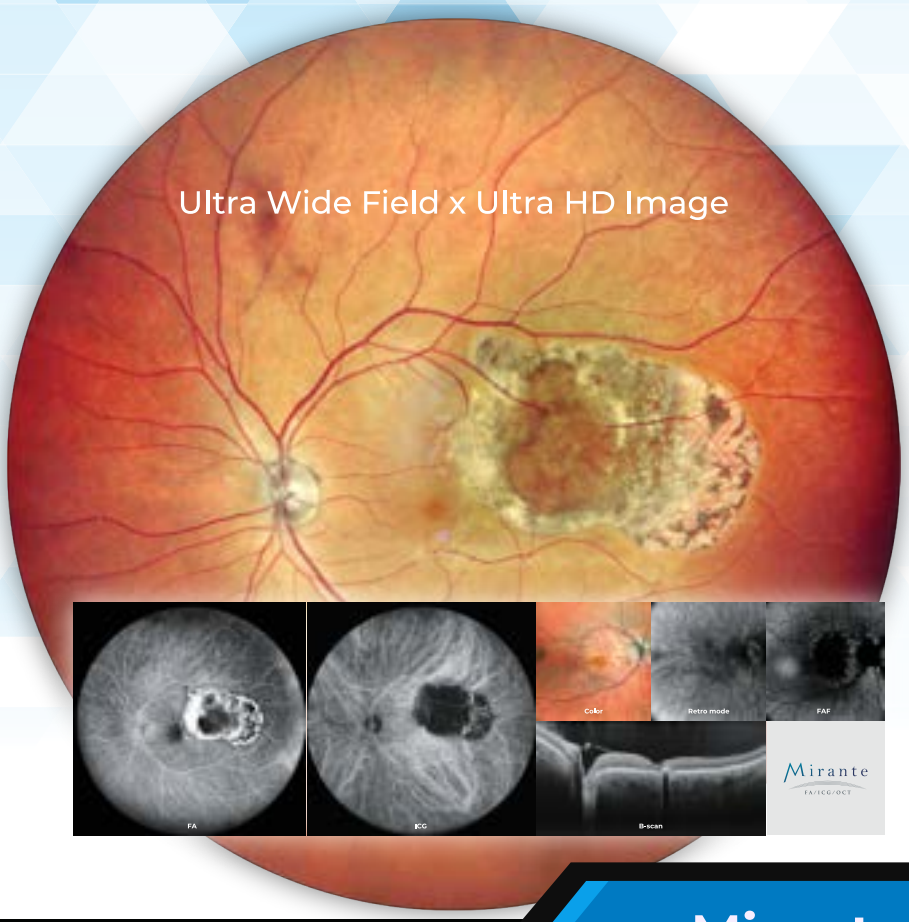
Given that a single OCTA scan can produce both en face OCT and en face OCTA, we believe that integrating these two imaging techniques presents an optimal approach for RNV screening. For detecting individual RNV lesions, en face OCT was significantly more sensitive than en face OCTA because the area of RNV membrane on en face OCT was larger than the area of RNV flow on en face OCTA. Thus, en face OCT may be a valuable tool for the initial screening of areas of small RNV in eyes with DR. ■

1. Pearce E, Sivaprasad S. A review of advancements and evidence gaps in diabetic retinopathy screening models. *Clin Ophthalmol Auckl N Z*. 2020;14:3285-3296.
2. Hirano T, Hoshiyama K, Hirabayashi K, et al. Vitreoretinal interface slab in OCT angiography for detecting diabetic retinal neovascularization. *Ophthalmol Retina*. 2020;4:588-594.
3. Schwartz R, Khalid H, Sivaprasad S, et al. Objective evaluation of proliferative diabetic retinopathy using OCT. *Ophthalmol Retina*. 2020;4:164-174.
4. Russell JF, Flynn HW, Sridhar J, et al. Distribution of diabetic neovascularization on ultra-widefield fluorescein angiography and on simulated widefield OCT angiography. *Am J Ophthalmol*. 2019;207:110-120.
5. Lee CS, Lee AY, Sim DA, et al. Reevaluating the definition of intraretinal microvascular abnormalities and neovascularization elsewhere in diabetic retinopathy using optical coherence tomography and fluorescein angiography. *Am J Ophthalmol*. 2015;159:101-110.e1.
6. Russell JF, Shi Y, Scott NL, et al. Longitudinal angiographic evidence that intraretinal microvascular abnormalities can evolve into neovascularization. *Ophthalmol Retina*. 2020;4:1146-1150.
7. Tsuboi K, Ishida Y, Wakabayashi T, Kamei M. Presumed glial sprouts as a predictor of preretinal neovascularization in retinal vein occlusion. *JAMA Ophthalmol*. 2022;140.
8. Tsuboi K, Mazloumi M, Guo Y, et al. Early sign of retinal neovascularization evolution in diabetic retinopathy: a longitudinal OCT angiography study. *Ophthalmol Sci*. 2023:100382.
9. Tsuboi K, Mazloumi M, Guo Y, et al. Utility of en face OCT for the detection of clinically unsuspected retinal neovascularization in patients with diabetic retinopathy. *Ophthalmol Retina*. 2023;7(8):683-691.

MIZUKI HAMADA, MD
- Assistant Professor, Department of Ophthalmology, Aichi Medical University, Nagakute, Aichi, Japan
- Financial disclosure: None

KOTARO TSUBOI, MD, PHD
- Assistant Professor, Department of Ophthalmology, Aichi Medical University, Nagakute, Aichi, Japan
- kotarotsuboi@gmail.com
- Financial disclosure: Honoraria (Alcon, Bayer, Chugai, Johnson & Johnson, Lumenis, Novartis, Santen, Senju)

The Ultimate Multimodal Imaging Platform



NEW!

Mirante SLO and SLO/OCT Combo

The Mirante SLO/OCT is the ultimate multimodal imaging platform that combines high definition SLO and OCT with ultra wide field imaging. The multimodal platform captures high quality color images, fluorescein angiography (FA), indocyanine green angiography (ICG), fundus autofluorescence (FAF) including Green-FAF and Blue-FAF, unique Retro mode images, and OCT.

LEARN MORE: **info@nidek.com · usa.nidek.com**

CALL US TODAY!
1-877-200-9892

Eye & Health Care
NIDEK INC.

March 13, 2023
2023-0009

CAPTURING GEOGRAPHIC ATROPHY WITH MULTIMODAL IMAGING

Noninvasive technologies are redefining how we diagnose and monitor atrophic AMD.

By Eric H. Souied, MD, PhD; Oudy Semoun, MD; and Vittorio Capuano, MD

Diagnosis of geographic atrophy (GA) relies on multimodal imaging, including color fundus photography, fundus autofluorescence (FAF) imaging, and structural OCT.[1] Diagnosis can be difficult and, at times, may require more invasive tests such as fluorescein angiography (FA) and ICG angiography (ICGA). More recently, OCT angiography (OCTA) has become a useful tool to capture associated choroidal neovascularization as part of mixed GA and wet AMD.[2] Here, we discuss noninvasive imaging techniques that can help clinicians establish a definitive diagnosis of GA and follow patients appropriately.

COLOR FUNDUS PHOTOGRAPHY

Color fundus imaging remains the first approach for the study of macular atrophy (Figure 1). It allows clinicians to rule out the main causes of macular atrophy other than GA, assess the possible presence of retinal hemorrhages, note any alterations within the retinal pigment epithelium (RPE), distinguish the form and size of atrophy, and visualize drusen and reticular pseudodrusen (RPD). Historically, the diagnosis of GA has been based on these images. The AREDS2 study defined GA as an absence of RPE from a spot larger than 175 µm in width where choroidal trunks are visible without evidence of exudation (detachment of the pigment epithelium or hemorrhage).[3]

Several types of fundus cameras are available, either with xenon flash (conventional cameras) or white LED light confocal devices. Image acquisition and interpretation vary by model. Newer-generation LED cameras penetrate better in cases of media opacification without oversaturation of the red channel like traditional fundus images,[4] but they produce false images of the fundus called *reconstructed images*.

AT A GLANCE

- Color fundus photography is often not sufficient for the diagnosis and monitoring of geographic atrophy (GA), and other imaging modalities are needed.
- OCT and fundus autofluorescence are the standard imaging modalities for the diagnosis of GA.
- Invasive techniques (ie, fluorescein angiography and ICG angiography) should be reserved for specific cases in which the diagnosis is unclear.
- OCT angiography may be useful to detect nonexudative macular neovascularization associated with GA.

GA is frequently characterized by a round or oval, regular or multilobed lesion with one or multiple foci and somewhat clear limits. The large choroidal trunks are visible in the absence of RPE, associated with a pale retina. Perilesional hyperpigmentation may also be visible.

However, color fundus photography is often not sufficient for the diagnosis and long-term monitoring of GA, and other imaging modalities are needed.

AUTOFLUORESCENCE IMAGING

FAF images are valuable for the diagnosis of GA. The pigment in the RPE cells sends physiological "autofluorescence" if properly stimulated. This physiologic fundus fluorescence (isoautofluorescence or normoautofluorescence) increases when pigment phagocytosis and lipofuscin formation are ongoing (hyperautofluorescence) (Figure 2). The absence of fluorescence (hypoautofluorescence) is due to the complete loss of metabolic activity of the RPE cells.

In GA, the atrophic lesion is characterized by hypoautofluorescence surrounded by a halo of hyperautofluorescence at the edge. Holz et al classified zones of perilesional hyperautoflourescence into several types: no hyperautoflourescence, hyperautoflourescence, focal, band and patch, and diffuse and trickling.[5] Other classifications have also been proposed in the past.

GA is characterized by enlargement of the atrophic lesion over time, progressing from the edge of atrophy (initially seen as hyperautofluorescent on FAF). The rate of progression is approximately 1.77 mm^2 per year but varies according to FAF pattern.[5]

NEAR INFRARED

Near-infrared reflectance (NIR) imaging (between 800 nm and 2,500 nm) penetrates deeper than FAF (between 420 nm and 500 nm) through the different layers of the retina. Thus, the combination of NIR and FAF images allows a more detailed assessment of fovea-sparing lesions (Figure 3).[6]

ADAPTIVE OPTICS

Adaptive optics is an imaging technique that allows for real-time correction of the changing lateral deformations of the front of the photoreceptors and the RPE and, therefore, the edges of the ellipsoid zone (EZ). This imaging modality is not used in routine clinical practice because of the high instrument cost and slow image acquisition.[7]

OCT

OCT is now the standard for diagnosing and following retinal disorders, and GA is no exception. The retinal complex is divided into two parts: the external retina and the RPE, and into subcategories of complete and incomplete. We identified the structures visible on OCT for this classification: the external limiting membrane (ELM) and EZ for the outer

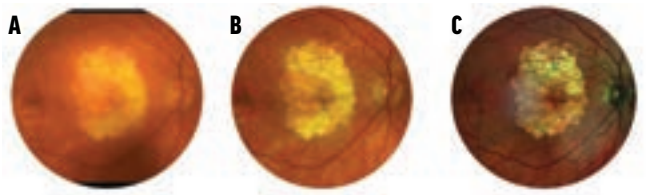


Figure 1. Depicted here are color images of GA captured with Topcon's conventional, or non-mydriatic, camera using xenon flash (A), Carl Zeiss Meditec's Clarius non-mydriatic camera (B), and Heidelberg Engineering's multicolor imaging (C).

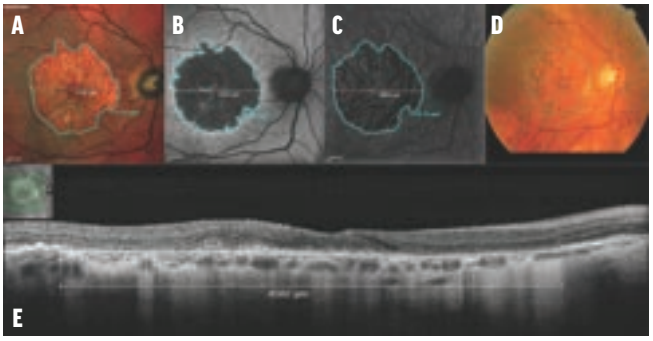


Figure 2. Clinicians can analyze GA lesions using multicolor imaging, which allows delineation of the lesion borders (A), FAF (B), NIR imaging (C), traditional color fundus imaging (D), and OCT, which shows the presence of cRORA (E).

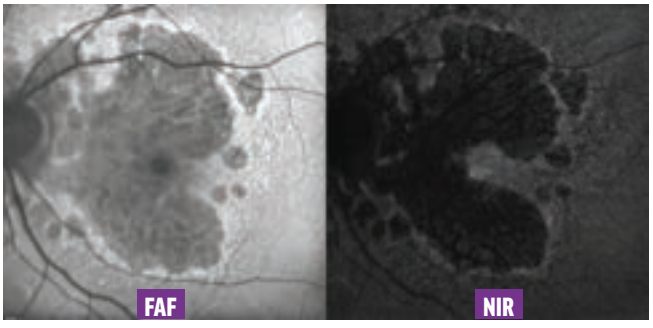


Figure 3. Because of the xanthophyll pigment, the foveal zone appears dark on FAF imaging, while the foveal sparing is more obvious on NIR imaging.

retina and RPE and the hypertransmission of the signal for RPE. Based on these findings, we identified four categories of retinal damage due to atrophic AMD (Figure 4)[8]:

1. Incomplete outer retinal atrophy (iORA): An intact ELM, intermittent EZ, and intact RPE without signal hypertransmission.
2. Complete outer retinal atrophy (cORA): The ELM and EZ are not visible, but the RPE is intact. Intermittent hypertransmission is possible.
3. Incomplete RPE and outer retinal atrophy (iRORA): The EZ and ELM are disrupted, the RPE is disrupted, and there is inconsistent hypertransmission of the signal.
4. Complete RPE and outer retinal atrophy (cRORA): Lack of visualization of the EZ, ELM, RPE, and hypertransmission of the signal.

These four entities are at least 250 µm wide. Of note, atrophy of the outer retina, including photoreceptors, can occur without affecting the RPE, whereas atrophy of the RPE

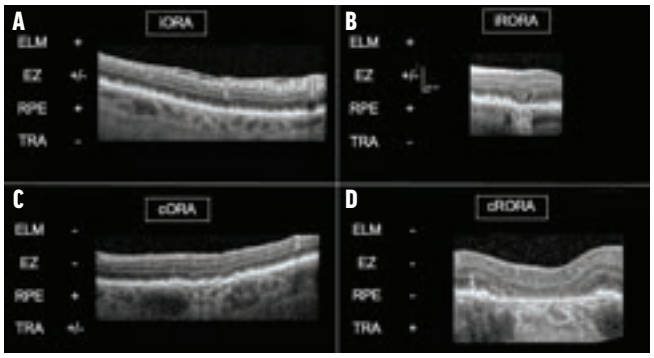


Figure 4. The OCT classification of GA includes iORA (A), iRORA (B), cORA (C), and cRORA (D).

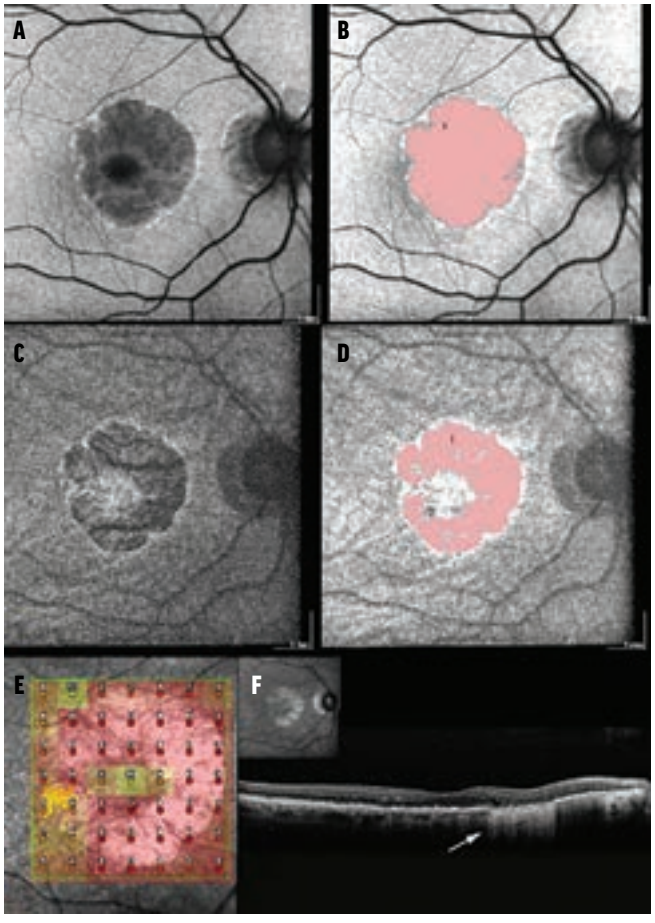


Figure 5. In the FAF of a GA lesion (A), the xanthophyll pigment appears even darker than the dark hypofluorescent zone of GA. In the same FAF image that was processed through automated quantification of the GA lesion (B), the foveal sparing is not detected. In the NIR image (C), the foveal sparing contrasts with the hypofluorescent atrophic lesion. In the same NIR image with automated quantification of the atrophic zone (D), the foveal sparing is detected, allowing a reliable quantification of GA. Microperimetry (E), used to evaluate the macular function, correlates with the foveal sparing detected in the NIR imaging. With OCT imaging (F), the limits of the atrophic zone (cRORA) show the foveal sparing.

is always accompanied by atrophy of the overlying photoreceptor layer (Figure 5). While outer retinal atrophy may be characteristic of AMD, cRORA may be due to several phenotypes of inflammation and infection of the retina and choroid, including wet AMD. Thus, the presence of cRORA in an OCT scan is not sufficient evidence to establish a diagnosis of GA. Each OCT section should be explored for signs of exudation, drusen, and RPD. The latter two will validate the diagnosis of GA. Drusen can also occur in areas of atrophy, called *ghost drusen*,[9] and are remnants of serous, conical drusen within an area of atrophy (Figure 6).

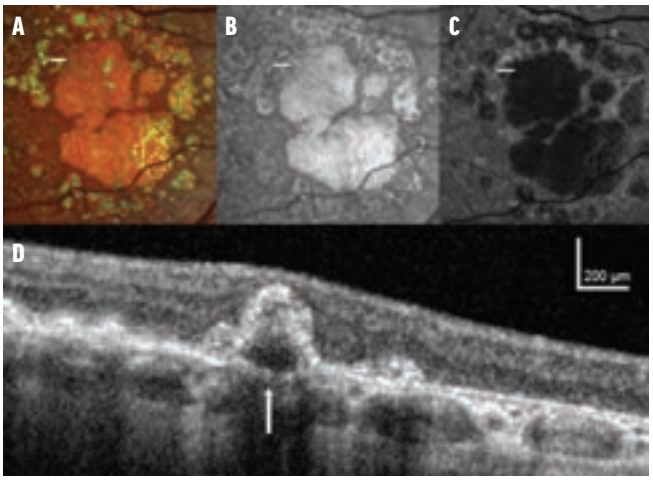


Figure 6. Multicolor (A), NIR (B), FAF (C), and OCT imaging (D) of hypereflective pyramidal structures, or ghost drusen, in GA.

We therefore recommend further study of the atrophied retina and the healthy peripheral retina, especially the temporal side because exudation often develops in this area.

More recently, nascent GA has been described on OCT imaging.[10] Several signs characteristic of GA have been observed over time on OCT, many of which can simulate exudation, such as wedge-shaped subretinal hyporeflectivity.[11]

In patients with GA, the choroidal thickness is reduced compared with the choroid of healthy patients and patients with other types of retinal atrophy, such as pseudovitelliform macular dystrophy.[12] Decreased choroidal thickness is diffuse throughout the macular region and is not associated with hyper- or hypofluorescence. *Caverns*, hyporeflective zones with well-defined edges in the choroid, will not fill with dye on ICGA and are not associated with a change in the rate of GA progression or an increase in the likelihood of exudation.[13] They appear to be linked to deposits of lipoprotein.

OCTA

OCTA allows us to noninvasively visualize the neovascular network. It is recommended that this test be done in the initial evaluation of all new patients with macular atrophy. In this context, one may find either a "dead tree" network characteristic of an old and inactive neovascularization, or a more "woody" but nonexudative aspect associated with structural OCT (Figure 7), called *quiescent neovascularization*.[14] This type of neovascularization represents a positive prognostic factor for the progression

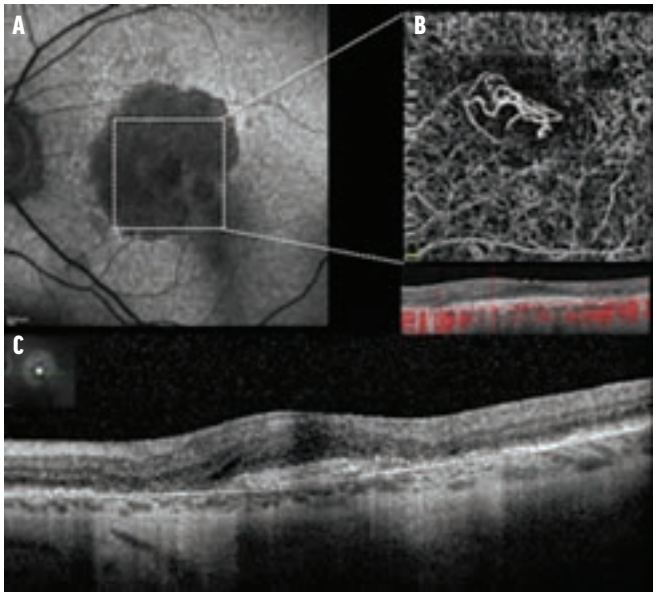


Figure 7. When imaging a mixed lesion (both GA and choroidal neovascularization), FAF shows a "C" shape atrophic lesion (hypofluorescent) with foveal sparing (A). OCTA shows a hyperreflective loop, revealing the choroidal neovascularization (B). The OCT B-scan shows the limits of the GA lesion with a foveal-sparing and hyperreflective lesion in the foveal area (C). No exudation is visible on the OCT B-scan.

FA AND ICGA ARE NOT RECOMMENDED AS FIRST-LINE IMAGING MODALITIES FOR THE DIAGNOSIS OF GA.

of atrophy. The mechanism suggests that the neovascular loop would be able to feed more RPE and the outer retina. In contrast, quiescent neovascularization switches to an exudative form in about 20% of cases.[14]

SECOND-LINE IMAGING

FA and ICGA are not recommended as first-line imaging modalities for the diagnosis of GA. Injection of dye is reserved for cases with an unclear diagnosis (eg, a patient with possible OCT signs of exudation but without interpretable OCTA images).

In an exudative macular neovascular lesion, leakage will be clearly visible in the late phases of FA; with quiescent neovascularization, there will be no diffusion but a simple alteration of the fluorescence due to alteration of the RPE and a plaque in the late phases of ICGA.[14]

In GA, hyperfluorescence (the *window effect* due to the absence of RPE) in early-phase FA is visible without staining or leakage changes during the angiographic sequence. On ICGA, if the RPE is not present, the large choroidal vessels will be visible early. Later, an isofluorescence will be visible.

Dark atrophy in late-phase ICGA, observed in patients with Stargardt disease,[15] is also seen in patients with GA and in those with central areolar choroidal dystrophy.[16]

FOCUS ON IMAGING

With the era of GA treatment upon us, clinicians must be ready to diagnose and follow these patients more closely. Multimodal imaging—including color fundus photography, FAF, OCT, and OCTA—is the key to doing just that, as long as you know what to look for. ■

1. Forte R, Querques G, Querques L, et al. Multimodal imaging of dry age-related macular degeneration. *Acta Ophthalmol.* 2012;90:e281-e287.
2. Crincoli E, De Rosa I, Miere A, Colantuono D, Mehanna CJ, Souied EH. Comparison of multimodal imaging for the characterization of geographic atrophy. *Transl Vis Sci Technol.* 2022;11(11):21.
3. Sacconi R, Corbelli E, Carnevali A, Querques L, Bandello F, Querques G. Optical coherence tomography angiography in geographic atrophy. Retina. 2018;38(12):2350-2355.
4. Sarao V, Veritti D, Borrelli E. A comparison between a white LED confocal imaging system and a conventional flash fundus camera using chromaticity analysis. *BMC Ophthalmol*. 2019;19:231.
5. Holz FG, Bindewald-Wittich A, Fleckenstein M, Dreyhaupt J, Scholl HP, Schmitz-Valckenberg S; FAM-Study Group. Progression of geographic atrophy and impact of fundus autofluorescence patterns in age-related macular degeneration. *Am J Ophthalmol*. 2007;143(3):463-472.
6. Querques G, Souied EH. Combined angiography for high-quality near-infrared autofluorescence images. *Optom Vis Sci.* 2014 Jan;91(1):e9-e13.
7. Querques G, Kamami-Levy C, George S, et al. Adaptive optics imaging of foveal sparing in geographic atrophy secondary to age-related macular degeneration. *Retina*. 2016 Feb;36(2):247-54
8. Sadda SR, Guymer R, Holz FG, et al. Consensus definition for atrophy associated with age-related macular degeneration on OCT: Classification of Atrophy Report 3. *Ophthalmology*. 2018;125:537-548.
9. Bonnet C, Querques G, Zerbib J, et al. Hyperreflective pyramidal structures on optical coherence tomography in geographic atrophy areas. *Retina*. 2014;34:1524-1530.
10. Sacconi R, Sarraf D, Sadda SR, et al. Nascent geographic atrophy as a predictor of type 3 macular neovascularization development. *Ophthalmol Retina*. 2023;7(7):586-592.
11. Querques G, Capuano V, Frascio P, Zweifels S, GeorgeS A, Souied EH. Wedge-shaped subretinal hyporeflectivity in geographic atrophy. *Retina*. 2015;35:1735-1742.
12. Coscas F, Puche N, Coscas G, et al. Comparison of macular choroidal thickness in adult onset foveomacular vitelliform dystrophy and age-related macular. *Invest Ophthalmol Vis Sci*. 2014;55(1):64-69.
13. Querques G, Costanzo E, Miere A, Capuano V, Souied EH. Choroidal caverns: a novel optical coherence tomography finding in geographic atrophy. *Invest Ophthalmol Vis Sci*. 2016;57(6):2578-2582.
14. Capuano V, Miere A, Querques L, et al. Treatment-naïve quiescent choroidal neovascularization in geographic atrophy secondary to nonexudative age-related macular degeneration. *Am J Ophthalmol.* 2017;182:45-55.
15. Giani A, Pellegrini M, Carini E. The dark atrophy with indocyanine green angiography in Stargardt disease. *Invest Ophthalmol Vis Sci*. 2012;53(7):3999-4004.
16. Guigi B, Semoun O, Querques G, et al. Indocyanine green angiography features of central areolar choroidal dystrophy. *Retin Cases Brief Rep.* 2009;3(4):434-437.

VITTORIO CAPUANO, MD
- Retina Specialist, Department of Ophthalmology University Paris Est Creteil, Centre Hospitalier Intercommunal de Creteil, Creteil, France
- Financial disclosure: Consultant (Novartis)

OUDY SEMOUN, MD
- Retina Specialist, Department of Ophthalmology University Paris Est Creteil, Centre Hospitalier Intercommunal de Creteil, Creteil, France
- Financial disclosure: Consultant (Abbvie, Bayer, Genentech/Roche, Novartis)

ERIC H. SOUIED, MD, PHD
- Retina Specialist, Department of Ophthalmology University Paris Est Creteil, Centre Hospitalier Intercommunal de Creteil, Creteil, France
- eric.souied@chicreteil.fr
- Financial disclosure: Consultant (Abbvie, Apellis, Bayer, Genentech/Roche, Novartis)

MULTIMODAL IMAGING IN UVEITIS

Recent imaging advances have improved our ability to diagnose and monitor this challenging condition.

By Eric Jung, MD, and Sumit Sharma, MD


For many physicians, evaluating a patient with uveitis can be a daunting task. Despite a thorough history and examination, a diagnosis often remains elusive. Thankfully, several imaging modalities in the clinic can help us make better-informed decisions when caring for these patients. These technologies can be critical in confirming a diagnosis or deciding to initiate treatment, as they can uncover findings that would have otherwise been missed on routine examination. Additionally, imaging allows us to objectively monitor the response to treatment. Here, we highlight ways in which specific imaging modalities have proven useful in our approach to patients with uveitis.

AT A GLANCE

- Multimodal imaging can be critical in confirming a diagnosis of uveitis or deciding to initiate treatment, as it can uncover findings that would have otherwise been missed on routine examination.
- With OCT imaging, characterization of the layers affected in retinitis may suggest specific etiologies, such as inner retinal infiltrates, outer retinal layers involved in white-dot syndromes, and full-thickness involvement classically seen with viral retinitis or toxoplasmosis.
- B-scan ultrasound biomicroscopy is highly useful in revealing vitreous opacities and can be compared with the fellow eye and interval follow-up for patients with vitritis.

SLIT-LAMP PHOTOGRAPHY

While a thorough examination is obligatory, imaging can help reduce the subjective element of an examiner's assessment. For certain patients, external and slit-lamp photos can document their initial presentation to compare with future examinations and gauge response to treatment. Ocular findings such as endothelial keratoprecipitates, iris nodules, conjunctival injection, and scleral thinning are difficult to quantify in an objective manner, and your future self (or uveitis colleague) will thank you for having a literal snapshot in time (Figure 1).

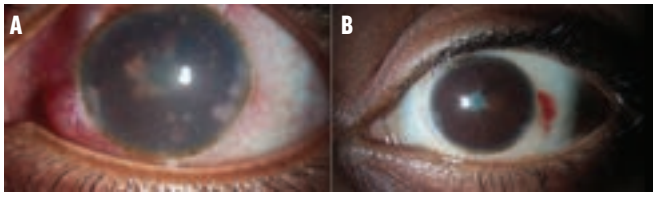


Figure 1. Slit-lamp photos of a patient with presumed sarcoidosis before (A) and 1 month after (B) treatment with oral prednisone.

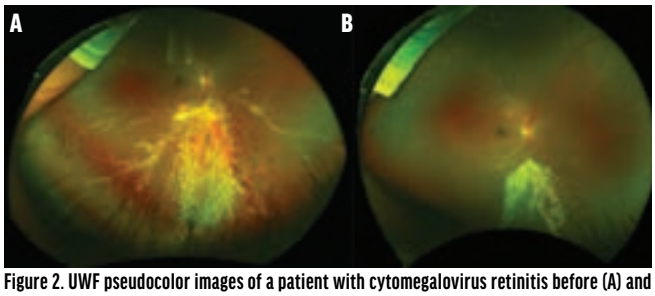


Figure 2. UWF pseudocolor images of a patient with cytomegalovirus retinitis before (A) and 3 weeks into (B) treatment.

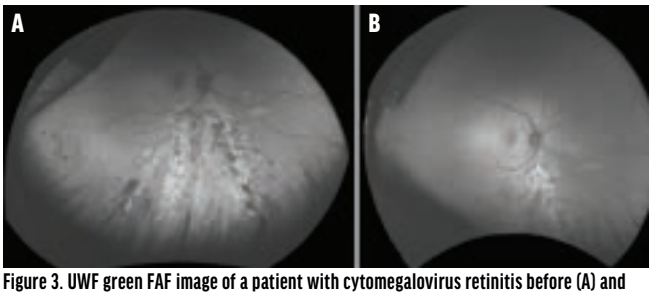


Figure 3. UWF green FAF image of a patient with cytomegalovirus retinitis before (A) and during (B) treatment.

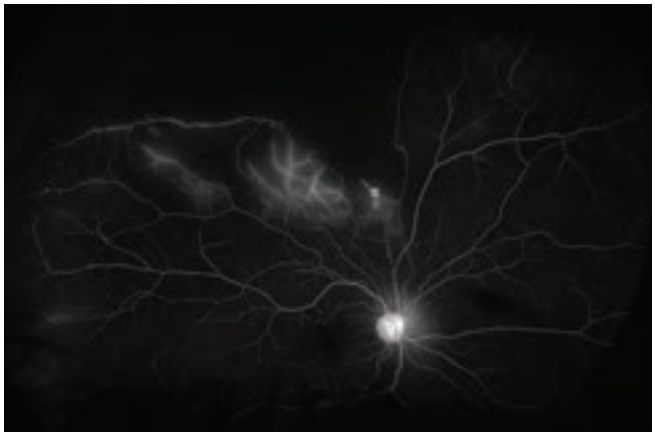


Figure 4. UWF FA of a patient with presumed sarcoidosis and superior occlusive vasculitis.

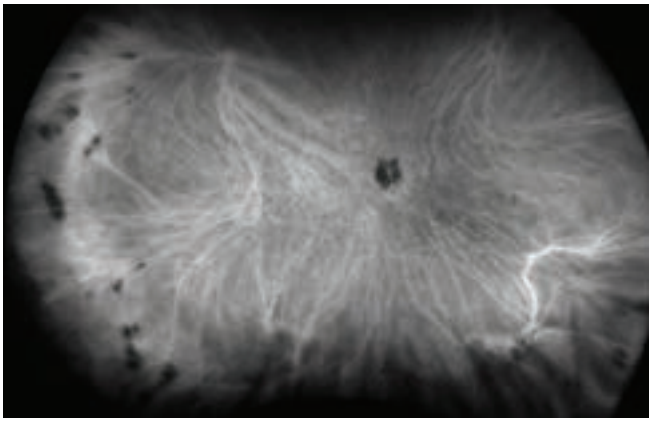


Figure 5. UWF ICGA of a patient with birdshot chorioretinopathy and multiple hypocyanescent lesions.

ULTRA-WIDEFIELD IMAGING

Ultra-widefield (UWF) imaging with a confocal scanning laser ophthalmoscope allows up to a 200° digital view of the retina. Just as with slit-lamp photos, UWF pseudocolor images can be critical in documenting the examination for comparison (Figure 2). Occasionally, these images can better highlight subtle examination findings, such as white dots, areas of early retinitis, and choroidal lesions. Furthermore, UWF pseudocolor images provide views of the peripheral retina in patients who would otherwise be challenging to examine due to a secluded pupil, significant photophobia, or age. When the pupil is very small, we find it helpful to get a view of the retina that is otherwise impossible at the slit lamp.

The Optos UWF system has conventionally used red and green laser spectrums to provide a pseudocolor image of the fundus. Recently, an update to Optos California added a third spectrum blue laser to provide a more real-to-life depiction of the fundus,[1] which may allow for an enhanced ability to discern and follow lesions.

Short-wave fundus autofluorescence (FAF) uses specific excitation wavelengths of light (green or blue) and generates images showing the emission signals of lipofuscin pigments primarily located in the retinal pigment epithelium (RPE) and photoreceptor outer segments. Thus, FAF can highlight areas of photoreceptor or RPE damage and inflammation of the choriocapillaris. In general, hyperautofluorescent lesions represent disease activity in most inflammatory maculopathies.[2] FAF may also highlight areas of pathology that may have been missed on fundoscopy, such as in subtle outer retinal or choroidal lesions (Figure 3). Often, active infection shows up on FAF prior to being readily apparent on examination. However, sometimes the hyperautofluorescent lesions do not resolve even when the disease is inactive, so FAF images must be interpreted with care.

Fluorescein angiography (FA) remains the standard for determining active retinal leakage and can provide supporting information about the presence of any concomitant vessel occlusion, optic disc leakage, capillary nonperfusion, and neovascularization (Figure 4). Using UWF FA allows for the identification of areas of leakage, which are increasingly being used in practice to influence the grading of active disease and the decision to treat.[3,4] FA can also permit a basic assessment of the retinal vasculature in eyes with significant media opacities and otherwise difficult views. We often use FA in patients with uveitis to gauge disease activity and treatment response. For some patients with uveitis, we get an FA at nearly every visit because it best highlights their disease activity.

ICG angiography (ICGA) can highlight choroidal lesions that are not easily discernible on examination. Active choroidal inflammation presents as hypocyanescent spots on ICGA (Figure 5). Often, these areas correspond with

WITH UVEITIS, A PICTURE IS TRULY WORTH A THOUSAND WORDS. A MULTIMODAL IMAGING APPROACH MAY AID IN EARLIER DIAGNOSIS, TREATMENT RESPONSE AND RECURRENCE DETECTION, AND IMPROVED OUTCOMES FOR PATIENTS WITH UVEITIS.

lesions seen on FAF. UWF ICGA allows the capture of the full peripheral extent of these lesions, which proves particularly useful when monitoring for treatment response. Not all hypocyanescent lesions will resolve; those associated with scar or chorioretinal atrophy will remain, while active inflammatory granulomas often will resolve with treatment.

OCT FINDINGS

Anterior-segment OCT may allow for an objective measure of anterior chamber (AC) inflammation that correlates well with examination grading.[5] In certain cases, OCT may identify trace AC cell that was missed on examination,[6] although their clinical significance remains unclear. In any case, anterior-segment OCT allows for a more objective and repeatable method of grading AC inflammation, which can be especially pertinent in the research setting.

Conventional spectral-domain OCT can be quite valuable in the evaluation of posterior uveitis. Characterization of the layers affected in retinitis may suggest specific etiologies, such as the inner retinal infiltrates typically seen in Behcet disease and bartonella-associated neuroretinitis,[7,8] outer retinal layers involved in white-dot syndromes,[9] and full-thickness involvement classically seen with viral retinitis or toxoplasmosis (Figure 6).[10]

OCT can also reveal overlying vitreous cell or underlying choroidal granulomas. Serous retinal detachments and bacillary detachments can be found on OCT in conditions such as Vogt-Koyanagi Harada (VKH) syndrome and can be monitored for treatment response.

In the absence of discrete areas of intraretinal fluid, diffuse macular edema can be measured and followed quantitatively by macular thickness measurements on OCT. This allows for an objective method to evaluate disease activity and treatment response in cases of uveitis associated with macular edema. Additionally, OCT can help reveal the presence of any uveitis-associated sequelae, including epiretinal membranes and vitreomacular traction.

Enhanced depth imaging OCT allows for improved imaging of the underlying choroid and sclera compared with conventional spectral-domain platforms.[11] Choroidal thickening seen in conditions such as acute VKH, sarcoidosis, and tuberculosis can be helpful for both the initial diagnosis and subsequent monitoring. Swept-source

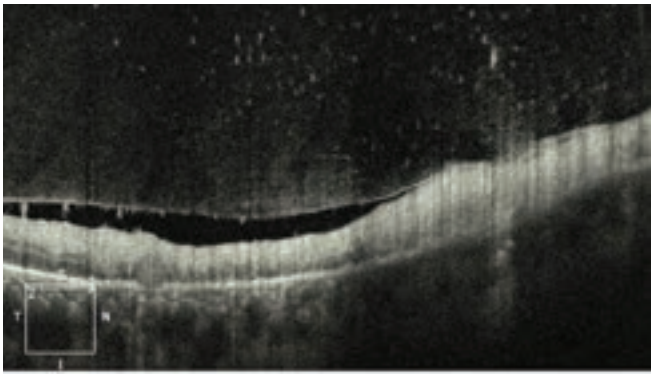


Figure 6. OCT of a patient with cytomegalovirus retinitis and full-thickness retinal involvement.

OCT uses a tunable laser, increased scan speed, and deeper penetration to simultaneously achieve detailed visualization of the vitreous, retina, and choroid. Now, UWF-guided OCT systems can image the retinal and choroidal layers through the far periphery, such as the Silverstone platform (Optos), HRA-OCT (Heidelberg Engineering), Plex Elite 9000 (Zeiss), and Xephilio OCT-S1 (Canon).

OCT angiography (OCTA) is a noninvasive imaging method that can be useful in identifying associated inflammatory choroidal neovascular membrane development, as well as choriocapillaris flow voids that may correspond to areas of ischemia. OCTA use remains limited by the smaller field of view, but its role in uveitis may evolve as we characterize the various vascular layers of the retina affected in different uveitic conditions. We often use OCTA in uveitis to characterize secondary choroidal neovascularization and its response to treatment. If widefield OCTA becomes readily available and validated, it may one day allow us to rely less on FA and ICGA.

ULTRASOUND

B-scan ultrasound biomicroscopy (UBM) is highly useful in revealing vitreous opacities and can be compared with the fellow eye and interval follow-up for patients with vitritis. B-scan can also highlight associated retinal pathology when there is no view. Fluid in the sub-tenon space (posterior scleritis T-sign), granulomas, and choroidal thickening can be identified on B-scan UBM. Extraocular lesions of MALT lymphoma hugging the globe can also best be seen on B-scan UBM. This imaging modality allows for the

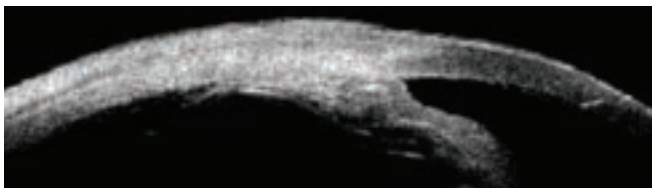


Figure 7. UBM showing atrophy of the ciliary processes in a patient with hypotony receiving CAR-NK infusions.

evaluation of the ciliary processes (Figure 7), and it can help clinicians investigate for rare causes of ocular inflammation, such as uveitis-glaucoma-hyphema syndrome, ciliary body malignancy, and even hidden intraocular foreign bodies.

WHY IMAGING MATTERS

With uveitis, a picture is truly worth a thousand words. A multimodal imaging approach may aid in earlier diagnosis, treatment response and recurrence detection, and improved outcomes for patients with uveitis. Recent imaging modalities, such as widefield OCT and OCTA, may hold promise for future imaging of uveitis and the retina. ■

1. Optos announces new ultra-widefield color image modality, providing additional retinal visualization to eyecare professionals [press release]. Optos. 30 May 30, 2023. Accessed March 4, 2024. bit.ly/4cbrLPh
2. Lee CS, Lee AY, Forooghian F, Bergstrom CS, Yan J, Yeh S. Fundus autofluorescence features in the inflammatory maculopathies. *Clin Ophthalmol*. 2014;8:2001-2012.
3. Pecen PE, Petro KF, Baynes K, Ehlers JP, Lowder CY, Srivastava SK. Peripheral findings and retinal vascular leakage on ultra-widefield fluorescein angiography in patients with uveitis. *Ophthalmol Retina*. 2017;1(5):428-434.
4. Campbell JP, Beardsley RM, Palejwala NV, et al. Peripheral vascular leakage in uveitis: clinical and angiographic findings. *Ophthalmology*. 2015;122(6):1269-1270.
5. Sharma S, Lowder CY, Vasanji A, Baynes K, Kaiser PK, Srivastava SK. Automated analysis of anterior chamber inflammation by spectral-domain optical coherence tomography. *Ophthalmology*. 2015;122(7):1464-1470.
6. Li Y, Lowder C, Zhang X, Huang D. Anterior chamber cell grading by optical coherence tomography. *Invest Ophthalmol Vis Sci*. 2013;54(1):258-265.
7. Tugal-Tutkun I, Ozdal PC, Oray M, Onal S. Review for diagnostics of the year: multimodal imaging in Behçet uveitis. *Ocul Immunol Inflamm*. 2017;25(1):7-19.
8. Oray M, Önal S, Koç Akbay A, Tuğal Tutkun İ. Diverse clinical signs of ocular involvement in cat scratch disease. *Turk J Ophthalmol*. 2017;47(1):9-17.
9. Onal S, Tugal-Tutkun I, Neri P, Herbort CP. Optical coherence tomography imaging in uveitis. *Int Ophthalmol*. 2014;34(2):401-435.
10. Invernizzi A, Agarwal AK, Ravera V, et al. Comparing optical coherence tomography findings in different aetiologies of infectious necrotising retinitis. *Br J Ophthalmol*. 2018;102(4):433-437.
11. Spaide RF, Koizumi H, Pozzoni MC. Enhanced depth imaging spectral-domain optical coherence tomography. *Am J Ophthalmol*. 2008;146(4):496-500.

ERIC JUNG, MD
- Vitreoretinal Surgery Fellow, Cole Eye Institute, Cleveland Clinic, Cleveland
- junge2@ccf.org
- Financial disclosure: None

SUMIT SHARMA, MD
- Vitreoretinal Surgeon, Cole Eye Institute, Cleveland Clinic, Cleveland
- sumitsharma.md@gmail.com
- Financial disclosure: Consultant (Abbvie, Alimera, Apellis, Bausch + Lomb, Clearside, Eyepoint, Genentech/Roche, Iveric Bio/Astellas, Regeneron, Regenxbio, Ripple); Institutional Research Funding (Abbvie, Genentech/Roche, Gilead, IONIS, Santen)

ADOPTING REMOTE MONITORING AND AI: LESSONS FROM CARDIOLOGY

Learning from colleagues in other medical specialties can guide ophthalmology's smooth transition.

By Judy E. Kim, MD, FARVO, FASRS, and Jagmeet P. Singh, MD, ScM, PhD, FHRS, FACC


The more ophthalmology embraces remote monitoring, the better it can meet the needs of patients and reduce treatment burden. As regulatory bodies move closer to approving home-based imaging platforms, such as home OCT and AI-based software, ophthalmologists must prepare for more data-driven care.

To learn more about what this transition entails, ophthalmology can turn to other specialties with experience in widespread adoption of AI and remote monitoring. Although we practice in separate domains of medicine—retina (Dr. Kim) and cardiology (Dr. Singh)—we share a passion for improving patient care through technology. Here, we discuss cardiology's adoption of remote monitoring and AI and how these experiences can inform ophthalmology's forthcoming embrace of such innovation.

STATE OF PLAY IN OPHTHALMOLOGY

Some remote monitoring platforms in ophthalmology leverage AI, while others only transmit information from real-world settings to a clinical log. For example, home tonometry with the iCare Home (iCare) has yet to include AI systems that anticipate IOP spikes or request data from specific timepoints to create a robust profile of pressure changes. Still, the ability to capture and transmit on-demand

AT A GLANCE

- The use of remote monitoring and AI is inevitable in the field of retina. However, concerns related to workflow, liability, and reimbursement hinder its adoption in day-to-day practice.
- Cardiology has found remote monitoring and AI to be fundamental to modern practice, benefitting both patients and providers.
- By learning about cardiology's experience with adopting remote monitoring and AI in clinical practice, ophthalmologists can anticipate (and adjust for) the new era in medicine.

Digital Health Model

Figure. Patients remain at the center of a health care framework that leverages digital remote monitoring, with monitoring centers and health care providers collaborating to provide more precise care.

IOP data between patient appointments builds a more complete picture than what was previously available.

Other remote monitoring platforms have already incorporated AI. The ForeseeHome AMD Monitoring Program (Notal Vision) uses an AI algorithm to interpret at-home tests captured by patients with intermediate AMD who are at risk of conversion to wet AMD. If the algorithm detects a statistically significant change in testing from baseline, the in-house clinical team at the monitoring center will review the results and alert the patient's provider (Figure). Patients continue to visit the clinic for in-person examinations, with at-home testing serving as an adjunctive monitoring system.

Home OCT, currently an investigational technology, may play a critical role in the management of wet AMD. Given the cost, treatment burden, chronicity, and complexity of managing this disease, retina specialists are likely to adopt such a tool to better personalize and simplify care.

Still, home OCT may fuel anxieties related to reimbursement for imaging interpretation and the fear of being swamped by alerts delivering too many false positives.

REMOTE MONITORING IN CARDIOLOGY

Cardiology's experience with remote data capture began decades ago with the advent of pacemakers that use transtelephonic monitoring to relay data to clinics.[1] Now, devices such as implantable cardioverter-defibrillators can transmit data to clinics and, through the use of focused AI algorithms, predict when patients are most likely to need in-person care.

Many in cardiology shied away from adopting these technologies at first, fearful that patient care would be compromised or that clinic routine disruptions would be too severe. But today, cardiology has embraced remote monitoring and AI systems as tenets of the specialty, rather than threats.

As patients and providers grow comfortable with these innovations, cardiology is edging toward exception-based care: the practice of only seeing patients in the clinic when they require in-person examination based on remote monitoring data. Patients still visit the clinic but far less frequently than they did before the era of remote monitoring. By leveraging narrow AI—a system designed to complete a specific task—cardiology has helped build models that anticipate acute crises before they occur.

OVERLAPPING QUESTIONS

Under an exception-based care model, patients benefit via reduced treatment burden and more personalized care. This is true of cardiology now, and may be the future of ophthalmology if home OCT comes to fruition. Patients could be monitored with home OCT between their regular office visits, and physicians could respond when retinal fluid crosses a set threshold. The process may offer an unprecedented view of how patients' eyes respond to different therapies, potentially assisting in individualized management.

This is good news for patients. But what about providers? The questions that ophthalmologists pose are valid and largely overlap with those first asked by cardiologists. How will remote monitoring disrupt carefully choreographed workflows and clinic schedules? How will it affect reimbursement? Will retina specialists be liable for unreviewed data that could potentially have been used for a preventive diagnosis?

Workflow

Cardiologists learned quickly that too many remote monitoring alerts led to clinics drowning in pings and patients experiencing unnecessary anxiety. By adjusting the threshold for triggering alerts, cardiologists identified sweet spots that work for them and their practices.

Similarly, ophthalmologists may be able to customize appropriate disease marker triggers. For example, we could determine which type of retinal fluid (eg, intraretinal vs subretinal, foveal vs extrafoveal) and how much of it should activate a prompt physician review of home OCT imaging.

In cardiology, technicians were cross-trained to review remote monitoring alerts, serving as a buffer between the AI algorithm and the provider. This had two effects: First, it improved confidence in the overall system, building patient and provider trust in remote monitoring/AI frameworks. Second, it created a new, engaging field in which technicians could grow.

There are worries that exception-based care will create erratic scheduling, with clinics packed on some days and slow on others. While practices will have to reserve space for patients who need to be seen promptly, clinics will remain busy regardless of urgent patient demand. Cardiologists and

ophthalmologists both see a wide spectrum of patients, and if the experience of cardiology holds true for ophthalmology, then eye care clinics will remain as busy in the age of remote monitoring as they were in the era before it. Retina specialists are already accustomed to taking emergency appointments; remote monitoring tools will help determine the urgency of these visits and offer more data-driven care.

Reimbursement

Cardiologists are reimbursed for reviewing remote alerts and have ensured that reimbursement is commensurate with their value and effort by demonstrating that remote monitoring strategies save health care systems time and money and improve patient outcomes. Luckily, conclusions in the literature regarding the efficacy of remote monitoring in cardiology echo efficacy findings from remote monitoring studies evaluating the ForeseeHome over 10 years.[2,3]

Ophthalmology next needs to demonstrate that remote monitoring leads to cost savings for health care systems, which can be used to justify reimbursement. The pathway of physician reimbursement and remote monitoring was already walked by cardiology, and a coalition of ophthalmology providers, industry, and advocacy groups can refer to this map when seeking reimbursement.

Clinical volume didn't decrease after remote monitoring became a common cardiology tool, which in turn meant that overall revenue didn't take a hit either.[4,5] The same can be expected in ophthalmology, a field in which the growing number of patients continues to exceed the limited number of providers, and new treatments continue to emerge.

Liability

To our knowledge, increased liability has not been an issue for cardiology thus far, in part because cardiologists ensure that patients understand the specific use of remote monitoring data. Physicians are only expected to monitor the parameters related to the device's indication.

It will be important for ophthalmologists to set appropriate expectations regarding the use of remote monitoring tools. Patients must understand that remote monitoring does not replace physician-determined visits, and overall vigilance toward the state of their vision remains paramount.

NEXT STEPS

We often overlook one of the chief impediments to the adoption of new technology: doctors themselves. Providers often resist adopting new technology due to their concern for patient health and convenience. However, if these new technologies improve health outcomes and patient convenience, ophthalmologists should consider adopting these innovations as they become available.

Ophthalmology sits in an advantageous position when it comes to adopting remote monitoring and leveraging AI systems to improve patient care. Unlike cardiology, which monitors patients passively via implantable devices, ophthalmology possesses more control because patients can actively perform tests and improve their monitoring adherence with teleconnected devices at home. These hands-on patients are active participants in their own outcomes and successes.

For ophthalmology, adoption of remote monitoring systems that leverage AI algorithms to improve patient care, reduce treatment burden, and offer personalized medicine need not come at the expense of reduced reimbursement, disrupted clinical routine, and increased liability. In fact, the opposite may be true: A clinic prepared to integrate innovations that expand its patient base may improve patient care, see increased revenue, and widen its clinical reach without incurring any substantive costs or disruptions. By embracing the lessons learned from cardiology, ophthalmology can more easily navigate the future. ■

1. Theuns DA, Jordaens LS. Remote monitoring in implantable defibrillator therapy. *Neth Heart J*. 2008;16(2):53-56.
2. Health Quality Ontario. Remote monitoring of implantable cardioverter-defibrillators, cardiac resynchronization therapy and permanent pacemakers: a health technology assessment. *Ont Health Technol Assess Ser*. 2018;18(7):1-199.
3. Mathai M, Reddy S, Elman MJ, et al; ALOFT study group. Analysis of the long-term visual outcomes of ForeseeHome remote telemonitoring: the ALOFT study. *Ophthalmol Retina*. 2022;6(10):922-929.
4. Cardiologists in the US – Market size, industry analysis, trends and forecasts (2023-2028). IBISWorld. June 2023. Accessed October 16, 2023. www.ibisworld.com/united-states/market-research-reports/cardiologists-industry
5. Scott M, Baykaner T, Bunch TJ, et al. Contemporary trends in cardiac electrophysiology procedures in the United States, and impact of a global pandemic. *Heart Rhythm O2*. 2023;4(3):193-199.

JUDY E. KIM, MD, FARVO, FASRS
- Jean and Tom Walter Distinguished Professor of Ophthalmology, Vitreoretinal Diseases and Surgery Professor with Tenure, Vice Chair of Education, Medical Director of Clinical Research, University of Texas Southwestern Medical Center, Dallas, Texas
- President, Foundation of American Society of Retina Specialists
- judy.kim2@utsouthwestern.edu
- Financial disclosure: Advisory Board/Consultant (Allergan/Abbvie, Amgen, Apellis, Bausch + Lomb, Clearside Biomedical, Coherus, Dutch Ophthalmic Research Center, Eyepoint, Genentech/Roche, Notal Vision, Outlook Therapeutics, Regeneron)

JAGMEET P. SINGH, MD, SCM, PHD, FHRS, FACC
- Professor of Medicine, Former Clinical Director of the Cardiology Division, and the Roman W. DeSanctis Endowed Chair in Cardiology, Massachusetts General Hospital Harvard Medical School, Boston
- Founding Director, Resynchronization and Advanced Cardiac Therapeutics Program
- Board of Trustees, Heart Rhythm Society
- Author, Future Care: Sensors, Artificial Intelligence, and the Reinvention of Medicine
- jsingh@mgh.harvard.edu
- Financial disclosure: Consultant (Abbott, Biosense Webster, Biotronik, Boston Scientific, Cardiac Rhythm Group, Cardiologs, CVRx, EBR, Implicity, Impulse Dynamics, Medscape, Medtronic, Microport, Notal Vision, Orchestra Biomed, Phillips, Sanofi); Research (American College of Cardiology, Biotronik, Boston Scientific, Cardiologs, Heart Rhythm Society, Medtronic, SentiAR)

GEOGRAPHIC ATROPHY:
GUIDING THE CONVERSATION WITH PATIENTS

The complexities of GA and the available treatment options require a skillful approach to patient education and communication.

Editorially Independent Content, Supported With Advertising From Astellas

By David S. Chin Yee, MD

Geographic atrophy (GA) is the advanced stage of dry age-related macular degeneration (AMD) and is characterized by a relentless loss of vision. Patients may struggle to understand the mechanism underlying GA, yet, in my experience, they possess an awareness of its prognosis.

During a recent interview, I shared my insights on guiding the conversation with patients with GA.

Speak in Pictures

The recent availability of treatment options for GA ushers in a new era of hope for patients.[1,2] Now, the challenge is to educate our patients about dry AMD and GA. Using analogies that paint a picture of what is happening helps patients understand the disease and treatment. And, as we have learned in other retinal pathologies, a picture is worth more than a thousand words. I compare the retinal pigment epithelium to a "vacuum cleaner" to remove waste in the eye.

As we age, this function weakens, causing waste to build up, which leads to GA and vision loss. Using OCT or fundus autofluorescence images of the patient's retina further enhances their understanding by visually depicting the disease and its progression.

The Balance Between Benefits and Risks

When administering complement inhibitors to treat GA, the goal is to slow lesion progression. We are in the early days of GA treatment, and there are no established biomarkers to identify treatment success or ideal patients. Serial imaging before and after treatment can indicate if a lesion is progressing slower, highlighting treatment effectiveness. Consequently, the challenge of measuring the benefits of complement inhibition underscores the importance of thorough risk education. In clinical trials for the two available complement inhibitors—pegcetacoplan (Syfovre, Apellis) and avacincaptad pegol intravitreal solution (Izervay, Iveric Bio, an Astellas Company)—there was an increased risk of conversion to wet AMD associated with treatment. This fact underscores the need for regular monitoring of any patient who is started on anti-complement therapy, regardless of agent choice.

Informed consent remains crucial throughout the process. The possibility of increased IOP post-injection is a manageable occurrence. I inform patients of the small risks of endophthalmitis and occlusive vasculitis post-injection and respect their decision to proceed with treatment. It should be noted that some cases of occlusive retinal vasculitis have been reported after treatment with pegcetacoplan since its release and use in the general public. To date, at least one case has been confirmed with avacincaptad pegol intravitreal solution.

There are strategies to assess the risk of adverse events and inform our patients, particularly those with bilateral GA. Starting treatment in the eye with poorer vision can serve as a test; if successful then, I am more confident in starting treatment in the eye with better vision.

The Ideal Patient Profile

GA treatment acceptance varies among patients, with roughly one-third unreceptive, one-third somewhat hopeful, and one-third eagerly awaiting treatment. As retina specialists, We prioritize identifying responsive patients, such as those with a family history of vision loss or those undergoing treatment for wet AMD in one eye. However, certain clinical aspects may limit treatment benefits:

1. Patients with large GA lesions, although the viability of treatment depends on the size and location of the lesions;
2. patients in hospice care; and
3. patients with severe dementia.

Lastly, a patient's lifestyle choices need to be considered and addressed during the conversation about treatment efficacy and disease progression. Advising patients to quit smoking is crucial, as it can make a substantial difference in managing the condition. Additionally, addressing diet, blood pressure, and cholesterol levels is important for overall systemic health and may help slow the progression of GA. ■

1. Carlton J, Barnes S, Haywood A. Patient perspectives in geographic atrophy (GA): exploratory qualitative research to understand the impact of GA for patients and their families. *British and Irish Orthoptic Journal*. 2019;15(1):133.
2. Enoch J, Ghulakhszian A, Sekhon M, et al. Exploring patient acceptability of emerging intravitreal therapies for geographic atrophy: a mixed-methods study. *Eye*. 2023;37:17.

DAVID S. CHIN YEE, MD
- Georgia Retina, Peachtree City, Georgia
- Email: dschinyee@gmail.com
- Disclosures: Consultant (Alcon, Alimera Sciences, Apellis, Genentech, Iveric Bio, Regeneron)

Scan this QR code to read the extended article.

RESEARCH CONSIDERATIONS DURING RETINA FELLOWSHIP

Two fellows offer their pearls to help others start their research journey.

BY OLUFEMI ADAMS, MD

The prospect of doing research during a busy vitreoretinal surgical fellowship can be daunting. On one hand, it is a useful adjunct to facilitate additional learning, networking, and professional development. On the other, it can be difficult to balance high-quality research with the clinical responsibilities of fellowship.

I interviewed two retina research fellows, Hana A. Mansour, MD, and Bita Momenaei, MD, from Wills Eye Hospital in Philadelphia, who offered practical strategies for success in pursuing research opportunities during fellowship.

OLUFEMI ADAMS, MD: WHY SHOULD CLINICIANS CONDUCT RESEARCH DURING THEIR RETINA FELLOWSHIP?

Drs. Mansour and Momenaei: Engaging in research during a retina fellowship offers numerous advantages and contributes significantly to both personal and professional growth. It provides a platform for continuous learning, allowing fellows to delve deeper into retina.

The field of retina is very dynamic, marked by constant technological advances and new diagnostic and treatment modalities. Staying on top of these innovations is important to deliver optimal patient care, keep knowledge and skills current and relevant, and contribute to the development of more effective approaches for the successful management of retinal conditions.

Additionally, being part of the broader ophthalmic research community creates an opportunity to network with other researchers and helps to foster meaningful connections, which can be valuable for meeting long-term professional goals. For fellows who are strongly considering a career in academic medicine, being involved in research is favorable, and research productivity can be associated with career advancements.

DR. ADAMS: HOW DO YOU IDENTIFY CLINICAL QUESTIONS TO PURSUE FOR RESEARCH?

Drs. Mansour and Momenaei: Being directly involved in patient care provides unique insights into the challenges and uncertainties of clinical management and helps to identify areas where evidence is currently substandard or lacking, or where a wide variation in treatment approaches exists. This creates an opportunity for fellows to identify and then explore ways to refine surgical or medical management techniques and improve patient care.

Being well-versed in recent developments in the field and regularly reviewing current literature also allows researchers to identify knowledge gaps or areas where conflicting evidence exists. This familiarity can help in formulating research questions that address pressing issues and contribute to additional discourse in the field. Offering to be a reviewer for different journals is another way to gain exposure and early access to cutting-edge research.

ABOUT THE INTERVIEWEES:

HANA A. MANSOUR, MD
- Retina Research Fellow, Wills Eye Hospital, Philadelphia

BITA MOMENAEI, MD
- Retina Research Fellow, Wills Eye Hospital, Philadelphia

Attending scientific conferences and national meetings provides a valuable opportunity to engage with peers, learn about ongoing endeavors in the field, gain insights into emerging trends in retina, and identify gaps in our current clinical understanding. This can be useful for generating meaningful research questions.

DR. ADAMS: HOW DO YOU MENTOR TRAINEES WHILE INVOLVED IN RESEARCH?

Drs. Mansour and Momenaei: Trainees, including medical students and residents, are tremendously helpful in moving a research project forward. Conducting high-quality research often requires a large degree of teamwork and collaboration. It is important to get a sense of how trainees can contribute early in the process. Structured training and formal education on the technically nuanced aspects of the project will ensure everyone is on the same page.

Assigning hands-on roles, offering constructive feedback, and acknowledging trainees' strengths are great ways to facilitate their professional growth and development and foster a culture of learning. Research fellows also serve as important intermediaries between attending physicians and trainees and can help trainees network with people who may be vital to their professional pursuits.

DR. ADAMS: WHAT TOOLS ARE HELPFUL WHEN CONDUCTING RESEARCH?

Drs. Mansour and Momenaei: There are many tools that are easily accessible and aim to streamline the research process. Large databases, such as PubMed, Scopus, and Google Scholar, can be very helpful in conducting comprehensive literature reviews, and most universities have online access to a vast array of publications.

Data visualization tools such as Microsoft Excel are useful for organizing the collected data. It is important to keep in mind the principles of HIPAA and ensure that collected data is stored in a secure fashion with guidance from the institutional review board overseeing the research study.

Statistical analysis is also a critical component of research. Accessible software programs, such as SPSS, R, and SAS, can be useful for data analysis, and depending on the complexity of the study and the research methodology, expert statistical guidance may also be required. Often, academic programs consult with a statistician. YouTube hosts a vast array of tutorials on popular statistical software that walk researchers through the step-by-step process of data input, analysis, and interpretation, and often include real-world examples, encouraging accessibility for both beginner and advanced users.

Additionally, various referencing tools, such as Zotero, Mendeley, and EndNote, can help organize and cite sources, making it easier to manage references throughout the research process.

DR. ADAMS: HOW WOULD YOU DESCRIBE THE PROCESS OF CONDUCTING A CLINICAL STUDY?

Drs. Mansour and Momenaei: The process really begins when a clinician identifies a research idea or question that has relevance, feasibility, and the potential to contribute to the scientific understanding and clinical practice of retina. A comprehensive literature review is then conducted to ensure there is originality and novelty to the investigation. Then, a detailed research proposal is presented to your local institutional review board.

Next, the researchers must identify the variables that will be measured or observed to answer the proposed research question. Statistical methods are then applied for interpretation and analysis, exploring any potential relationship between variables. Subsequently, a manuscript is prepared, including an introduction, the study's methods and results, and a discussion.

DR. ADAMS: WHAT STRATEGIES ARE USEFUL WHEN PUBLISHING A MANUSCRIPT?

Drs. Mansour and Momenaei: Crafting a manuscript is a very dynamic process. Some writers start with the results section to establish a clear understanding of their findings before writing the introduction. Others start with the introduction to set the stage and give some context. It is important to understand your own writing style prior to starting this process.

The method section should provide a detailed description of the study design, data collection process, and statistical analysis. Tables and graphs help present complex data in a visually pleasing and accessible format to provide a quick overview of the key findings, as is also the goal of an abstract.

The discussion section should highlight the study's key findings and their potential clinical implications. Acknowledging the limitations of the study and highlighting the strengths and weaknesses help readers interpret the results within the context of these constraints and contextualize the findings within the broader scientific landscape. A suggestion of future research is usually made at the end of the manuscript.

Selecting a suitable journal and adhering to its specific guidelines should remain a point of consideration throughout the process. It often takes numerous submissions to different journals, with peer-reviewed feedback and corrections before a manuscript is published. ■

OLUFEMI ADAMS, MD
- Vitreoretinal Surgery Fellow, Wills Eye Hospital, Philadelphia
- Clinical Instructor of Ophthalmology, Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia
- oladams@midatlanticretina.com
- Financial disclosure: None

RISING STARS IN RETINA

Get to know outstanding retina fellows from the class of 2024.

Inês Laíns, MD, PhD

***Retina Today:* When did you first know that you wanted to become a retina specialist?**

I am from Portugal and started an ophthalmology residency there. Retina was my first rotation, and after seeing the retina and understanding the significant effect that vitreoretinal surgeons can have on patients' quality of life, I knew I wanted to become a retina specialist. My passion for our field has continued to grow exponentially, and it is what motivated me to become involved in clinical research and move to the United States.

***RT:* Who do you look to as mentors in the field?**

I have been fortunate to work with many outstanding mentors. All the retina faculty at Massachusetts Eye and Ear (MEE) have positively affected my life, but some people have played a special role. Joan W. Miller, MD, and Deeba Husain, MD, have supported me since I moved to the United States. Dean Eliott, MD, has been an incredible mentor who constantly pushes me to be better. Lucia Sobrin, MD, MPH, is one of the brightest clinicians I know, and I look to her as an example of exceptional work/life balance. John B. Miller, MD, has provided outstanding support throughout my training. Finally, Mark W. Johnson, MD, has become a close mentor who sets the example of how to care for patients.

***RT:* What has been one of the most memorable experiences of your fellowship thus far?**

Being on call. MEE has a very busy emergency department, and we see many interesting patients who make me appreciate the beauty and complexity of vitreoretinal surgery. I love the diagnostic challenges that we face, but also the fact that we can see many cases in a short period. Especially when I was a first-year fellow, it's amazing to reflect on how much I grew after a few days on call.

***RT:* What are you hoping to accomplish once you are in practice?**

I am staying at MEE and hope to establish a career as a clinician-scientist by combining my passions for patient care, research, and teaching. My current research interest is in the metabolomics and genetics of AMD. I also hope to share my knowledge and experience with trainees and encourage them to see the effect that clinician-scientists can have, much like my mentors have done for me.

FIRST CAREER MILESTONE

Dr. Laíns is staying at Massachusetts Eye and Ear as a clinician-scientist.

***RT:* What advice can you offer to residents who are considering retina?**

Retina is an amazing and very rewarding field, but it requires a strong commitment because it is challenging. You should be passionate about any field you choose, but that is particularly true for retina. I would invest in building a strong clinical foundation by caring for as many patients as possible and learning from each one. Seek research opportunities and collaborations, and identify mentors early! Finally, be humble and willing to learn every day. ■

INÊS LAÍNS, MD, PHD
- Vitreoretinal Surgery Fellow, Massachusetts Eye and Ear, Harvard School of Medicine, Boston
- ines_lains@meei.harvard.edu
- Financial disclosure: None

MANAGING LARGE MACULAR HOLES: ILM FLAP VS PEEL


The literature continues to identify scenarios in which one technique is more effective than the other.

BY KAITLYN RICHARDS, BS, AND ANKOOR R. SHAH, MD

Patients with a full-thickness macular hole (FTMH) have an anatomical defect in the fovea that leads to a significant reduction in central visual acuity and, subsequently, reduced quality of life. While many FTMHs can be idiopathic, they can also be secondary to vitreoretinal traction, high myopia, proliferative diabetic retinopathy, and inflammation.[1] The conventional treatment for a FTMH has been pars plana vitrectomy, internal limiting membrane (ILM) peel, and total gas-fluid exchange with long-lasting gas tamponade. This technique is effective in terms of both closure rate and visual acuity improvement, with a 90% success rate for the closure of an acute FTMH noted in numerous studies.[2,3] However, alternative treatments for chronic, large, or recalcitrant FTMHs have been developed due to lower closure rates of these subsets of FTMHs with traditional methods.

ALTERNATIVE APPROACHES

Surgeons have recently explored variations of ILM manipulation, such as inverted ILM flaps, ILM free flaps, and hinged ILM flaps. Inverted ILM flaps involve peeling a portion of the ILM and folding it over the macular hole.[4] Several studies have looked at using this technique to improve closure rates for large macular holes.[5-7] Free flaps can be used when an ILM peel has previously been performed and entail harvesting an ILM flap from a distal site, placing it over the FTMH, and inserting a gas tamponade.[8] A prior study noted a success rate of 86% with an ILM free flap compared with a 91.6% success rate for an inverted ILM flap.[9]

Several studies suggest the ILM flap technique is a valuable option when treating large FTMHs.[9] Dera et al noted a 90.8% closure rate when using an ILM flap and a 59.6% closure rate for a conventional ILM peel in patients with a FTMH > 400 µm.[10] Another study found similar closure rates of 95.6% and 78.6% for large FTMHs, respectively.[11]

Not only have these studies shown positive outcomes for ILM flap closure, but many have also hypothesized that the ILM flap acts as a scaffold for migration and proliferation of Müller cells.[12] These cells secrete neurotrophic and growth factors that enhance the survival of retinal neurons.[12] However, other studies suggest that an ILM flap for a large FTMH has no obvious advantages over ILM peeling related to anatomical morphology and visual function.[13,14]

In addition to manipulating the ILM, other techniques have been developed for recalcitrant holes. For example, a macular hole hydrodissection includes a standard ILM peel and a soft-tip cannula to reflux fluid into the FTMH, releasing any retina-to-retinal pigment epithelium adhesion at the hole margin.[15] An additional technique to consider is autologous retinal transplantation, which has had good success rates but can be technically challenging.[16]

OUR STUDY

In our recent study presented at the 2023 American Society of Retina Specialists Meeting, we analyzed an inverted ILM flap technique, which entails peeling an ILM flap 2x3 disc diameters wide temporal to and past the FTMH to relieve all traction, laying the ILM back in place, and inverting the temporally peeled portion over the FTMH with insertion of a gas tamponade (Figures 1 and 2). We compared success rates between large FTMHs to determine if one surgical technique is better than another.

We analyzed available data from a retina-specific practice to compare anatomical and functional outcomes in patients who received surgical intervention for

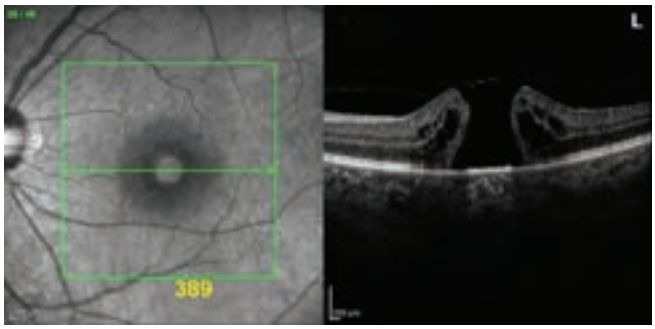


Figure 1. OCT documented a chronic FTMH prior to treatment with the inverted ILM flap technique.

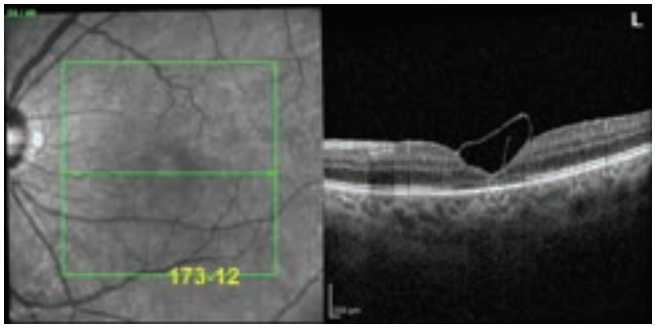


Figure 2. Postoperative OCT showed a closed, chronic FTMH with an inverted ILM flap. Note that the scroll of the ILM overlying the closed hole is visible.

large (> 400 µm) FTMHs by either the ILM flap or peel technique. For overall anatomical outcomes, our study showed an almost identical FTMH closure rate between the ILM flap and peel technique: 94.6% and 93.6%, respectively. Although closure rates were similar within our study, the preoperative mean base diameter was greater in the flap versus non-flap group with a trend toward worse initial visual acuity.

In our subgroup analysis, we looked at FTMH closure rates based on different basal diameters. There was a trend toward lower closure rates for larger holes, which held true for both the ILM flap and peel groups. There was no statistical difference noted between either surgical technique across macular hole diameters. It is unclear if this was due to a limitation in the number of cases studied within each subgroup, the difference in the sizes of the macular holes at onset, or the fact that there is no difference in closure rates between the two techniques.

For overall functional outcomes, there was a statistically significant improvement in both the ILM flap and peel groups postoperatively. These findings are consistent with prior studies overseeing postoperative visual acuity for both treatment groups.[17,18] There was an overall improvement in VA of 0.46 logMAR compared with preoperatively in each surgical cohort to the last follow-up. Similar to studies that support visual improvement from 6 months to 2 years postoperatively, our data demonstrated continued improvement within each cohort up to 3 years.[19,20]

While we have shown that the inverted ILM flap and peel techniques allow for significant anatomical and functional improvement postoperatively, additional research is warranted to distinguish which FTMH scenario responds best to which technique. With many emerging surgical approaches to treat large, complex FTMHs, surgeons must give more consideration to which surgical approach would benefit which patient. ■

1. Hong-Kee N, Azhany Y, Lieh-Bin O. Full thickness macular hole: early intervention is an important factor in visual prognosis. *Malays Fam Physician*. 2014;9(3):42-48.
2. Jaycock P, Bunce C, Xing W, et al. Outcomes of macular hole surgery: implications for surgical management and clinical governance. *Eye*. 2005;19:879-884.
3. Abdul-Kadir MA, Lim LT. Update on surgical management of complex macular holes: a review. *Int J Retin Vitr*. 2021;7:75.
4. Michalewska Z, Michalewski J, Adelman RA, Nawrocki J. Inverted internal limiting membrane flap technique for large macular holes. *Ophthalmology*. 2010;117(10):2018-2025.
5. Major JC Jr, Lampen SIR, Wykoff CC, et al. The Texas Taco technique for internal limiting membrane flap in large full-thickness macular holes: a short-term pilot study. *Retina*. 2020;40(3):552-556.
6. Chen G, Tzekov R, Jiang F, et al. Inverted ILM flap technique versus conventional ILM peeling for idiopathic large macular holes: a meta-analysis of randomized controlled trials. *PLoS One*. 2020;15(7):e0236431.
7. Koçak N, Yeter V, Birinci H. Comparative study of conventional internal limiting membrane peeling versus temporal inverted internal limiting membrane flap for large macular hole treatment. *Indian J Ophthalmol*. 2023;71(1):188-194.
8. Fung NSK, Mak AKH, Yiu R, et al. Treatment of large, chronic and persistent macular hole with internal limiting membrane transposition and tuck technique. *Int J Retin Vitr*. 2020;6:3.
9. Velez-Montoya R, Ramirez-Estudillo JA, Sjoholm-Gomez de Liano C, et al. Inverted ILM flap, free ILM flap and conventional ILM peeling for large macular holes. *Int J Retina Vitreous*. 2018;4:8.
10. Dera AU, Stoll D, Schoeneberger V, et al. Anatomical and functional results after vitrectomy with conventional ILM peeling versus inverted ILM flap technique in large full-thickness macular holes. *Int J Retin Vitr*. 2023;9:68.
11. Rizzo S, Tartaro R, Barca F, et al. Internal limiting membrane peeling versus inverted flap technique for treatment of full-thickness macular holes: a comparative study in a large series of patients. *Retina*. 2018;38:S73-S78.
12. Shiode Y, Morizane Y, Matoba R, et al. The role of inverted internal limiting membrane flap in macular hole closure. *Invest Ophthalmol Vis Sci*. 2017;58(11):4847-4855.
13. Iwasaki M, Kinoshita T, Miyamoto H, Imaizumi H. Influence of inverted internal limiting membrane flap technique on the outer retinal layer structures after a large macular hole surgery. *Retina*. 2019;39(8):1470-1477.
14. Chen Y, Xu Y, Ye X, et al. The effect comparison of ILM flap and traditional ILM peeling in IMH. *Front Med*. 2023;10.
15. Felfeli T, Mandelcorn E. Macular hole hydrodissection: surgical technique for the treatment of persistent, chronic, and large macular holes. *Retina*. 2019;39(4):743-752.
16. Mahmoud T, Moysidis S, Koulisis, et al. Autologous retinal transplantation for primary and refractory macular holes and macular hole retinal detachments: the Global Consortium. *Ophthalmology*. 2021;128(5):672-685.
17. Kwok AK, Lai TY, Wong VW. Idiopathic macular hole surgery in Chinese patients: a randomised study to compare indocyanine green-assisted internal limiting membrane peeling with no internal limiting membrane peeling. *Hong Kong Med J*. 2005;11(4):259-266.
18. Nourinia R, Nikzad P, Abolhosseini M, et al. RONA technique: a novel ilm peeling method for treatment of large full-thickness macular holes. *Retina*. 2023;43(4):692-697.
19. Kwak JJ, Byeon SH. Comparison of long-term visual and anatomical outcomes between internal limiting membrane flap and peeling techniques for macular holes with a propensity score analysis. *Eye (Lond)*. 2023;37(6):1207-1213.
20. Bleidißel N, Friedrich J, Klaas J, et al. Inverted internal limiting membrane flap technique in eyes with large idiopathic full-thickness macular hole: long-term functional and morphological outcomes. *Graefes Arch Clin Exp Ophthalmol*. 2021;259(7):1759-1771.

KAITLYN RICHARDS, BS
- Research Subject Recruitment Supervisor, Retina Consultants of Texas, Houston
- kaitlyn.richards@retinaconsultantstexas.com
- Financial disclosure: None

ANKOOR R. SHAH, MD
- Vitreoretinal Surgeon, Retina Consultants of Texas, Houston
- Assistant Professor of Clinical Ophthalmology, Houston Institute for Academic Medicine, Houston
- Clinical Assistant Professor of Ophthalmology, Weill Cornell Medical College, New York
- arsmd@retinaconsultantstexas.com
- Financial disclosure: Consultant (Notal Vision, Regeneron, RegenexBio); Shareholder (Apellis)

eyetube

THE LATEST FROM EYETUBE

CLINICAL MINUTE RETINA

Ramin Tadayoni, MD, PhD, and guests discuss the latest research and clinical studies in retina.

GATHER2 Data at 1 and 2

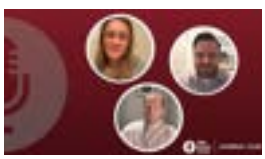
Ramin Tadayoni, MD, PhD, and Arshad Khanani, MD, MA

NEW RETINA RADIO | JOURNAL CLUB

This series is dedicated to reviewing the latest journal articles and how they relate to day-to-day clinical practice in retina.

Visual Outcomes Following Surgical RRD Repair Relative to Foveal Status and Time of Surgery

Lediana Goduni, MD; Matt Starr, MD; and Joshua Uhr, MD



NEW RETINA RADIO

New Retina Radio is a place to hear stories about retina that are told nowhere else.

Diagnosing Geographic Atrophy and Identifying Eligible Patients for Therapy

John W. Kitchens, MD; Scott Walter, MD; and Esther Kim, MD

OCULAR EFFECTS OF CAR-T CELL THERAPY

Know the risks and potential therapeutic benefits associated with this treatment modality.

BY LARS H. ANDERSEN, MD; JASKIRAT S. TAKHAR, MD; AND JOSE J. ECHEGARAY, MD

The advent of chimeric antigen receptor-T (CAR-T) cell therapy in the late 2010s heralded a new era in the treatment of hematologic malignancies and provided new hope in refractory cases. To date, the FDA has approved CAR-T cell class therapies for B-cell acute lymphoblastic leukemia (B-ALL), B-cell non-Hodgkin lymphoma, mantle cell lymphoma, and multiple myeloma.[1-5]

Leukemia can affect nearly any structure of the eye either due to direct tissue infiltration or, more commonly, secondary to anemia, thrombocytopenia, blood hyperviscosity, or immunosuppression.[6,7] Treatment options for ocular disease in the setting of systemic leukemia include systemic chemotherapy, intrathecal chemotherapy, radiotherapy, and bone marrow transplantation.[7] In cases of isolated ocular disease, intravitreal methotrexate and adjunct intrathecal chemotherapy are alternative management options.[8]

ABOUT CAR-T CELLS

CAR-T cells are manufactured from autologous T-cells that have been isolated and genetically modified to express cancer-specific antigen recognition domains on their cell surface.[9,10] This is typically achieved via DNA transfection or transduction via a viral vector into an isolated T-cell population to express CAR-T molecules.[10] These consist of an extracellular domain, an attached transmembrane domain, and an intracellular domain.[10] An effector cellular response can be activated by these CAR-T cells in response to malignant cells expressing specific antigens independent of major histocompatibility complexes, which may be downregulated by malignant cells.[11] The process of manufacturing CAR-T cells takes 2 to 5 weeks, and patients are lymphodepleted prior to the readministration.[12,13]

The effects of CAR-T cell agents on the eye, both therapeutic and deleterious, have been increasingly described in the literature since the initial approval of tisagenlecleucel (Kymriah, Novartis) in 2017. Herein, we present a review of the ocular therapeutic benefits and adverse effects related to CAR-T cell therapies.

THERAPEUTIC POTENTIAL

While the systemic benefits of CAR-T cell therapy are promising, comparatively little is known about the efficacy of CAR-T cell therapy in cases of ocular involvement of hematologic malignancy or in primary malignancies arising in the eye. Prospective studies remain limited due to the infrequency of primary ocular malignancy compared with systemic malignancy.

Preclinical investigations have determined a possible role for CAR-T cell therapy in the treatment of retinoblastoma; in one study, use of chimeric receptors against *CD171* and *GD2* resulted in destruction of nearly all retinoblastoma lines in vitro.[14] In addition, in vitro assays and mouse models of uveal melanoma have shown promising responses to CAR-T cell agents targeted to *HER2*.[15]

A key determinant in the efficacy of CAR-T cell therapy for ocular disease is its ability to penetrate the blood-aqueous and blood-retina barriers. There is single-case evidence demonstrating cytology-proven anterior chamber CAR-T infiltration in a 2-year-old patient treated for combined central nervous system relapse of B-ALL.[16] In addition, promising clinical results have been reported with use of tisagenlecleucel in conjunction with radiotherapy for isolated ocular relapse of B-ALL in a 21-year-old patient.[17]

Another case involved a 61-year-old patient with intravascular lymphoma presenting with a primary vitreoretinal lymphomatous-like lesion. This patient experienced mild

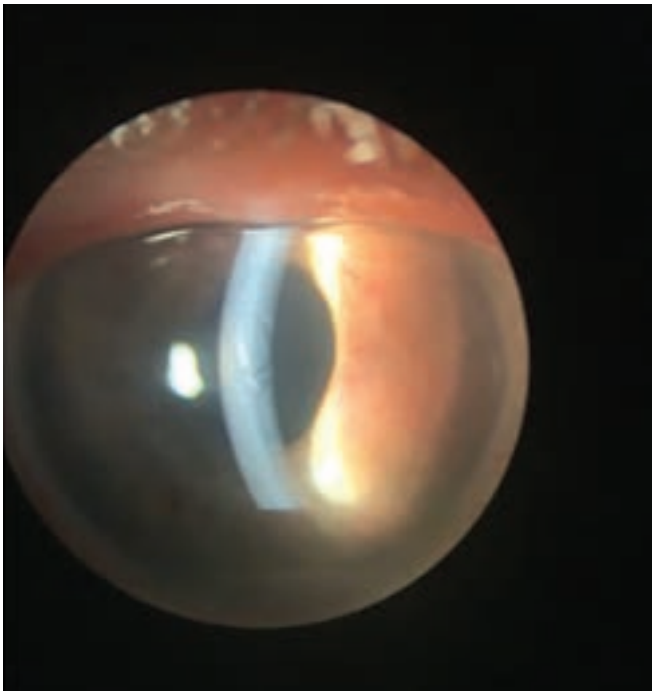


Figure 1. Ocular recurrence of acute lymphoblastic leukemia with pseudohypopyon, iris neovascularization, and nodularity. Uveal infiltration was confirmed via biopsy.

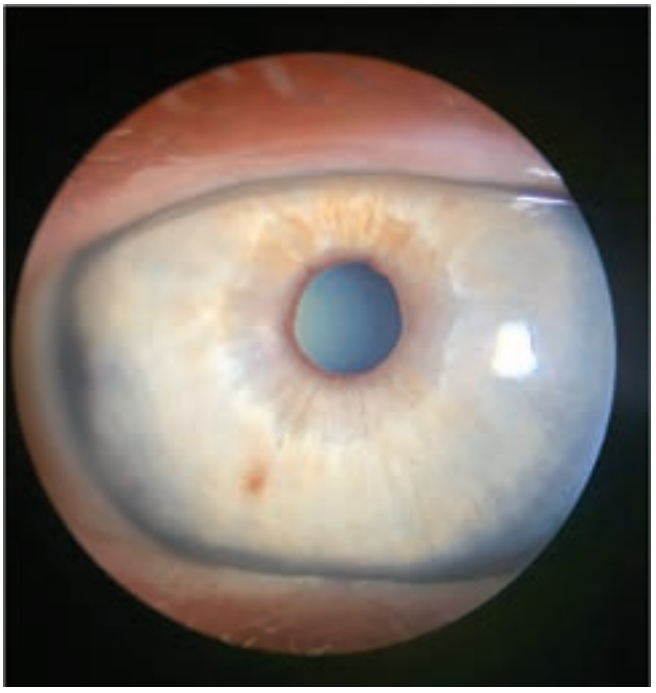


Figure 2. Resolution of iris neovascularization and nodularity with smooth-appearing iris contour.

benefit from local intravitreal methotrexate, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone, and systemic high-dose methotrexate therapy, but, thereafter, responded more robustly to CAR-T cell therapy with resolution of the retinal lesion.[18] A recent patient of ours with relapsing ALL (Figure 1) also responded to *CD19*-targeted CAR-T cell therapy with complete resolution (Figure 2).

Conversely, there was a report of ocular recurrence of vitreoretinal lymphoma despite good systemic response to CAR-T cell therapy, as well as presumed recurrence or possible persistent malignancy in the eye despite systemic disease control in a pediatric patient treated with tisagenlecleucel.[19,20] Bilateral orbital plasmacytoma causing ptosis and proptosis as the first sign of plasma cell leukemia recurrence after CAR-T cell therapy has also been reported.[21]

The ability of CAR-T cells to be introduced intravenously and treat diseases in the central nervous system, eyes, and testes begs the question: Which factors determine the success or failure of this treatment in the eyes, as well as other immune-privileged structures?[22] CAR-T cell therapy is a welcome addition to the armamentarium for the treatment of ocular malignancy in the setting of multicentric or systemic disease, but further investigation is warranted.

ADVERSE EVENTS

Serious but medically treatable systemic adverse events associated with CAR-T cell therapy are relatively common, including myelosuppression, cytokine release syndrome (CRS), and immune effector cell-associated neurotoxicity syndrome. The lymphodepletive course required for most patients prior to CAR-T therapy can result in neutropenia, anemia, thrombocytopenia, B- and T-cell aplasia, and resultant opportunistic infections.[11,12]

CRS represents the most common adverse effect directly attributable to CAR-T cell therapy and has been documented in up to 90% of treatment cases.[10] CRS is characterized by varying degrees of fever, hypotension, and hypoxia and can typically be treated with supportive care in a hospital setting but may progress to circulatory collapse and death. Therefore, in rare cases, it requires more aggressive treatment in the form of corticosteroids or intravenous tocilizumab (Actemra, Genentech/Roche).[23] In our own experience with CRS after a single CAR-T cell infusion, subsequent infusion was deferred. However, the patient did well regarding local and systemic control of disease with the single CAR-T cell infusion, without relapse for 15 months.

Neurotoxicity is another common complication of CAR-T cell therapy, occurring in 60% of patients in the ZUMA-3 trial, with severity ranging from mild (depressed level of consciousness) to severe (comatose).[10] Coagulopathy and encephalopathy syndromes have also been reported with use of CAR-T cell agents.[24,25]

Several ophthalmic adverse effects of CAR-T cell therapy have also been reported, including a variety of new visual, ophthalmic, or periorbital complaints, such as ocular graft-versus-host disease, herpes zoster ophthalmicus, and suspected acute retinal necrosis.[26] Exudative retinal detachment (RD) has been reported secondary to systemic

A KEY DETERMINANT IN THE EFFICACY OF CART-T CELL THERAPY FOR OCULAR DISEASE IS ITS ABILITY TO PENETRATE THE BLOOD-AQUEOUS AND BLOOD-RETINA BARRIERS.

inflammatory syndrome associated with CAR-T cell therapy.[27] Bilateral RD and leukemic infiltration into the retina and optic nerve have also been associated with CAR-T cell use.[28] Cytomegalovirus retinitis confirmed by DNA analysis of a vitreous sample and resultant RD have been reported with CAR-T cell therapy targeted toward multiple myeloma.[29,30] In addition, papilledema has been reported in a patient affected by CAR-T cell therapy-associated encephalopathy.[31]

Overall, ocular adverse events are rare compared with systemic side effects. Many occur secondary to systemic immunosuppression or cytokine release and inflammation secondary to the mechanism of action of CAR-T cell therapy.

FURTHER APPLICATIONS

CAR-T cell therapy has already demonstrated its promise as a treatment for refractory systemic hematologic malignancies, which has garnered interest in expanding its clinical uses. From an ophthalmic standpoint, there has been success with its use in vitro and in animal models for the treatment of retinoblastoma and uveal melanoma, and case reports have shown adequate short-term local control. Further studies of the treatment of primary ocular malignancies and secondary infiltration of ocular and periorbital structures by systemic malignancies with CAR-T cell therapy are warranted to further confirm their potential for ophthalmic care. ■

1. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. *N Engl J Med*. 2017;377(26):2531-2544.
2. Hansen DK, Sidana S, Peres LC, et al. Idecabtagene vicleucel for relapsed/refractory multiple myeloma: real-world experience from the Myeloma CAR T Consortium. *J Clin Oncol*. 2023;41(11):2087-2097.
3. Abramson JS, Solomon SR, Arnason J, et al. Lisocabtagene maraleucel as second-line therapy for large B-cell lymphoma: primary analysis of the phase 3 TRANSFORM study. *Blood*. 2023;141(14):1675-1684.
4. Abebe EC, Shiferaw MY, Admasu FT, Dejenie TA. Ciltacabtagene autoleucel: the second anti-BCMA CAR T-cell therapeutic armamentarium of relapsed or refractory multiple myeloma. *Front Immunol*. 2022;13:991092.
5. Wang Y, Jain P, Locke FL, et al. Brexucabtagene autoleucel for relapsed or refractory mantle cell lymphoma in standard-of-care practice: results from the US Lymphoma CAR T Consortium. *J Clin Oncol*. 2023;41(14):2594-2606.
6. Talcott KE, Garg RJ, Garg SJ. Ophthalmic manifestations of leukemia. *Curr Opin Ophthalmol*. 2016;27(6):545-551.
7. Sharma T, Grewal J, Gupta S, Murray PI. Ophthalmic manifestations of acute leukaemias: the ophthalmologist's role. *Eye*. 2004;18(7):663-672.
8. Vishnevskia-Dai V, Sella King S, Lekach R, Fabian ID, Zloto O. Ocular manifestations of leukemia and results of treatment with intravitreal methotrexate. *Sci Rep*. 2020;10(1):1994.
9. Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. *N Engl J Med*. 2018;378(5):439-448.
10. Buie LW. Balancing the CAR T: perspectives on efficacy and safety of CAR T-cell therapy in hematologic malignancies. *Am J Manag Care*. 2021;27(13 Suppl):S243-S252.
11. Zhang X, Zhu L, Zhang H, Chen S, Xiao Y. CAR-T cell therapy in hematological malignancies: current opportunities and challenges. *Front Immunol*. 2022;13:927153.
12. Luo W, Li C, Zhang Y, et al. Adverse effects in hematologic malignancies treated with chimeric antigen receptor (CAR) T cell therapy: a systematic review and meta-analysis. *BMC Cancer*. 2022;22(1):98.
13. Amini L, Silbert SK, Maude SL, et al. Preparing for CAR T cell therapy: patient selection, bridging therapies and lymphodepletion. *Nat Rev Clin Oncol*. 2022;19(5):342-355.
14. Andersch L, Radke J, Klaus A, et al. CD171- and GD2-specific CAR-T cells potently target retinoblastoma cells in preclinical in vitro testing. *BMC Cancer*. 2019;19(1):895.
15. Forsberg EMV, Lindberg MF, Jespersen H, et al. HER2 CAR-T cells eradicate uveal melanoma and T-cell therapy-resistant human melanoma in IL2 transgenic NOD/SCID IL2 receptor knockout mice. *Cancer Res*. 2019;79(5):899-904.
16. Jacoby E, Zloto O, Dai VV. Anterior chamber infiltration of CAR T-cells. *Am J Ophthalmol Case Rep*. 2021;24:101223.
17. Gomel N, Levinger E, Ram R, Limon D, Habot-Wilner Z. Acute lymphoblastic leukemia relapse limited to the anterior chamber of the eye and treated with novel CAR T-cell therapy. *Case Rep Ophthalmol*. 2021;12(3):994-1001.
18. Asakage M, Umazume K, Takoi H, et al. A case of intravascular lymphoma diagnosed with a primary vitreoretinal lymphoma-like fundus lesion. *J Ophthalmic Inflamm Infect*. 2021;11(1):47.
19. Willier S, Raedler J, Blaeschke F, et al. Leukemia escape in immune desert: intraocular relapse of pediatric pro-B-ALL during systemic control by CD19-CAR T cells. *J Immunother Cancer*. 2020;8(2).
20. Taher A, Abadir E, McCluskey P, Hamad N, Lo T, Heydon P. Presumptive recurrence of intraocular lymphoma despite chimeric antigen receptor t-cell therapy. *Retin Cases Brief Rep*. 2023;17(5):562-566.
21. Nogués-Castell J, Feu-Basilio S, Felguera García Ó, et al. Bilateral orbital plasmacytomas as first sign of extramedullary progression post CAR-T therapy: case report and literature review. *Front Oncol*. 2023;13:1217714.
22. Chen X, Wang Y, Ruan M, et al. Treatment of testicular relapse of B-cell acute lymphoblastic leukemia with CD19-specific chimeric antigen receptor T cells. *Clin Lymphoma Myeloma Leuk*. 2020;20(6):366-370.
23. Obstfeld AE, Frey NV, Mansfield K, et al. Cytokine release syndrome associated with chimeric-antigen receptor T-cell therapy: clinicopathological insights. *Blood*. 2017;130(23):2569-2572.
24. Gust J, Taraseviciute A, Turtle CJ. Neurotoxicity associated with CD19-targeted CAR-T cell therapies. *CNS Drugs*. 2018;32(12):1091-1101.
25. Wang Y, Qi K, Cheng H, et al. Coagulation disorders after chimeric antigen receptor T cell therapy: analysis of 100 patients with relapsed and refractory hematologic malignancies. *Biol Blood Marrow Transplant*. 2020;26(5):865-875.
26. Mumtaz AA, Fischer A, Lutfi F, et al. Ocular adverse events associated with chimeric antigen receptor T-cell therapy: a case series and review. *Br J Ophthalmol*. 2023;107(7):901-905.
27. Khanna S, Mackin AG, Dao DT, et al. Exudative retinal detachment following chimeric antigen receptor T-cell therapy in relapsed B-cell acute lymphoblastic leukemia. *Ophthalmic Surg Lasers Imaging Retina*. 2022;53(2):113-115.
28. Denton CC, Gange WS, Abdel-Azim H, et al. Bilateral retinal detachment after chimeric antigen receptor T-cell therapy. *Blood Adv*. 2020;4(10):2158-2162.
29. Zu C, Xu Y, Wang Y, et al. Cytomegalovirus retinitis and retinal detachment following chimeric antigen receptor T cell therapy for relapsed/refractory multiple myeloma. *Curr Oncol*. 2022;29(2):490-496.
30. Bin Dokhi H, Alharbi AO, Ibnouf NH, Alahmari B, Refka MN. Post-CD19 chimeric antigen receptor T-cell therapy cytomegalovirus retinitis. *Cureus*. 2022;14(3):e23002.
31. Garcia-Robledo JE, Valencia-Sanchez C, Knox MG, et al. It is in the eye of the beholder: ocular ultrasound enhanced monitoring of neurotoxicity after CAR-T cell therapy. *Hematol Rep*. 2022;15(1):1-8.

LARS H. ANDERSEN, MD
- Ophthalmology Resident, University Hospitals, Case Western Reserve University, Cleveland
- Financial disclosure: None

JOSE J. ECHEGARAY, MD
- President and Owner, Retina Consultants of Orlando, Altamonte Springs, Florida
- Adjunct Professor, Department of Ophthalmology, University Hospitals, Case Western Reserve University, Cleveland
- jjechegaray@retinaconsultantsorlando.com
- X/Twitter @jjeche; Instagram @retina_consultants_orlando
- Financial disclosure: None

JASKIRAT S. TAKHAR, MD
- Ophthalmology Resident, University Hospitals, Case Western Reserve University, Cleveland
- Financial disclosure: None

YoungMD Connect | RETINA

Brought to you by: bmc vision RT

Join Our Ask-Me-Anything Mentoring Sessions

Calling all trainees and new-to-practice ophthalmologists:

Participate in monthly mentoring sessions with retina thought leaders and peer mentors.

2024 MONTHLY MENTOR LINEUP

Roger A. Goldberg, MD, MBA
Thursday, April 25
Bay Area Retina Associates

Sarwar Zahid, MD
Tuesday, June 4
Empire State Retina

Xuejing Chen, MD, MS
Tuesday, July 16
Boston University Eye Associates

Nita Valikodath, MD, MS
Tuesday, August 6
Kellogg Eye Center

Deepak Sambhara, MD
Tuesday, September 10
Eye Clinic of Wisconsin

Sabah Shah, MD
Tuesday, November 12
NYU Langone Health

Alexis Warren, MD
Tuesday, November 19
University of Chicago

Murtaza Adam, MD
Wednesday, December 4
Colorado Retina Associates

Additional mentors to be announced soon!

Enjoy 50% off 1-year membership ($18.50)

Discount automatically applied using the QR code.

Gain Exclusive Access To:

- ✔ **MENTORING SESSIONS** to build connections with thought leaders.
- ✔ **EDUCATIONAL WORKSHOPS** to complement your clinical training.
- ✔ ***BOOKMARKED* EDITORIAL FORUM** to read the latest articles in eye care.
- ✔ **RESOURCES** to build new skills.
- ✔ **JOB BOARD** to land your first job or make a change.
- ✔ **IN-PERSON EVENTS** to fasttrack your networking opportunities and engage with industry.

YMDC members engaging with retina thought leaders, Audina Berrocal, MD, and Dean Eliott, MD, during in-person events and virtual mentoring sessions.

YMDC is made possible with industry support from:

VISIONARY: abbvie Johnson&Johnson

FOUNDATIONAL: Apellis Dompé REGENERON

PARTNER: BAUSCH+LOMB Genentech A Member of the Roche Group LUMIBIRD MEDICAL

GUIDING: Alcon AMGEN Rare Disease astellas EYE CARE PARTNERS GLAUKOS TRANSFORMING VISION tarsus

(Continued from page 29)

IT CAN BE CHALLENGING FOR THE INEXPERIENCED USER TO IDENTIFY THE APPROPRIATE CLINICAL SCENARIOS THAT WOULD BENEFIT FROM OCTA IMAGING AND TO INTERPRET THE RESULTS.

been time-consuming or impossible to find with traditional techniques. In these cases, targeting the appropriate retinal layer with the en face slab and correlating structural changes seen on the en face slab with functional abnormalities on the OCT B-scan flow overlay was key to correctly detecting the presence or absence of flow. ■

1. Jia Y, Tan O, Tokayer J, et al. Split-spectrum amplitude-decorrelation angiography with optical coherence tomography. *Opt Express*. 2012;20(4):4710-4725.
2. Spaide RF, Waheed NK, Fujimoto JG. Image artifacts in optical coherence tomography angiography. *Retina*. 2015;35(11):2163-2180.
3. Holmen IC, Konda SM, Pak JW, et al. Prevalence and severity of artifacts in optical coherence tomographic angiograms. *JAMA Ophthalmol*. 2020;138(2):119-126.
4. Cheung CMG, Lai TYY, Teo K, et al. Polypoidal choroidal vasculopathy: consensus nomenclature and non-indocyanine green angiograph diagnostic criteria from the Asia-Pacific Ocular Imaging Society PCV Workgroup. *Ophthalmology*. 2021;128(3):443-452.
5. Wang M, Zhou Y, Gao SS, et al. Evaluating polypoidal choroidal vasculopathy with optical coherence tomography angiography. *Invest Ophthalmol Vis Sci*. 2016;57(9):OCT526-OCT532.
6. Cheung CMG, Yanagi Y, Akiba M, et al. Improved detection and diagnosis of polypoidal choroidal vasculopathy using a combination of optical coherence tomography and optical coherence tomography angiography. *Retina*. 2019;39(9):1655-1663.

NICOLE L. DECKER, BS
- MD Candidate, Department of Ophthalmology, Northwestern University, Chicago
- Financial disclosure: None

AMANI A. FAWZI, MD
- Cyrus Tang and Lee Jampol Professor of Ophthalmology, Department of Ophthalmology, Feinberg School of Medicine, Northwestern University, Chicago
- afawzimd@gmail.com
- Financial disclosure: Consultant (3Helix, Boehringer Ingelheim, Genentech/Roche, Regeneron, Regenxbio); Research Support (Boehringer Ingelheim)

IVY ZHU, MD
- Vitreoretinal Surgery Fellow, Department of Ophthalmology, Feinberg School of Medicine, Northwestern University, Chicago
- ivyzhu1@gmail.com
- Financial disclosure: None

INDEX OF ADVERTISERS

Alcon.....19
www.alcon.com
Apellis.....11, 12
www.apellis.com
Genentech.....59, Cover 4
www.gene.com
Iridex.....41
www.iridex.com
Iveric Bio.....Cover 2, 3, 4
www.ivericbio.com
MedOne Surgical.....15
www.medone.com
Nidek.....33
www.nidek.com
Notal Vision.....7
www.notalvision.com
Oculus.....23
www.oculussurgical.com

This advertiser index is published as a convenience and not as part of the advertising contract. Although great care will be taken to index correctly, no allowances will be made for errors due to spelling, incorrect page number, or failure to insert.

(Continued from page 58)

FIGURE 2

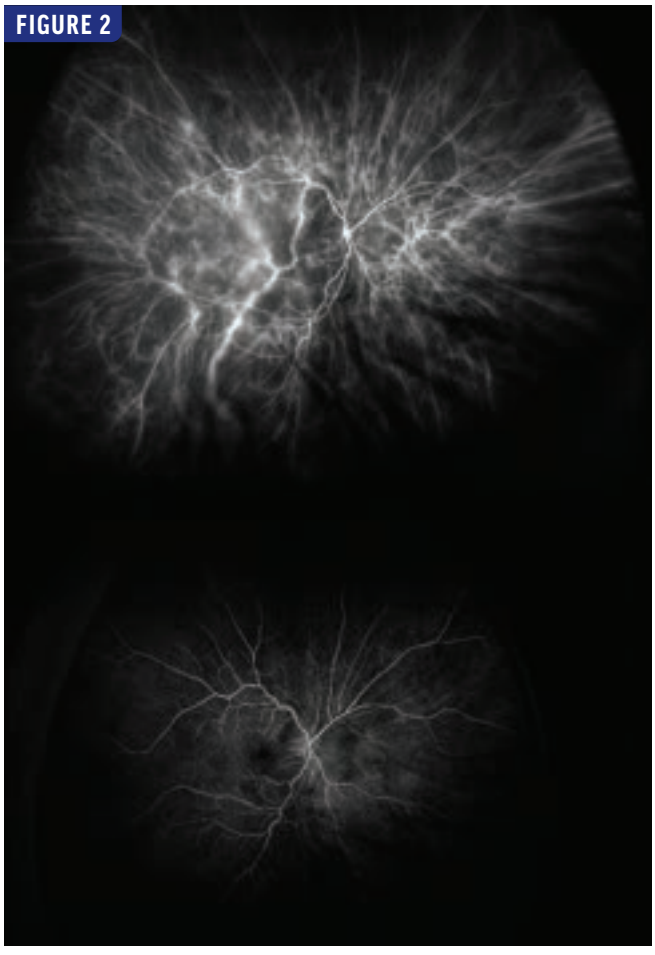
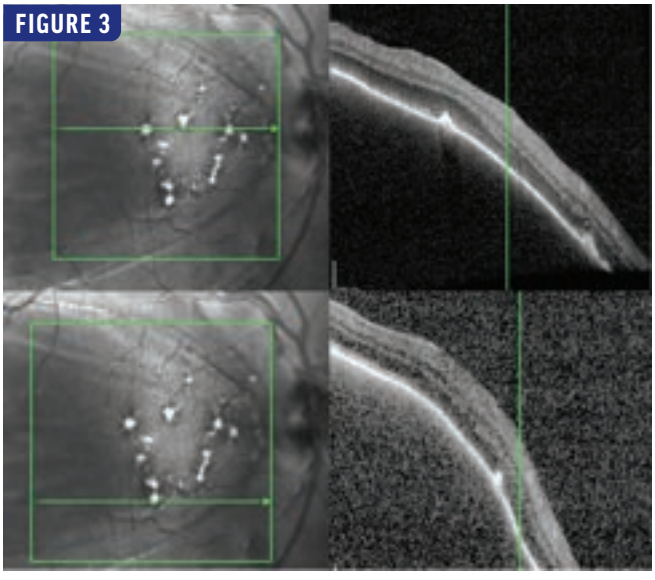


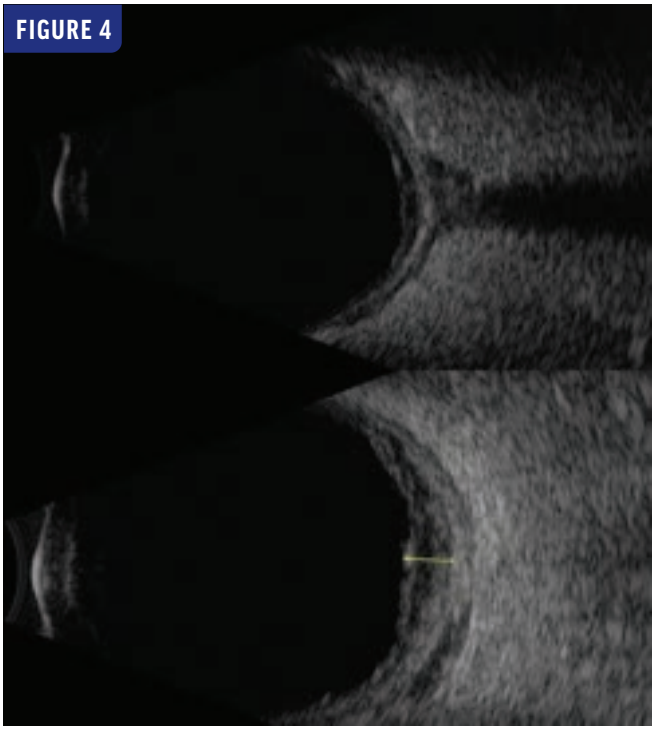
FIGURE 3



DISCUSSION

Reactive lymphoid hyperplasia is a rare condition that typically affects middle-aged adults. It is usually unilateral and has no predilection based on race or sex.[1] It is characterized by multifocal, static, creamy choroidal infiltrates, diffuse thickening of the choroid, and pigmentary alterations in the overlying retinal pigment epithelium.[1] It can lead to secondary narrow glaucoma, exudative retinal detachments, and shifting subretinal fluid.[1] The literature generally recommends observation, although at least one case reported successfully using a combination of antibiotics and steroids to address the postulated immunogenic etiology of this condition.[2] ■

FIGURE 4



1. Chang TS, Byrne SF, Gass JD, Hughes JR, Johnson RN, Murray TG. Echographic findings in benign reactive lymphoid hyperplasia of the choroid. *Arch Ophthalmol*. 1996;114(6):669-675.
2. Francis JH, Winebrake JP, Abramson DH. Uveal lymphoid hyperplasia: treatment with combination antibiotics and steroids. *Br J Ophthalmol*. 2023;107(6):786-789.

J. FERNANDO AREVALO, MD, PHD
- Chairman of Ophthalmology, Wilmer Eye Institute, Johns Hopkins University School of Medicine, Baltimore
- arevalojf@jhmi.edu
- Financial disclosure: None

LOKA THANGAMATHESVARAN, MD
- Vitreoretinal Surgery Fellow, Wilmer Eye Institute, Johns Hopkins University School of Medicine, Baltimore
- Financial disclosure: None

If you have images you would like to share, email Manish Nagpal, MS, FRCS, FASRS, at drmanishnagpal@yahoo.com.

Note: Photos should be 400 dpi or higher and at least 10 inches wide.

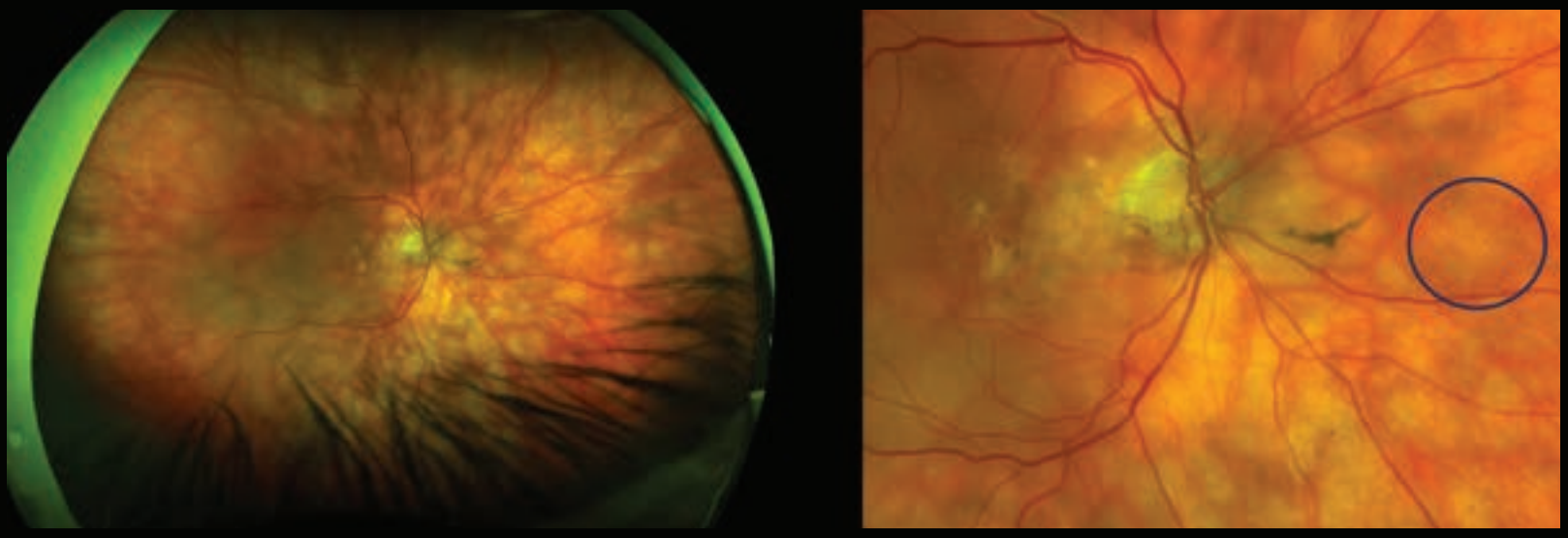


FIGURE 1

UVEAL REACTIVE LYMPHOID HYPERPLASIA


Be on the lookout for this rare cause of choroidal lesions.

BY LOKA THANGAMATHESVARAN, MD, AND J. FERNANDO AREVALO, MD, PHD

A 72-year-old man with no past medical or ocular history presented for evaluation of a choroidal lesion found in his right eye on routine examination. His BCVA was 20/30 OD and 20/20 OS. The anterior segment was normal in each eye. Fundus examination of the right eye showed multifocal, creamy yellow choroidal infiltrates with peripapillary hyperpigmentation and focal subretinal yellow deposits (Figure 1).

ICG angiography showed hypofluorescence corresponding to the choroidal lesions in the right eye. Fluorescein angiography showed early peripapillary blockage with late staining of the lesion in the right eye (Figure 2). Macular OCT showed choroidal elevation with an intact overlying retina and scattered subretinal hyperreflective lesions (Figure 3). B-scan ultrasonography showed peripapillary fundus thickening (Figure 4).

DIAGNOSIS AND FOLLOW-UP

The differential diagnosis was broad and included infectious (syphilis, tuberculosis [TB], and human immunodeficiency virus [HIV]), inflammatory (sarcoidosis, acute posterior multifocal placoid pigment epitheliopathy, and posterior scleritis), and oncologic (primary vitreoretinal lymphoma, reactive lymphoid hyperplasia of the uvea, metastatic lesions, diffuse melanoma, and uveal effusion syndrome) etiologies.

An extensive lab workup was ordered, including tests for HIV, TB, syphilis, angiotensin-converting enzyme, lysozyme, toxoplasmosis, anti-double-stranded DNA, anti-myeloperoxidase antibody, anti-proteinase 3, and toxocariasis. Imaging included chest X-ray and MRI of the brain and orbits.

The workup was positive for prior exposure to toxoplasmosis (IgG positive and IgM negative), and MRI showed asymmetric thickening of the right retina and choroid. Given the otherwise negative workup, the most likely diagnosis was reactive lymphoid hyperplasia of the uvea. The patient was subsequently followed for 6 years with stable appearance of the lesions and visual acuity.

(Continued on page 57)

VABYSMO™
faricimab-svoa injection 6 mg

VABYSMO® (faricimab-svoa) injection, for intravitreal use

This is a brief summary. Before prescribing, please refer to the full Prescribing Information

1 INDICATIONS AND USAGE

VABYSMO is a vascular endothelial growth factor (VEGF) and angiopoietin 2 (Ang-2) inhibitor indicated for the treatment of patients with:

1.1 Neovascular (wet) Age-Related Macular Degeneration (nAMD)

1.2 Diabetic Macular Edema (DME)

1.3 Macular Edema Following Retinal Vein Occlusion (RVO)

4 CONTRAINDICATIONS

4.1 Ocular or Periocular Infections

VABYSMO is contraindicated in patients with ocular or periocular infections.

4.2 Active Intraocular Inflammation

VABYSMO is contraindicated in patients with active intraocular inflammation.

4.3 Hypersensitivity

VABYSMO is contraindicated in patients with known hypersensitivity to faricimab or any of the excipients in VABYSMO. Hypersensitivity reactions may manifest as rash, pruritus, urticaria, erythema, or severe intraocular inflammation.

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis and Retinal Detachments

Intravitreal injections have been associated with endophthalmitis and retinal detachments *[see Adverse Reactions (6.1)]*. Proper aseptic injection techniques must always be used when administering VABYSMO. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay, to permit prompt and appropriate management *[see Dosage and Administration (2.6) and Patient Counseling Information (17)]*.

5.2 Increase in Intraocular Pressure

Transient increases in intraocular pressure (IOP) have been seen within 60 minutes of intravitreal injection, including with VABYSMO *[see Adverse Reactions (6.1)]*. IOP and the perfusion of the optic nerve head should be monitored and managed appropriately *[see Dosage and Administration (2.6)]*.

5.3 Thromboembolic Events

Although there was a low rate of arterial thromboembolic events (ATEs) observed in the VABYSMO clinical trials, there is a potential risk of ATEs following intravitreal use of VEGF inhibitors. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause).

The incidence of reported ATEs in the nAMD studies during the first year was 1% (7 out of 664) in patients treated with VABYSMO compared with 1% (6 out of 662) in patients treated with aflibercept *[see Clinical Studies (14.1)]*.

The incidence of reported ATEs in the DME studies from baseline to week 100 was 5% (64 out of 1,262) in patients treated with VABYSMO compared with 5% (32 out of 625) in patients treated with aflibercept *[see Clinical Studies (14.2)]*.

The incidence of reported ATEs in the RVO studies during the first 6 months was 1.1% (7 out of 641) in patients treated with VABYSMO compared with 1.4% (9 out of 635) in patients treated with aflibercept *[see Clinical Studies (14.3)]*.

5.4 Retinal Vasculitis and/or Retinal Vascular Occlusion

Retinal vasculitis and/or retinal vascular occlusion, typically in the presence of intraocular inflammation, have been reported with the use of VABYSMO *[see Adverse Reactions (6.2)]*. Discontinue treatment with VABYSMO in patients who develop these events. Patients should be instructed to report any change in vision without delay.

6 ADVERSE REACTIONS

The following potentially serious adverse reactions are described elsewhere in the labeling:

- Hypersensitivity *[see Contraindications (4)]*
- Endophthalmitis and retinal detachments *[see Warnings and Precautions (5.1)]*
- Increase in intraocular pressure *[see Warnings and Precautions (5.2)]*
- Thromboembolic events *[see Warnings and Precautions (5.3)]*
- Retinal Vasculitis and/or Retinal Vascular Occlusion *[see Warnings and Precautions (5.4)]*

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in other clinical trials of the same or another drug and may not reflect the rates observed in practice.

The data described below reflect exposure to VABYSMO in 2,567 patients, which constituted the safety population in six Phase 3 studies *[see Clinical Studies (14.1, 14.2, 14.3)]*.

Table 1: Common Adverse Reactions (≥ 1%)

Adverse Reactions	VABYSMO			Active Control (aflibercept)		
	AMD N=664	DME N=1,262	RVO N=641	AMD N=662	DME N=625	RVO N=635
Cataract	3%	15%	< 1%	2%	12%	1%
Conjunctival hemorrhage	7%	8%	3%	8%	7%	4%
Vitreous detachment	3%	5%	2%	3%	4%	2%
Vitreous floaters	3%	4%	2%	2%	3%	2%
Retinal pigment epithelial tear[a]	3%			1%		
Intraocular pressure increased	3%	4%	1%	2%	3%	3%
Eye pain	3%	3%	< 1%	3%	3%	< 1%
Intraocular inflammation[b]	2%	1%	1%	1%	1%	< 1%
Eye irritation	1%	< 1%	< 1%	< 1%	1%	< 1%
Lacrimation increased	1%	1%	0%	1%	< 1%	< 1%
Ocular discomfort	1%	1%	< 1%	< 1%	< 1%	< 1%

[a]AMD only
[b]Including iridocyclitis, iritis, uveitis, vitritis

Less common adverse reactions reported in < 1% of the patients treated with VABYSMO were corneal abrasion, eye pruritus, ocular hyperemia, blurred vision, sensation of foreign body, endophthalmitis, conjunctival hyperaemia, visual acuity reduced, visual acuity reduced transiently, vitreous hemorrhage, retinal tear and rhegmatogenous retinal detachment.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of VABYSMO. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Eye disorders: retinal vasculitis with or without retinal vascular occlusion.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate and well-controlled studies of VABYSMO administration in pregnant women.

Administration of VABYSMO to pregnant monkeys throughout the period of organogenesis resulted in an increased incidence of abortions at intravenous (IV) doses 158 times the human exposure (based on C_{max}) of the maximum recommended human dose *[see Animal Data]*. Based on the mechanism of action of VEGF and Ang-2 inhibitors, there is a potential risk to female reproductive capacity, and to embryo-fetal development. VABYSMO should not be used during pregnancy unless the potential benefit to the patient outweighs the potential risk to the fetus.

All pregnancies have a background risk of birth defect, loss, and other adverse outcomes. The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects is 2%-4% and of miscarriage is 15%-20% of clinically recognized pregnancies.

Data

Animal Data

An embryo fetal developmental toxicity study was performed on pregnant cynomolgus monkeys. Pregnant animals received 5 weekly IV injections of VABYSMO starting on day 20 of gestation at 1 or 3 mg/kg. A non-dose dependent increase in pregnancy loss (abortions) was observed at both doses evaluated. Serum exposure (C_{max}) in pregnant monkeys at the low dose of 1 mg/kg was 158 times the human exposure at the maximum recommended intravitreal dose of 6 mg once every 4 weeks. A no observed adverse effect level (NOAEL) was not identified in this study.

8.2 Lactation

Risk Summary

There is no information regarding the presence of faricimab in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. Many drugs are transferred in human milk with the potential for absorption and adverse reactions in the breastfed child.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for VABYSMO and any potential adverse effects on the breastfed child from VABYSMO.

8.3 Females and Males of Reproductive Potential

Contraception

Females of reproductive potential are advised to use effective contraception prior to the initial dose, during treatment and for at least 3 months following the last dose of VABYSMO.

Infertility

No studies on the effects of faricimab on human fertility have been conducted and it is not known whether faricimab can affect reproduction capacity. Based on the mechanism of action, treatment with VABYSMO may pose a risk to reproductive capacity.

8.4 Pediatric Use

The safety and efficacy of VABYSMO in pediatric patients have not been established.

8.5 Geriatric Use

In the six clinical studies, approximately 58% (1,496/2,571) of patients randomized to treatment with VABYSMO were ≥ 65 years of age. No significant differences in efficacy or safety of faricimab were seen with increasing age in these studies. No dose adjustment is required in patients 65 years and above.

17 PATIENT COUNSELING INFORMATION

Advise patients that in the days following VABYSMO administration, patients are at risk of developing endophthalmitis. If the eye becomes red, sensitive to light, painful, or develops a change in vision, advise the patient to seek immediate care from an ophthalmologist *[see Warnings and Precautions (5)]*.

Patients may experience temporary visual disturbances after an intravitreal injection with VABYSMO and the associated eye examinations *[see Adverse Reactions (6)]*. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

VABYSMO® [faricimab-svoa]
Manufactured by:
Genentech, Inc.
A Member of the Roche Group
1 DNA Way
South San Francisco, CA 94080-4990
U.S. License No.: 1048

M-US-00022310(v1.0) 11/23

START NOW | WITH DUAL-PATHWAY VABYSMO

VABYSMO™
faricimab-svoa injection 6 mg

THE POWER 2 OPEN THEIR WORLD

VABYSMO® (faricimab-svoa) delivers **powerful efficacy** with **1–4 month dosing**[1]*†

Discover more at vabysmo-hcp.com

*Primary endpoint of non-inferiority vs aflibercept 2 mg in the mean change from baseline in BCVA was measured by the ETDRS letter score and tested using a margin of 4 letters. **nAMD:** VABYSMO met its primary endpoint of non-inferiority at year 1 (avg. of weeks 40, 44, and 48). Differences in LS means for VABYSMO were +0.7 letters (CI: [95%] -1.1, +2.5) in TENAYA; and 0.0 letters (CI: [95%] -1.7, +1.8) in LUCERNE. **DME:** VABYSMO met its primary endpoint of non-inferiority at year 1 (avg. of weeks 48, 52, and 56). Differences in LS means in YOSEMITE were +0.7 letters (CI: [97.5%] -1.1, +2.5) for VABYSMO Q4W–Q16W and -0.2 letters (CI: [97.5%] -2.0, +1.6) for VABYSMO Q8W. Differences in LS means in RHINE were +0.5 letters (CI: [97.5%] -1.1, +2.1) for VABYSMO Q4W–Q16W and +1.5 letters (CI: [97.5%] -0.1, +3.2) for VABYSMO Q8W. A non-inferiority margin was not available for year 2. **RVO:** VABYSMO met its primary endpoint of non-inferiority at week 24. Differences in LS means for VABYSMO were -0.6 letters (CI: [95%] -2.2, +1.1) in BALATON; and -0.4 letters (CI: [95%] -2.5, +1.6) in COMINO.[1]

†**nAMD:** 4 monthly loading doses followed by OCT and visual acuity evaluations 8 and 12 weeks later to inform Q16W (weeks 28 and 44), Q12W (weeks 24, 36, and 48), Q8W (weeks 20, 28, 36, and 44), or Q4W (no added benefit) dosing. **DME:** at least 4 monthly loading doses followed by extensions ≤4 weeks or reductions ≤8 weeks based on OCT and visual acuity evaluations OR 6 monthly loading doses followed by Q8W. Q4W dosing may be needed (no added benefit). **RVO:** every month (4 weeks) for 6 months.[1]

INDICATIONS
VABYSMO (faricimab-svoa) is a vascular endothelial growth factor (VEGF) inhibitor and angiopoietin-2 (Ang-2) inhibitor indicated for the treatment of patients with Neovascular (Wet) Age-Related Macular Degeneration (nAMD), Diabetic Macular Edema (DME), and Macular Edema following Retinal Vein Occlusion (RVO).

IMPORTANT SAFETY INFORMATION

Contraindications
VABYSMO is contraindicated in patients with ocular or periocular infection, in patients with active intraocular inflammation, and in patients with known hypersensitivity to faricimab or any of the excipients in VABYSMO. Hypersensitivity reactions may manifest as rash, pruritus, urticaria, erythema, or severe intraocular inflammation.

Warnings and Precautions
Endophthalmitis and Retinal Detachments
Intravitreal injections have been associated with endophthalmitis and retinal detachments. Proper aseptic injection techniques must always be used when administering VABYSMO. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay, to permit prompt and appropriate management.

Increase in Intraocular Pressure
Transient increases in intraocular pressure (IOP) have been seen within 60 minutes of intravitreal injection, including with VABYSMO. IOP and the perfusion of the optic nerve head should be monitored and managed appropriately.

Thromboembolic Events
Although there was a low rate of arterial thromboembolic events (ATEs) observed in the VABYSMO clinical trials, there is a potential risk of ATEs following intravitreal use of VEGF inhibitors. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause).

The incidence of reported ATEs in the nAMD studies during the first year was 1% (7 out of 664) in patients treated with VABYSMO compared with 1% (6 out of 662) in patients treated with aflibercept.

The incidence of reported ATEs in the DME studies from baseline to week 100 was 5% (64 out of 1,262) in patients treated with VABYSMO compared with 5% (32 out of 625) in patients treated with aflibercept.

The incidence of reported ATEs in the RVO studies during the first 6 months was 1.1% (7 out of 641) in patients treated with VABYSMO compared with 1.4% (9 out of 635) in patients treated with aflibercept.

Retinal Vasculitis and/or Retinal Vascular Occlusion
Retinal vasculitis and/or retinal vascular occlusion, typically in the presence of intraocular inflammation, have been reported with the use of VABYSMO. Healthcare providers should discontinue treatment with VABYSMO in patients who develop these events. Patients should be instructed to report any change in vision without delay.

Adverse Reactions
The most common adverse reactions (≥5%) reported in patients receiving VABYSMO were cataract (15%) and conjunctival hemorrhage (8%).

Pregnancy, Lactation, Females and Males of Reproductive Potential
Based on the mechanism of action of VEGF and Ang-2 inhibitors, there is a potential risk to female reproductive capacity, and to embryo-fetal development. VABYSMO should not be used during pregnancy unless the potential benefit to the patient outweighs the potential risk to the fetus. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for VABYSMO and any potential adverse effects on the breastfed child from VABYSMO. Females of reproductive potential are advised to use effective contraception prior to the initial dose, during treatment and for at least 3 months following the last dose of VABYSMO.

You may report side effects to the FDA at (800) FDA-1088 or www.fda.gov/medwatch.
You may also report side effects to Genentech at (888) 835-2555.

Please see additional Important Safety Information in the full VABYSMO Prescribing Information.

References: 1. VABYSMO [package insert]. South San Francisco, CA: Genentech, Inc; 2023.

BCVA=best corrected visual acuity; CI=confidence interval; ETDRS=Early Treatment Diabetic Retinopathy Study; LS=least squares; OCT=optical coherence tomography; Q4W=every 4 weeks; Q8W=every 8 weeks; Q12W=every 12 weeks; Q16W=every 16 weeks.

M-US-00020375(v2.0) 11/23

Genentech
A Member of the Roche Group