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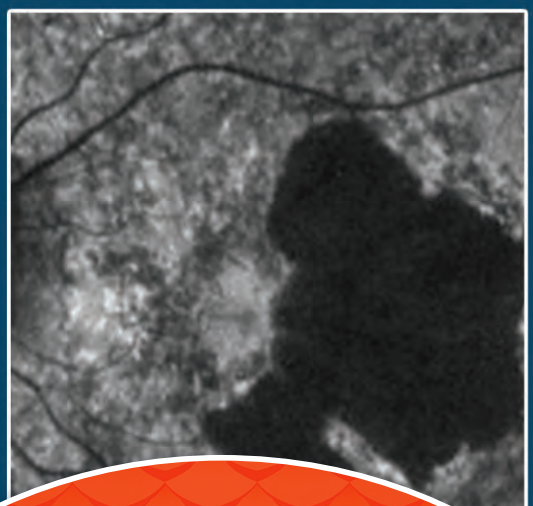
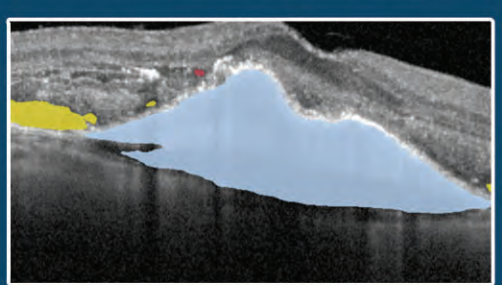
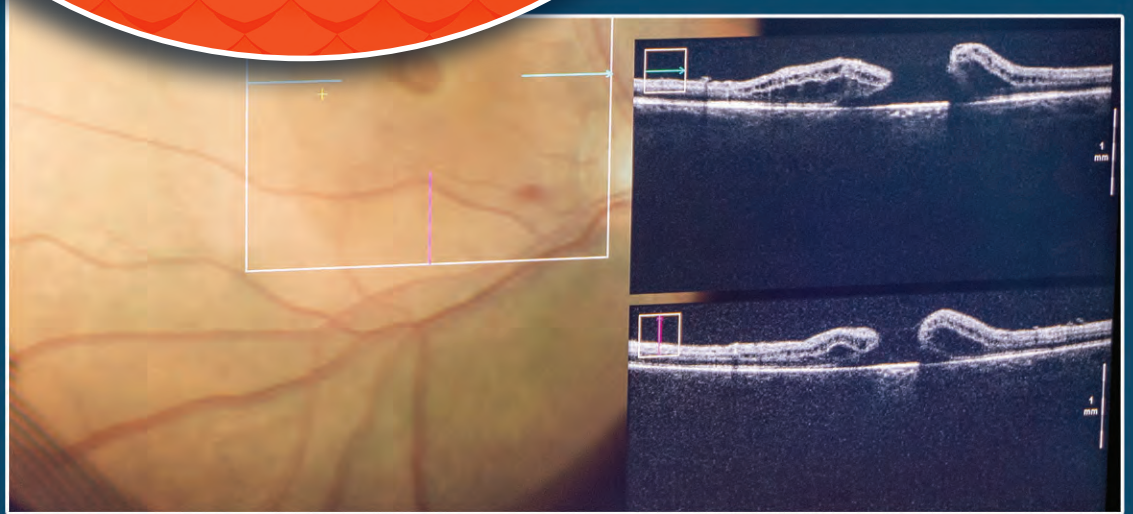


IMAGING and VISUALIZATION

With Guest Editors
Cynthia A. Toth, MD,
and Amani A. Fawzi, MD





LEVERAGING AI TO ALLEVIATE DIABETIC VISION LOSS

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VOLUME PROBLEMS

BY CYNTHIA A. TOTH, MD, AND AMANI A. FAWZI, MD


If you could identify one word that crops up more than you would ever expect in your day-to-day practice, what would it be? We would like to suggest *volume*. It's no surprise that the first association that pops into our minds is related to our workload. Patient volumes seem to be at an all-time high, and conference halls are ringing with concerns about how to handle the growing volume of pharmaceuticals we must stock. (Is anyone else oddly familiar with the price of high-capacity refrigerators these days?)

Or maybe you are an OCT enthusiast and *volume* immediately brings to mind OCT volume scans—intraretinal and subretinal fluid volumes are trusty indicators of disease activity and treatment success, after all.

Are you starting to see the trend? Volume is showing up—and causing pressure—everywhere in our practices! Perhaps nowhere else is the issue of volume more apparent than with our imaging tools. Not only do we have myriad modalities to choose from (fundus photos, OCT, OCT angiography [OCTA], fundus autofluorescence, fluorescein angiography, and ICG, to name a few), but each machine spits out untold amounts of data. The sheer volume of scans, slabs, images, and readouts we have for each patient encounter can be daunting, to say the least. The pile of information, though interesting and useful, can at times feel more like something we must dig ourselves out of than something to guide our disease management.

To further complicate matters, that data is becoming increasingly crucial as we learn more about various retinal diseases; for example, geographic atrophy therapy is pushing us to identify this condition earlier than ever before—and that means digging into our OCT and OCTA scans to find subtle changes. The panelists in this issue's roundtable article on OCTA suggest that we all set aside time after patients are out of the office to look over OCTA images with our fellows. Doing so can help us learn together without the pressures of a busy clinic demanding our immediate attention.

Luckily, we are quite good at finding unique solutions to our volume problems. We hire and train fantastic imaging technicians to help capture and wade through the scans, and researchers are hard at work fine tuning deep-learning artificial intelligence (AI) algorithms that can make sense of all the data for us.

This issue—dedicated to imaging and visualization in retina—shares some of the latest innovations that are pushing the boundaries when it comes to retinal imaging. In addition to the OCTA roundtable, experts discuss the value of fundus autofluorescence for diagnosing inherited retinal disease and assessing retinal displacement after retinal detachment repair. We also asked colleagues to provide an update on where we stand with AI in retina and, boy, did they deliver, with articles on classifying retinopathy of prematurity, screening for diabetic eye disease, and detecting retinal abnormalities.

For those of you who are interested in the latest technology to navigate increasing surgical volumes, Reem Amine, MD; Leanne Clevenger, MD; and Justis P. Ehlers, MD, provide an excellent how-to guide to using 3D heads-up displays in the OR.

We hope the tips, tricks, and updates within these pages reinvigorate your love for retinal imaging. Hopefully they give you the push you needed to dust off that pile of OCTA scans, consider fundus autofluorescence for that tricky patient, or more closely follow the latest updates on AI technology. Don't let the volume get in your way. ■

LOVE IMAGING and PODCASTS?

We have a few New Retina Radio episodes you might like!

The Utility of OCTA in the Clinic

Cynthia A. Toth, MD, and Amani A. Fawzi, MD, sit down with experts Philip J. Rosenfeld, MD, PhD; SriniVas Sadda, MD; and Nadia K. Waheed, MD, MPH, to discuss the value of OCT angiography in the retina clinic. From assessing macular neovascularization to tracking treatment effect in patients with plaque choroidal retinopathies, this imaging modality can augment current tools—and even replace them, at times.

Innovations in Retinal Imaging

John Kitchens, MD, invites Aleksandra Rachitskaya, MD, and Jonathan Russell, MD, PhD, to discuss the use of imaging technology in the retina clinic. The surgeons discuss cases in which they share their approach to imaging to evaluate wet AMD, retinal detachments, and more.

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IMAGING and VISUALIZATION

Cover image credit: ©iStockphoto.com

ONLINE FEATURE:

Wayfinding AI: A New Way to Detect Retinal Disease

By Taiji Sakamoto, MD; Shozo Sonoda, MD, PhD; and Hideki Shiihara, MD

DEPARTMENTS

NOW APPROVED: the first and only FDA-approved treatment for GA secondary to AMD[1]

GA unravels so much

Save retinal tissue by slowing progression[1-3]

INDICATION

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

IMPORTANT SAFETY INFORMATION

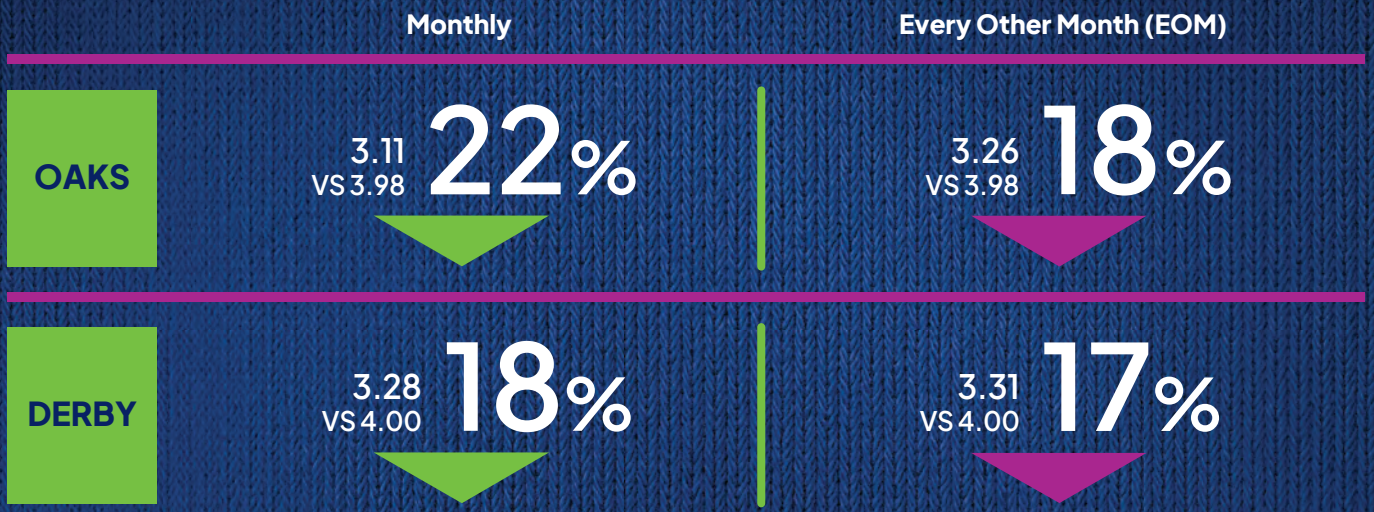
CONTRAINDICATIONS

- 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.
- **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.

SYFOVRE achieved continuous reductions in mean lesion growth rate* (mm^2) vs sham pooled from baseline to Month 24[1]



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]
AMD=age-related macular degeneration; GA=geographic atrophy; SE=standard error.

Explore more at SyfovreECP.com

IMPORTANT SAFETY INFORMATION (CONT'D)

WARNINGS AND PRECAUTIONS (CONT'D)

- **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.

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.

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

Apellis

SYFOVRE™
(pegcetacoplan injection)
15 mg / 0.1 mL

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.

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.

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 neovascular AMD, endophthalmitis, and retinal detachments. 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-17Feb2023-1.0

2/23 US-PEGGA-2200163 v2.0

STUDY SUGGESTS RETINAL CHANGES AS POTENTIAL BIOMARKER FOR ALZHEIMER DISEASE

Investigators at Cedars-Sinai recently found a correlation between changes in the retina and the brain and cognitive changes in patients with Alzheimer disease (AD). The study provides a deeper understanding of the susceptibility of the retina to AD processes and proposes that the retina could be a reliable biomarker for detecting and monitoring AD.[1]

The researchers analyzed retinal and brain tissue samples from AD patients with normal cognitive function, early-stage mild cognitive impairment, and late-stage AD dementia—collecting samples from 86 human donors over a 14-year period. They mapped and measured the markers of inflammation and functional cell loss in the retina and analyzed the proteins present in retinal and brain tissues.[1]

Key findings in patients with mild cognitive impairment and AD include an overabundance of amyloid beta 42 (which causes clumping and plaque formation in the brain, disrupting brain function), amyloid beta protein accumulation in the ganglion cells (which bridge visual input from the retina to the optic nerve), and a higher number of microglia (astrocytes and immune cells) tightly surrounding the amyloid beta plaques.

The study also revealed that up to 80% fewer microglial cells are clearing amyloid beta proteins from the retina and brain and identified specific molecules and biological pathways responsible for inflammation and cell and tissue death.[2]

The researchers noted that the retinal changes, which correlated with the stage of disease and the patient's cognitive status, were found even in patients who appeared cognitively normal.[1]

1. Koronyo Y, Rentsendorj A, Mirzaei N, et al. Retinal pathological features and proteome signatures of Alzheimer's disease. *Acta Neuropathol*. 2023;145(4):409-438.
2. Cedars-Sinai analysis evaluates how retinal changes correspond to cognitive changes in Alzheimer's disease [press release]. Eyewire+. March 8, 2023. Accessed March 21, 2023. eyewire.news/news/new-insights-eye-damage-in-alzheimers-disease-patients

NEW 24-MONTH DATA DEMONSTRATES VISION IMPROVEMENT IN DRY AMD WITH LIGHT DELIVERY SYSTEM

LumiThera released 24-month data from its LIGHTSITE III clinical trial, revealing that the use of its Valeda Light Delivery System demonstrated sustained improvement in vision among patients with dry AMD.[1]

The trial involved 100 subjects with early to intermediate dry AMD who were treated every 4 months. At 24 months, the primary efficacy endpoint was BCVA, and there were minimal safety risks and high patient compliance, with 80% of patients completing the trial.

In the modified intent-to-treat population with at least one follow-up visit, the analysis included 91 eyes in the photobiomodulation (PBM) treatment group and 54 eyes in the sham group. The PBM-treated group showed a statistically significant visual acuity improvement at 21 months, with sustained vision benefits throughout the trial's conclusion. At 24 months, BCVA improvement from baseline was 5.9 versus 1 letters in the PBM treatment group compared with sham (P = .0015). In addition, approximately 58% of the treated eyes had > 5 letter gain (mean = 8.5 + 0.5 letters).

1. LumiThera announces sustained vision improvement for 24 months in dry AMD subjects from US LIGHTSITE III Trial [press release]. Eyewire+. March 15, 2023. Accessed March 21, 2023. eyewire.news/news/lumithera-announces-sustained-vision-improvement-for-24-months-in-dry-amd-subjects-from-us-lightsite-iii-clinical-trial-data

GENE THERAPY SHOWS SUSTAINED EFFICACY AND SAFETY IN LHON PATIENTS AT 3 YEARS

The REFLECT phase 3 clinical trial showed sustained efficacy and favorable safety for bilateral intravitreal injection of the gene therapy lenadogene nolparvovec (Lumevoq, GenSight Biologics) at 3 years post-treatment.[1] The results also demonstrated a statistically significant improvement in visual acuity from baseline in both treated eyes—showing an additional benefit of a bilateral injection.

The study involved 98 patients with vision loss due to Leber hereditary optic neuropathy caused by a mutated

Pharma Updates From Eyewire+

- The FDA accepted Aldeyra's new drug application for methotrexate injection USP (ADX-2191) for the treatment of primary vitreoretinal lymphoma under priority review with a Prescription Drug User Fee Act date of June 21, 2023. Acceptance was based on past data and positive safety and tolerability data from the phase 3 GUARD trial.
- A post-hoc analysis of the GATHER1 and GATHER2 data showed an up to 59% reduction in the rate of vision loss due to geographic atrophy associated with treatment with 2 mg avacincaptad pegol compared with sham treatment at 12 months.
- EyePoint Pharmaceuticals and Rallybio are partnering on research to evaluate Rallybio's complement component 5 inhibitor used in combination with EyePoint's proprietary Durasert technology to provide sustained intraocular drug delivery. The financial terms of the partnership were not disclosed, but their initial area of interest will focus on treating patients with geographic atrophy.
- Horizon Therapeutics presented new MRI imaging data from the phase 3 clinical trial of inebilizumab-cdon (Uplizna) showing that treatment with the drug reduced the formation of subclinical optic nerve lesions in patients with neuromyelitis optic spectrum disorder. The drug is the first FDA-approved B-cell depleting monotherapy for treatment of adults with neuromyelitis optic spectrum disorder.

Want more retina news from *Eyewire+*?

ND4 mitochondrial gene. All subjects received an intravitreal injection of lenadogene nolparvovec in their first affected eye, with the second eye randomized to either a second injection of lenadogene nolparvovec or placebo.

The 3-year post-treatment data found that the treatment effect was maintained over time for all subjects. There also continued to be a favorable safety profile with the main adverse ocular event being mild intraocular inflammation, which was responsive to treatment.

1. GenSight reports topline efficacy and safety results at 3 years post-treatment with Lumevoq [press release]. Eyewire+. March 14, 2023. Accessed March 21, 2023. eyewire.news/news/gensight-reports-topline-efficacy-and-safety-results-at-3-years-post-treatment-with-lumevoq

ELECTRICAL STIMULATION THERAPY FOR RP SHOWS PROMISE

A team of researchers have found that noninvasive electrical stimulation therapy significantly slowed disease progression in patients with retinitis pigmentosa (RP).[1] The OkuStim device (Okuvision) uses transcorneal electrical stimulation (TES), in which an electrode is placed on the lower lid in contact with the inferior corneal limbus to deliver electrical impulses.[2] In the study, 52 total participants (average age = 42 years) received weekly treatment with either TES (n = 32) or sham (n = 20) for 1 year. Participants in the investigative treatment group experienced a 64% lower decrease in visual field area measured by kinetic perimetry in the treated eye versus their contralateral untreated eye (P = .013) and a 72% lower decrease than the sham group (P = .103). The degree of progression delay was dose-dependent on the extent of electrical stimulation applied. The most common adverse event (n = 23) was symptoms of dry eye.[1]

These data suggest TES has the potential to significantly slow visual field loss not only in early disease stages, but also in moderate and severe RP, as decrease in progression did not correlate with baseline visual acuity.[1]

1. Stett A, Schatz A, Gekeler F, Franklin J. Transcorneal electrical stimulation dose-dependently slows the visual field loss in retinitis pigmentosa. *Transl Vis Sci Technol*. 2023;12(2):29.
2. New evidence of efficacy of transcorneal electrical stimulation (TES) [press release]. Okuvision. February 27, 2023. Accessed March 20, 2023. okuvision.de/en/new-evidence-of-efficacy-of-transcorneal-electrical-stimulation

DR IN AMERICAN INDIAN AND ALASKA NATIVE POPULATIONS LOWER THAN PREVIOUSLY ESTIMATED

The results of a study published in *JAMA Ophthalmology* suggest that estimates of diabetic retinopathy (DR) incidence and progression in American Indian and Alaska Native individuals may be lower than the rates initially estimated before 1992.[1]

The retrospective cohort study was conducted from January 2015 to December 2019 and used data from the Indian Health Service teleophthalmology program. The cohort included 8,374 individuals with diabetes and no evidence of DR or mild nonproliferative DR (NPDR) in 2015 who were reexamined at least once between 2016 and 2019 using nonmydriatic ultra-widefield imaging or nonmydriatic fundus photography. Of those with no DR in 2015, 18% had mild NPDR or worse upon reexamination, 6.2% had moderate NPDR or worse, and 0.1% had proliferative DR. Of patients with mild NPDR in 2015, 27.2% progressed to moderate NPDR or worse, and 2.3% to severe NPDR or worse.[1]

The authors concluded that these new data provide lower estimates than previously reported in this population and suggest that follow-up intervals may safely be extended for patients with no DR or mild NPDR if compliance is not compromised. ■

1. Fonda SJ, Bursell SE, Lewis DG, Clary D, Shahon D, Cavallerano J. Incidence and progression of diabetic retinopathy in American Indian and Alaska Native individuals served by the Indian Health Service, 2015-2019 [Preprint published online ahead of print March 9, 2023]. *JAMA Ophthalmology*.

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

For vision and anatomic outcomes

EYLEA Is the #1 Prescribed Anti-VEGF FDA Approved for DME[1,*]

*IQVIA U.S. Medical Claims Data: number of injections administered from Q4 2020 through Q3 2021; Data on file.

Established efficacy data

Proven **vision and anatomic outcomes** in DME[1,2]

Demonstrated safety profile

Evaluated in **over 850 patients** across DME pivotal studies[1]

Real-world experience

More than 57 million doses administered worldwide since launch across all indications[1,3]

Broad market access

82% of lives with DME have access to EYLEA first line with **no step edit** required[1,†]

†Data represent payers across the following channels as of November 2022: Medicare Part B, Commercial, Medicare Advantage, and VA. Individual patient coverage is subject to patient's specific plan.

FIND OUT MORE
at hcp.eylea.us

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

- EYLEA is contraindicated in patients with ocular or periocular infections, active intraocular inflammation, or known hypersensitivity to aflibercept or to any of the excipients in EYLEA.

WARNINGS AND PRECAUTIONS

- Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately. Intraocular inflammation has been reported with the use of EYLEA.
- Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with VEGF inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately.
- There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA compared with 1.5% (9 out of 595) in patients treated with ranibizumab; through 96 weeks, the incidence was 3.3% (60 out of 1824) in the EYLEA group compared with 3.2% (19 out of 595) in the ranibizumab group. The incidence in the DME studies from baseline to week 52 was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

ADVERSE REACTIONS

- Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment.
- The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and intraocular pressure increased.
- Patients may experience temporary visual disturbances after an intravitreal injection with EYLEA and the associated eye examinations. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

INDICATIONS

EYLEA® (aflibercept) Injection 2 mg (0.05 mL) is indicated for the treatment of patients with Neovascular (Wet) Age-related Macular Degeneration (AMD), Macular Edema following Retinal Vein Occlusion (RVO), Diabetic Macular Edema (DME), and Diabetic Retinopathy (DR).

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

References: 1. EYLEA® (aflibercept) Injection full U.S. Prescribing Information. Regeneron Pharmaceuticals, Inc. February 2023. **2.** Brown DM, Schmidt-Erfurth U, Do DV, et al. Intravitreal aflibercept for diabetic macular edema: 100-week results from the VISTA and VIVID studies. *Ophthalmology.* 2015;122(10):2044-2052. doi:10.1016/j.ophtha.2015.06.017 **3.** Data on file. Regeneron Pharmaceuticals, Inc.

REGENERON®

777 Old Saw Mill River Road, Tarrytown, NY 10591 02/2023 EYL.23.02.0167

EYLEA® (aflibercept) Injection
For Intravitreal Injection

BRIEF SUMMARY—Please see the EYLEA full Prescribing Information available on HCP.EYLEA.US for additional product information.

1 INDICATIONS AND USAGE
EYLEA is a vascular endothelial growth factor (VEGF) inhibitor indicated for the treatment of patients with:

Neovascular (Wet) Age-Related Macular Degeneration (AMD), Macular Edema Following Retinal Vein Occlusion (RVO), Diabetic Macular Edema (DME), Diabetic Retinopathy (DR).

4 CONTRAINDICATIONS

4.1 Ocular or Periocular Infections
EYLEA is contraindicated in patients with ocular or periocular infections.

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

4.3 Hypersensitivity
EYLEA is contraindicated in patients with known hypersensitivity to aflibercept or any of the excipients in EYLEA. Hypersensitivity reactions may manifest as rash, pruritus, urticaria, severe anaphylactic/anaphylactoid reactions, or severe intraocular inflammation.

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis and Retinal Detachments
Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments [*see Adverse Reactions (6.1)*]. Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately [*see Patient Counseling Information (17)*].

5.2 Increase in Intraocular Pressure
Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA [*see Adverse Reactions (6.1)*]. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with vascular endothelial growth factor (VEGF) inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately.

5.4 Thromboembolic Events
There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA compared with 1.5% (9 out of 595) in patients treated with ranibizumab; through 96 weeks, the incidence was 3.3% (60 out of 1824) in the EYLEA group compared with 3.2% (19 out of 595) in the ranibizumab group. The incidence in the DME studies from baseline to week 52 was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

6 ADVERSE REACTIONS
The following potentially serious adverse reactions are described elsewhere in the labeling:
- Hypersensitivity [*see Contraindications (4.3)*]
- 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 (5.4)*]

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 other clinical trials of the same or another drug and may not reflect the rates observed in practice.
A total of 2980 adult patients treated with EYLEA constituted the safety population in eight phase 3 studies. Among those, 2379 patients were treated with the recommended dose of 2 mg. Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment. The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and intraocular pressure increased.

Neovascular (Wet) Age-Related Macular Degeneration (AMD). The data described below reflect exposure to EYLEA in 1824 patients with wet AMD, including 1223 patients treated with the 2-mg dose, in 2 double-masked, controlled clinical studies (VIEW1 and VIEW2) for 24 months (with active control in year 1).
Safety data observed in the EYLEA group in a 52-week, double-masked, Phase 2 study were consistent with these results.

Table 1: Most Common Adverse Reactions (≥1%) in Wet AMD Studies

	Baseline to Week 52		Baseline to Week 96	
Adverse Reactions	**EYLEA (N=1824)**	**Active Control (ranibizumab) (N=595)**	**EYLEA (N=1824)**	**Control (ranibizumab) (N=595)**
Conjunctival hemorrhage	25%	28%	27%	30%
Eye pain	9%	9%	10%	10%
Cataract	7%	7%	13%	10%
Vitreous detachment	6%	6%	8%	8%
Vitreous floaters	6%	7%	8%	10%
Intraocular pressure increased	5%	7%	7%	11%
Ocular hyperemia	4%	8%	5%	10%
Corneal epithelium defect	4%	5%	5%	6%
Detachment of the retinal pigment epithelium	3%	3%	5%	5%
Injection site pain	3%	3%	3%	4%
Foreign body sensation in eyes	3%	4%	4%	4%
Lacrimation increased	3%	1%	4%	2%
Vision blurred	2%	2%	4%	3%
Intraocular inflammation	2%	3%	3%	4%
Retinal pigment epithelium tear	2%	1%	2%	2%
Injection site hemorrhage	1%	2%	2%	2%
Eyelid edema	1%	2%	2%	3%
Corneal edema	1%	1%	1%	1%
Retinal detachment	<1%	<1%	1%	1%

Less common serious adverse reactions reported in <1% of the patients treated with EYLEA were hypersensitivity, retinal tear, and endophthalmitis.

Macular Edema Following Retinal Vein Occlusion (RVO). The data described below reflect 6 months exposure to EYLEA with a monthly 2 mg dose in 218 patients following central retinal vein occlusion (CRVO) in 2 clinical studies (COPERNICUS and GALILEO) and 91 patients following branch retinal vein occlusion (BRVO) in one clinical study (VIBRANT).

Table 2: Most Common Adverse Reactions (≥1%) in RVO Studies

	CRVO		BRVO	
Adverse Reactions	**EYLEA (N=218)**	**Control (N=142)**	**EYLEA (N=91)**	**Control (N=92)**
Eye pain	13%	5%	4%	5%
Conjunctival hemorrhage	12%	11%	20%	4%
Intraocular pressure increased	8%	6%	2%	0%
Corneal epithelium defect	5%	4%	2%	0%
Vitreous floaters	5%	1%	1%	0%
Ocular hyperemia	5%	3%	2%	2%
Foreign body sensation in eyes	3%	5%	3%	0%
Vitreous detachment	3%	4%	2%	0%
Lacrimation increased	3%	4%	3%	0%
Injection site pain	3%	1%	1%	0%
Vision blurred	1%	<1%	1%	1%
Intraocular inflammation	1%	1%	0%	0%
Cataract	<1%	1%	5%	0%
Eyelid edema	<1%	1%	1%	0%

Less common adverse reactions reported in <1% of the patients treated with EYLEA in the CRVO studies were corneal edema, retinal tear, hypersensitivity, and endophthalmitis.

Diabetic Macular Edema (DME) and Diabetic Retinopathy (DR). The data described below reflect exposure to EYLEA in 578 patients with DME treated with the 2-mg dose in 2 double-masked, controlled clinical studies (VIVID and VISTA) from baseline to week 52 and from baseline to week 100.

Table 3: Most Common Adverse Reactions (≥1%) in DME Studies

	Baseline to Week 52		Baseline to Week 100	
Adverse Reactions	**EYLEA (N=578)**	**Control (N=287)**	**EYLEA (N=578)**	**Control (N=287)**
Conjunctival hemorrhage	28%	17%	31%	21%
Eye pain	9%	6%	11%	9%
Cataract	8%	9%	19%	17%
Vitreous floaters	6%	3%	8%	6%
Corneal epithelium defect	5%	3%	7%	5%
Intraocular pressure increased	5%	3%	9%	5%
Ocular hyperemia	5%	6%	5%	6%
Vitreous detachment	3%	3%	8%	6%
Foreign body sensation in eyes	3%	3%	3%	3%
Lacrimation increased	3%	2%	4%	2%
Vision blurred	2%	2%	3%	4%
Intraocular inflammation	2%	<1%	3%	1%
Injection site pain	2%	<1%	2%	<1%
Eyelid edema	<1%	1%	2%	1%

Less common adverse reactions reported in <1% of the patients treated with EYLEA were hypersensitivity, retinal detachment, retinal tear, corneal edema, and injection site hemorrhage.
Safety data observed in 269 patients with nonproliferative diabetic retinopathy (NPDR) through week 52 in the PANORAMA trial were consistent with those seen in the phase 3 VIVID and VISTA trials (see Table 3 above).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Risk Summary
Adequate and well-controlled studies with EYLEA have not been conducted in pregnant women. Aflibercept produced adverse embryofetal effects in rabbits, including external, visceral, and skeletal malformations. A fetal No Observed Adverse Effect Level (NOAEL) was not identified. At the lowest dose shown to produce adverse embryofetal effects, systemic exposures (based on AUC for free aflibercept) were approximately 6 times higher than AUC values observed in humans after a single intravitreal treatment at the recommended clinical dose [*see Animal Data*].
Animal reproduction studies are not always predictive of human response, and it is not known whether EYLEA can cause fetal harm when administered to a pregnant woman. Based on the anti-VEGF mechanism of action for aflibercept, treatment with EYLEA may pose a risk to human embryofetal development. EYLEA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
All pregnancies have a background risk of birth defect, loss, or 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 and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data
Animal Data
In two embryofetal development studies, aflibercept produced adverse embryofetal effects when administered every three days during organogenesis to pregnant rabbits at intravenous doses ≥3 mg per kg, or every six days during organogenesis at subcutaneous doses ≥0.1 mg per kg.
Adverse embryofetal effects included increased incidences of postimplantation loss and fetal malformations, including anasarca, umbilical hernia, diaphragmatic hernia, gastroschisis, cleft palate, ectrodactyly, intestinal atresia, spina bifida, encephalomeningocele, heart and major vessel defects, and skeletal malformations (fused vertebrae, sternebrae, and ribs; supernumerary vertebral arches and ribs; and incomplete ossification). The maternal No Observed Adverse Effect Level (NOAEL) in these studies was 3 mg per kg. Aflibercept produced fetal malformations at all doses assessed in rabbits and the fetal NOAEL was not identified. At the lowest dose shown to produce adverse embryofetal effects in rabbits (0.1 mg per kg), systemic exposure (AUC) of free aflibercept was approximately 6 times higher than systemic exposure (AUC) observed in adult patients after a single intravitreal dose of 2 mg.

8.2 Lactation
Risk Summary
There is no information regarding the presence of aflibercept in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production/excretion. Because many drugs are excreted in human milk, and because the potential for absorption and harm to infant growth and development exists, EYLEA is not recommended during breastfeeding. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for EYLEA and any potential adverse effects on the breastfed child from EYLEA.

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 after the last intravitreal injection of EYLEA.

Infertility
There are no data regarding the effects of EYLEA on human fertility. Aflibercept adversely affected female and male reproductive systems in cynomolgus monkeys when administered by intravenous injection at a dose approximately 1500 times higher than the systemic level observed in adult patients with an intravitreal dose of 2 mg. A No Observed Adverse Effect Level (NOAEL) was not identified. These findings were reversible within 20 weeks after cessation of treatment.

8.4 Pediatric Use
The safety and effectiveness of EYLEA have been demonstrated in two clinical studies of pre-term infants with ROP. These two studies randomized pre-term infants between initial treatment with EYLEA or laser. Efficacy of each treatment is supported by the demonstration of a clinical course which was better than would have been expected without treatment.

8.5 Geriatric Use
In the clinical studies, approximately 76% (2049/2701) of patients randomized to treatment with EYLEA were ≥65 years of age and approximately 46% (1250/2701) were ≥75 years of age. No significant differences in efficacy or safety were seen with increasing age in these studies.

10 OVERDOSAGE
Overdosing with increased injection volume may increase intraocular pressure. Therefore, in case of overdosage, intraocular pressure should be monitored and if deemed necessary by the treating physician, adequate treatment should be initiated.

17 PATIENT COUNSELING INFORMATION
In the days following EYLEA administration, patients are at risk of developing endophthalmitis or retinal detachment. If the eye becomes red, sensitive to light, painful, or develops a change in vision, advise patients to seek immediate care from an ophthalmologist [*see Warnings and Precautions (5.1)*].
Patients may experience temporary visual disturbances after an intravitreal injection with EYLEA and the associated eye examinations [*see Adverse Reactions (6)*]. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

REGENERON®

Manufactured by:
Regeneron Pharmaceuticals, Inc.
777 Old Saw Mill River Road
Tarrytown, NY 10591

Issue Date: 02/2023
Initial U.S. Approval: 2011

Based on the February 2023 EYLEA® (aflibercept) Injection full Prescribing Information.

EYL.23.02.0006

PRACTICE PEARLS FROM THE 2022 RETINA FELLOWS FORUM

This year's guest speaker, David S. Boyer, MD, FASRS, discussed the three As of success.

BY REBECCA HEPP, EDITOR-IN-CHIEF

Second-year retina fellows gathered in early December for some much-anticipated learning and connecting. As the first class to interview for their fellowship virtually (thanks to the COVID-19 pandemic), the attendees were eager to spend time with each other and foster the lasting relationships that help define the field of retina. The 23rd annual Retina Fellows Forum, organized by Carl C. Awh, MD, FASRS; David R. Chow, MD, FASRS(C); and Tarek S. Hassan, MD, FASRS, was packed with panel discussions, case presentations, clinical lectures, and—as always—a few games.

This year's distinguished speaker was David S. Boyer, MD, FASRS, who spoke to the fellows about what he knows best: how to thrive in private practice (Figure). Dr. Boyer organized his lecture around the three As of success: availability, affability, and ability.

"Everyone here has ability, so we won't talk about that," he quipped. Below are his pearls for practice success in any setting.

ANSWER YOUR PHONE!

Availability is key, he began. Most patients work from 8 AM to 5 PM, as do their optometrists, so consider seeing patients earlier or later, Dr. Boyer suggested. "Saturdays are busy for optometrists, so being available for them is a significant referral driver."

Taking calls is the best way to build your practice and meet doctors in the community, he added. Many well-established retina specialists are too busy for new referrals—but those who are new to practice may not be. "If you are available to the referring physician when others are not, you can get those first few referrals," Dr. Boyer explained. "And if you do a good job, they will likely keep sending patients to you because you answer their calls and are available when they need you."

> "The Retina Fellows Forum is a one-of-a-kind meeting that lets the brightest next-generation retina specialists learn from and engage with leaders in the field. But equally as special, it fosters lifelong friendships among contemporaries–it brought back a lot of fun and nostalgic memories from my own experience 9 years ago!"
>
> – *Christina Y. Weng, MD, MBA, Retina Fellows Forum Faculty and Associate Professor, Ophthalmology, Baylor College of Medicine, Houston*

And those emergency calls at 10 PM? Take them. "Accept emergency patients with a smile and be happy, even if the emergency referral wasn't actually an emergency," Dr. Boyer explained. "Be grateful that the doctor thought of you as the right person to see their patient."

COMMUNICATE WITH KINDNESS

Constant contact with staff, patients, colleagues, and referring doctors is one of the most important parts of the job, but you must go about it the right way, he added. To build a successful practice, you must communicate with referring doctors about each patient's case, diagnosis, and ongoing care. "Some just want you to take care of the patient and leave them alone, but most doctors want communication," Dr. Boyer noted. "Whether you text, fax letters, or call, make sure you tell them what happened."

Treat staff with respect, he continued. "Yelling at them will not make them go faster," Dr. Boyer noted. "Really think before you blow up, and never have a confrontation in front of other employees. In the OR, the nurses are your friends, and upsetting them will only make the case take longer." Treating all the staff with respect will go a long way, he advised, eliciting agreement from the panel.

Dr. Boyer then spent time discussing the ins and outs of patient communication because that can make or break a practice. The number one thing to remember is that you should be a haven for your patients, he said. These patients are very upset, and they cling to every word, so be careful what you say. "Whatever you are going to do, make sure you are both on the same wavelength and the patient understands exactly what is going to happen," Dr. Boyer advised. Patients need to know what medicine they are getting, why they are getting it, and why you are prescribing a certain

RETINA FELLOWS FORUM

Figure. Drs. Hassan and Awh present Dr. Boyer with an engraved wine decanter as a thank you for attending the Retina Fellows Forum as the 2022 distinguished guest speaker.

drug. You do not want your idea of success to be different from theirs, he warned—that's a recipe for disappointment.

If you *do* have a patient with a bad result, take extra care of them. "Don't let them sit in the waiting room," he warned. "Never rush them through because you feel bad and don't want to be reminded of the bad outcome." Instead, face the patient, make eye contact, and let them speak. Your body language is important, so don't spend the entire time caring for the computer, he joked.

That brought the conversation around to second opinions. Not only should you have a low threshold to seek a second opinion if the patient is dissatisfied, but also never speak ill of another physician if you are the one providing the second opinion. "You weren't there, you don't know what happened, and you should never say that you could have done better," Dr. Boyer explained. "Don't dwell on what occurred; instead, tell the patient what you are going to do to help them."

"This was one of my favorite meetings of the year! They kept us motivated and engaged throughout the weekend and incorporated friendly competition through the surgical videos contest–Fellows Fighting at the Forum. This meeting is an invaluable resource to all senior surgical retina fellows."

– Hong-Uyen Hua, MD, Vitreoretinal Surgery Fellow, Cleveland Clinic Cole Eye Institute, Cleveland

"Fellows Forum was a fantastic experience. It was wonderful to network with industry, learn crucial practice pearls from leaders in the field, and connect with colleagues we didn't have the opportunity to meet in person during the virtual interviews due to COVID-19. What made it even better was the relaxed atmosphere. It was the perfect way to end the 2022 meeting series for fellowship."

– Maxwell Wingelaar, MD, Vitreoretinal Surgery Fellow, The Retina Institute, St. Louis, Missouri

FOSTER HOPE

Here, Dr. Boyer touched on an important aspect of patient care that can get lost in the shuffle of a busy practice: Give the patient hope. "Even if they will likely have monthly injections for life, you can share information about gene therapy or longer-acting drugs," he explained. "Patients don't want to hear that they are going blind from AMD, because they won't—the lights won't go out in the traditional sense, and they likely won't have problems for years, so give them hope." Even if he is seeing a trauma patient with little to no treatment options, he shares information about investigational technology if he can. This means that you must stay abreast of new treatments that you can share with your patients, he added.

EXTRA PRACTICE PEARLS

Throughout the session, Dr. Boyer provided many practice-building tips, including the following:

- As a new doctor, you have about 9 months to build your potential referral services. Talk to doctors in your own practice and meet with local doctors in the community.
- To start a clinical trial center, you must have complete buy-in from your partners. Once you have the green light, pick trials that benefit your patient population.
- Use your new office's billing practices; with coding, you don't want to stand out.
- Make handouts and use the AAO's handouts to educate patients; it helps them better understand the postoperative course and improves compliance.
- Don't talk about a previous patient in front of another patient; they internalize your words and assume that's how you talk about them once they leave.
- Don't be afraid to ask for help from your partners, who have likely seen plenty of uncommon cases.
- Stay active and engaged with the community and the field; write papers, attend meetings, go to society dinners, speak at hospitals, and meet with doctors in your area.

Most importantly, under promise and over deliver. ■

SAVE THE DATE

24th Annual Retina Fellows Forum
January 26-27, 2024
Check medconfs.com for details about registration information.

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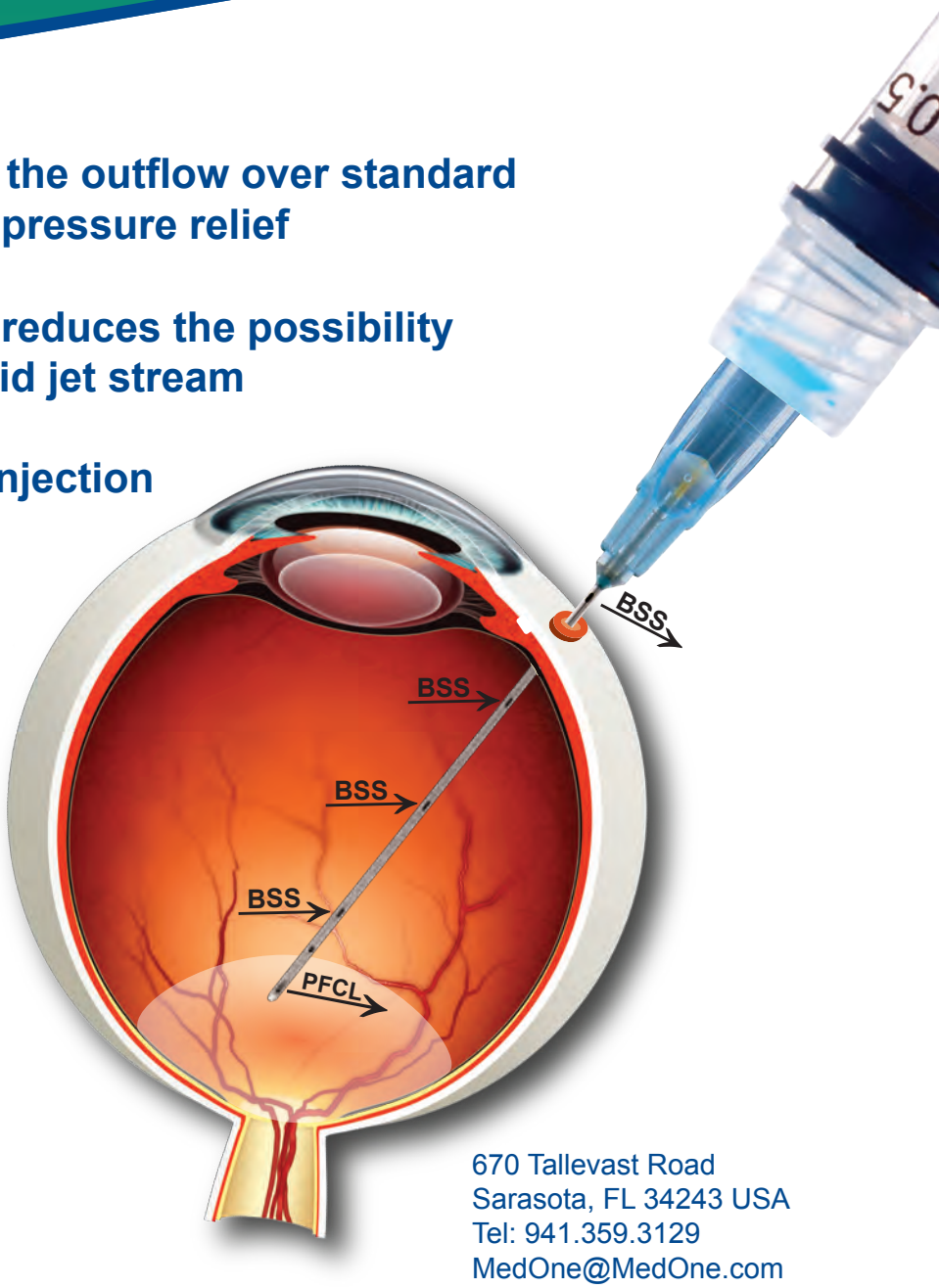

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WHERE IT ALL BEGAN

The parents of Murtaza Adam, MD, immigrated to the United States from India in the early 1980s. He was raised in southeastern Wisconsin and spent much of his youth exploring local trails, swimming and wakeboarding on the lake, experimenting with photography, and obsessing over astronomy and comparative religion. Academically, a lack of direction led him down a path with varied career options. Dr. Adam decided on a career in medicine because of the challenges, rewards, stories, and curiosities that come with treating disease and healing patients.

HIS PATH TO RETINA

Dr. Adam was on his MS3 anesthesia rotation at the Medical College of Wisconsin and had no concept of what an ophthalmologist did; he remembered little from the first-year medical school ophthalmology didactics. After placing a patient's IV, he followed them back to the OR for surgery with Dennis Han, MD, who became his first mentor in ophthalmology. What he witnessed in the OR defied his imagination, he recalled. "Beautiful" was the only word that came to mind when he first saw Dr. Han focus his microscope on the posterior pole. Dr. Adam was floored by the ingenuity, optics, and skill required to peel a membrane off of the macula. From that moment, he was sold on a career in retina.

SUPPORT ALONG THE WAY

He credits Dr. Han and Douglas J. Covert, MD, for their mentorship and encouragement to pursue a residency in ophthalmology. Many individuals during his residency and fellowship at Wills Eye Hospital in Philadelphia contributed to his professional and personal growth, including M. Ali Khan, MD, FACS; Christopher J. Brady, MD; John Pitcher, MD; Ehsan Rahimy, MD; Marc Spirn, MD; Joseph Maguire, MD; Julia A. Haller, MD; Arunan Sivalingam, MD; Sunir Garg, MD, FACS; Jason Hsu, MD; Omesh P. Gupta, MD, MBA; Carl Regillo, MD; and Allen C. Ho, MD. These people, and so many others, inspire him and are still sounding boards for questions and ideas.

Dr. Adam's Advice: Expect to feel challenged and distraught at times, but don't bottle those feelings up.

AN EXPERIENCE TO REMEMBER

Dr. Adam recalls treating a young patient in his first year of practice who presented with bilateral retinal detachments. She had a bumpy postoperative course but recovered well. Now, 5 years later, she is a third-year medical student who has aspirations to become a retina surgeon! She has already coauthored several abstracts and papers with Dr. Adam. He said that it has been a gratifying experience to mentor someone who has the makings of a future leader in retina and truly understands the journey of a retina patient.

ADVICE FOR THOSE WHO FOLLOW

No matter how many patients you treat in fellowship, cutting the umbilical cord of training is hard. Dr. Adam remembers feeling the true burden of responsibility on his shoulders after starting practice. The field of retina is simultaneously challenging and rewarding because retina specialists treat the most complex part of the eye in some of the most vulnerable patients. The retina always finds a way to humble us, and it is all too easy to forget your successes and linger on your failures. If you focus first and foremost on the patient in your chair, ask colleagues and mentors for help when you need it, and maintain the same level of curiosity you had in training, you have the recipe for an incredible career. ■

Murtaza Adam, MD, is a partner physician at Colorado Retina Associates in Denver. He is the chair of the Clinical Research department and serves as principal investigator on several trials. Dr. Adam is a speaker and/or consultant for Apellis, Genentech/Roche, NorthGauge Healthcare Advisors, Regeneron, and Regenxbio. He can be reached at **madam@retinacolorado.com.**

CATARACT FORMATION IN CHILDREN AFTER A PRIMARY VITRECTOMY

Shedding light on the rate and timing of cataract extractions for pediatric patients after vitrectomy.

BY PRETHY RAO, MD, MPH; EMMANUEL CHANG, MD, PHD; AND G. BAKER HUBBARD III, MD

Cataracts after pars plana vitrectomy are common in adults, but they pose a particular challenge in pediatric patients because of their ongoing visual development. The rate of cataract formation in adults after vitrectomy ranges between 45% and 80% within 6 months to 2 years of a primary vitrectomy.[1,2] Researchers have described mechanisms for cataract formation, including light toxicity, oxidation of lens proteins, increased oxygen tension, use of intraocular gas, and the length of operative time.[1] However, the rates and timing of cataract extraction after pediatric vitrectomy (< 18 years of age) are less established. Only a few studies report a low prevalence with specific retinal diseases, such as retinopathy of prematurity.[3] The scant literature is, in part, due to the rarity of pediatric retinal diseases and the paucity of pediatric retina surgeons.

Understanding the risk of cataract formation is important for counseling families and providing a multidisciplinary approach across comprehensive, pediatric ophthalmology, glaucoma, and pediatric retina specialties. To that end, our team took advantage of the unique opportunity the AAO IRIS Registry provides to study these rare rates on a larger scale. Through a grant sponsored by the Research to Prevent Blindness and the AAO IRIS Registry, we evaluated the rate and timing of cataract extraction after a primary pediatric vitrectomy in a cohort of patients included in the IRIS Registry between 2013 and 2019—a much larger cohort than we could have found otherwise. In this article, we describe the nuts, bolts, and ultimate results of the study.

THE NUTS AND BOLTS

The study had three main objectives:

- **Primary objective:** determine the rate of cataract extraction after any vitrectomy in patients younger than 18 years of age between 2013 and 2019.
- **Secondary objective:** determine the timing of cataract extraction after pediatric vitrectomy.
- **Tertiary objective:** determine the common etiologies and demographics associated with cataract extraction.

Between January 2013 and December 2019, a total of 821,152 eyes underwent a vitrectomy, of which 5,037 (0.6%) were pediatric. We further excluded eyes that had undergone previous cataract surgery or lensectomy before or at the time of their primary vitrectomy, leading to a final cohort of 4,127 eyes (3,579 patients).

Limitations of this study include the small sample size and the lack of current procedural terminology (CPT) codes and international classification of diseases codes specific to pediatric retinal disease and surgery. Additionally, this study may be underreporting the rates of cataract extraction because lensectomy is often bundled into retinal detachment (RD) repair codes (67108, 67113). Furthermore, pediatric RDs are challenging, and the severity of some RDs after primary repair may not warrant further surgery due to a poor prognosis.

WHAT WE FOUND

The average age at the time of the first vitrectomy was 10.35 years of age, with vitrectomy occurring more frequently in males (64.95%). There was also a significant number occurring predominantly in the southern United States (44.88%). The most common CPT vitrectomy code was 67113 for a complex RD repair, which accounted for 35% of all primary vitrectomies. On average, the eyes underwent 1.69 (range 1 to 6) vitrectomies before cataract extraction.

The overall rate of cataract extraction was 5.82% after a primary vitrectomy over the entire 6-year period. The 1- and 2-year incidences of cataract extraction after a primary vitrectomy were 3.94% and 4.18%, respectively. The average

THE RATE OF CATARACT EXTRACTION AFTER A PRIMARY PEDIATRIC VITRECTOMY IS LOW, REGARDLESS OF ETIOLOGY. HOWEVER, IF CATARACTS DEVELOP, NEARLY 85% OF EXTRACTIONS OCCUR WITHIN 2 YEARS OF A PRIMARY VITRECTOMY.

time to cataract surgery after a primary vitrectomy was 426.5 days (median 374.5 days).

Cataract extraction after a pediatric vitrectomy was a rare event. However, in those that developed cataracts, nearly 85% occurred within 2 years of the primary vitrectomy.

In a subset analysis, the rate of cataract extraction increased by age at the time of initial vitrectomy. The older a child was at the time of their initial vitrectomy, the higher the risk of undergoing cataract surgery. Less than 1% of pediatric eyes under the age of 2 required cataract surgery within 6 years of their vitrectomy, while nearly 10% of children ages 15 to 17 underwent cataract surgery. The most common etiology for a vitrectomy was a rhegmatogenous RD (28.8%).

WHAT MAY BE HAPPENING

The exact reason for the low rates is unknown, but it may be a function of the degree of vitreous removal and the goals of the surgery. In pediatric vitrectomy, the anterior hyaloid face is often left intact, and a "full" vitrectomy is minimized. The goals of surgery are often to relieve just enough tractional forces to allow the retina to settle; thus, the younger the patient, the more likely a greater amount of vitreous is left behind. For example, in RDs associated with stage 4A/B retinopathy of prematurity, the goal of the surgery is to relieve specific tractional forces (ridge to ridge, ridge to eyewall, ridge to optic nerve, or ridge to lens) rather than remove the entire anterior or posterior hyaloid. Children with persistent fetal vasculature also require vitrectomy, but a minimal vitrectomy is emphasized with the goal of cutting the stalk. In contrast, in older children undergoing vitrectomy secondary to rhegmatogenous RD or proliferative vitreoretinopathy, removing the posterior hyaloid and vitreous is key.

Age may also have a protective effect in and of itself. It may be that younger children have a higher metabolic capacity to counteract the presumed damage from oxygen-induced radicals compared with older children.

The type of tamponade may also be a factor. Our study did not specifically evaluate different tamponade agents, but macular holes and primary and complex RD codes (67042, 67108, and 67113) often require a tamponade agent, such as gas or silicone oil. Our study demonstrated higher cataract extraction rates in these specific codes (3% to 10%) and lowest with primary vitrectomy-only codes (CPT 67036, approximately 1.84%).

WHERE WE ENDED UP

The rate of cataract extraction after a primary pediatric vitrectomy is low, regardless of etiology. However, if cataracts develop, nearly 85% of extractions occur within 2 years of a primary vitrectomy. The low rates of cataract extraction in the pediatric population are consistent with prior studies in children who underwent a lens-sparing vitrectomy for retinopathy of prematurity (5.9%) and in younger adults (< 50 years of age).[3-4] These rates aid in patient and parent counseling, as well as care coordination and planning across the retina, pediatric retina, and comprehensive specialties. ■

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CHOROIDAL METASTASIS ASSOCIATED WITH OROPHARYNGEAL CARCINOMA

A rare case highlights pearls for diagnosing and treating bilateral metastatic choroidal lesions.

BY BREN DAVIS, MD; TRAVIS PECK, MD; AND BRIAN K. DO, MD

The oropharynx comprises the middle part of the throat, located between the nasopharynx and hypopharynx, and includes the soft palate, walls of the throat, tonsils, and posterior one-third of the tongue. Risk factors for oropharyngeal carcinoma (OPC) include human papilloma virus (HPV) infection and excessive alcohol and tobacco use.

Orbital involvement in OPC is extremely rare. Of all uveal metastases associated with OPC, 90% are to the choroid, while 8% are to the iris and 2% are to the ciliary body.[1] The choroid is particularly vulnerable because of its robust blood supply; choroidal metastasis is the most common type of intraocular malignancy.[1,2] There are published reports of OPC from the gingiva, tongue, buccal mucosa, and tonsil metastasizing to the choroid.[3-7]

Shields et al described many of the clinical features of uveal metastases in a retrospective analysis of 1,111 patients.[1] Breast and lung were the most common primary sites, responsible for 37% and 27% of cases, respectively. The primary cancer was diagnosed prior to discovery of uveal metastasis in 67% of patients. The primary site was never determined in 16% of cases.

This report describes a case of presumed choroidal metastasis secondary to OPC and details the patient's examination findings, multimodal imaging, and response to therapy.

CASE REPORT

A 44-year-old man was referred for evaluation by his ophthalmologist due to blurry vision and presence of multiple deep retinal or choroidal lesions within the posterior pole in each eye.

His past medical history included hypertension, hypothyroidism, and OPC of the left tonsil. Biopsy of the affected tonsil previously demonstrated HPV-positive squamous cell carcinoma (SCC), for which he had previously undergone radiotherapy and three cycles of cisplatin chemotherapy. After completion of treatment, his tumor was reported to have been in remission for 18 months prior to onset of symptoms. Shortly before the onset of his visual symptoms, positron emission tomography (PET) and CT scans suggested metastases to the hilar and mediastinal lymph nodes. Bronchoscopy and biopsy confirmed metastatic carcinoma. Soon after, repeat PET and MRI of the brain suggested additional metastases in the bones, muscles, and brain. Around the same time, he began to note blurring of his vision in each eye, which was subjectively worse in his left eye.

SEROUS RETINAL DETACHMENT IN THE SETTING OF MULTIFOCAL CHOROIDAL LESIONS SHOULD BE HIGHLY CONCERNING FOR A METASTATIC PROCESS.

His past ocular history was significant for mild myopia, for which he wore glasses while driving at night. At presentation, his BCVA was 20/50 OU with no relative afferent pupillary defect in either eye. IOPs were 12 mm Hg OD and 11 mm Hg OS. The anterior segment examination was unremarkable. There were no vitreous opacities or cells noted. The optic nerve was normal in appearance with normal cup-to-disc ratios and sharp margins without edema. The retinal vasculature appeared to have normal course and caliber.

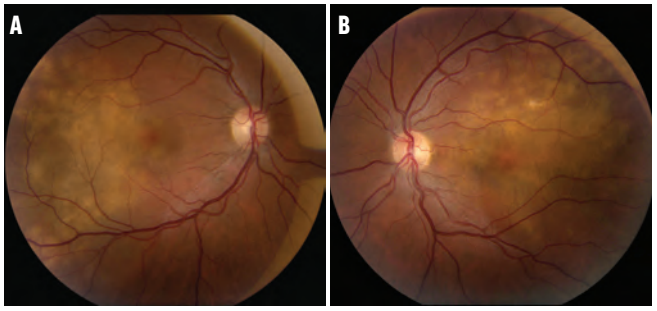

Figure 1. Color fundus photographs of the right (A) and left (B) eyes at presentation.

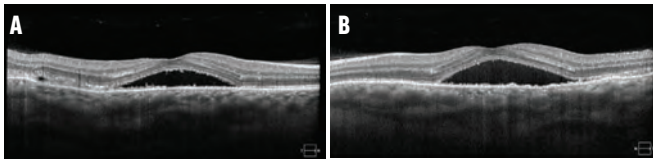

Figure 2. Macular OCT of the right (A) and left (B) eyes at presentation.

IMAGING

Dilated fundus examination showed numerous discrete yellow/white choroidal lesions with areas of confluence in the temporal macula in each eye that extended from the fovea to the temporal midperiphery (Figure 1).

Spectral-domain OCT (SD-OCT) revealed retinal thickening, significant ellipsoid zone and interdigitation zone disruption, and irregularity of the choroid/retinal pigment epithelium in the temporal macula of each eye. Subretinal fluid extended under the fovea with "shaggy" photoreceptors and subretinal hyperreflective material. The choroid appeared thickened, with obscuration of the deep choroidal vasculature (Figure 2). ICG angiography showed large, wedge-shaped areas of hypocyanescence extending from the fovea to the temporal mid-periphery in the right eye and from the peripapillary area to the temporal mid-periphery in the left eye (Figure 3).

The presumed diagnosis at this time was bilateral choroidal metastases from OPC, given the absence of clinical or angiographic signs of intraocular inflammation. He was instructed to follow-up in 1 month. Shortly thereafter, he began eight cycles of carboplatin and 5-fluorouracil chemotherapy, combined with pembrolizumab immunotherapy.

At follow-up, he reported significant improvement in his visual acuity but still noted a mild metamorphopsia, with mild blurring that was worse in his peripheral visual field. His BCVA had improved to 20/20 OU. The choroidal lesions appeared smaller and less prominent in each eye on fundus examination (Figure 4). On SD-OCT, the subretinal fluid had resolved in the right eye and had improved significantly in the left (Figure 5).

DISCUSSION

This patient demonstrated many of the typical characteristics of choroidal metastases. In a large review by Shields et al, 73% of patients with choroidal metastases were found to have

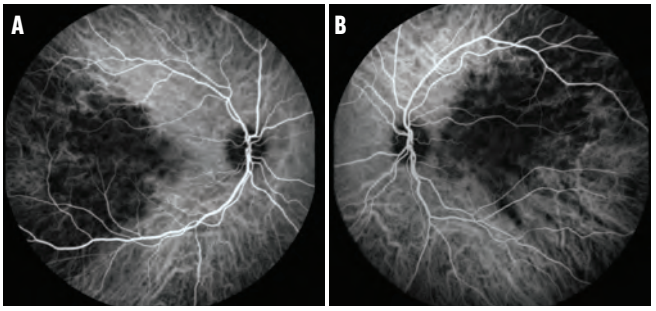

Figure 3. ICG angiography of the right (A) and left (B) eyes at presentation.

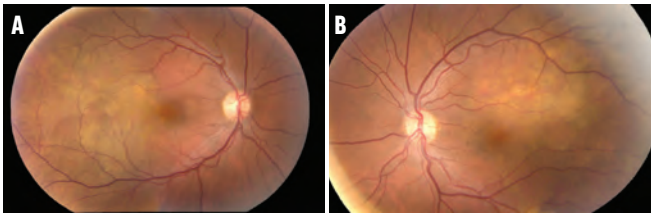

Figure 4. Fundus photographs of the right (A) and left (B) eyes at the 1-month follow-up.

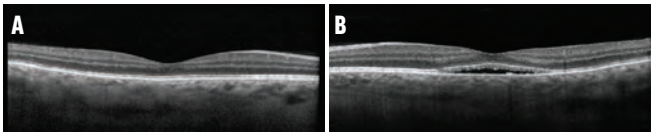

Figure 5. Macular SD-OCT of the right (A) and left (B) eyes at the 1-month follow-up.

subretinal fluid and 57% showed retinal pigment epithelium alterations.[2] The epicenter of the lesions was located between the equator and the macula in 80% of patients; in the macula in 12%; and between the equator and ora serrata in 8%.[2]

Our patient had subretinal fluid and multiple, bilateral, yellow choroidal lesions. The epicenter was between the equator and the macula temporally. These features helped to distinguish the lesions from other entities that could be part of the differential diagnosis for choroidal metastases, such as choroidal melanoma, choroidal nevus, or other choroidal tumors. In addition, there was no anterior chamber or vitreous cell, as would typically accompany the serous retinal detachments seen in Vogt-Koyanagi-Harada syndrome or other inflammatory or infectious conditions.

In cases suspicious for choroidal metastasis where there is no known primary cancer, clinicians should refer patients for prompt systemic imaging and work-up with an oncologist. Chemotherapy for the primary malignancy is the first-line treatment for choroidal metastases. As was seen in our patient, choroidal lesions and secondary subretinal fluid often respond well to systemic treatment. In cases of visually significant subretinal fluid that persists despite systemic treatment, photodynamic therapy has been used with success.[8]

Clinicians may also consider plaque brachytherapy or external beam radiation therapy (EBRT) for unresponsive lesions. Brachytherapy is preferred for smaller choroidal malignancies.[9] Brachytherapy and EBRT often cause significant ocular side effects, including retinopathy,

(Continued on page 54)

MACULAR HOLE FORMATION AFTER PPV WITH ILM PEELING

A serious potential complication of surgical management for optic disc pit maculopathy.

BY FARHAD FAZEL, MD; AMIN DEHGHAN, MD; NILOOFAR JAVADI, MD; AND MOHAMMADREZA FAZEL, MD

Optic disc pit (OPD) can cause visual impairment in 75% of cases due to a type of serous retinal detachment called optic disc pit maculopathy (ODP-M).[1,2] ODP can be confirmed by detecting a grayish depression in the optic nerve on fundoscopy. OCT can be used to detect the presence of subretinal fluid.[1]

In addition to conservative management, several interventions have been proposed to treat this condition, with pars plana vitrectomy (PPV) being the most common.[1] Given the key role of the internal limiting membrane (ILM) in the development of ODP-M, PPV with ILM peeling is a promising surgical management for this condition.[3,4]

This report describes macular hole formation as a severe complication that occurred a few weeks after the surgical management of a patient with ODP-M.

CASE REPORT

A 42-year-old woman presented with blurred vision for almost 1 year. Her medical and surgical histories were unremarkable. On initial examination, VA was 20/20 OD and 1 m counting fingers OS. Her pupils were round with no relative afferent pupillary defect. Anterior segment findings and IOPs were normal in each eye. Dilated fundus examination revealed macular elevation and an ODP in her left eye. Spectral-domain OCT (SD-OCT) confirmed macular schisis extending from the ODP with serous macular detachment, which led to the diagnosis of ODP-M (Figure 1A).

The patient underwent a three-port fovea-sparing PPV for hyaloid detachment. After ILM peeling, fluid-gas exchange was performed with 20% SF_6. At the 1-month follow-up, the patient reported improvements in her vision, and the examination demonstrated an improvement in VA to 20/200 OS. Imaging showed a decrease in subretinal fluid (Figure 1B).

On postoperative day 45, however, the patient complained of sudden vision loss to 2 m counting fingers OS. Subsequent SD-OCT showed a full-thickness macular hole (Figure 2A). Surgical management was ultimately selected with the patient's consent. During the second surgery, which occurred 3 months after the initial procedure, ILM peeling was extended, a free ILM flap was inserted into the hole, and fluid-gas exchange was performed with 20% C_3F_8. The patient complied with the recommended prone position for 1 week. Thirty days later, SD-OCT showed the closure of the macular hole (Figure 2B). VA improved to 20/100 OS and remained stable at the 1-year follow-up.

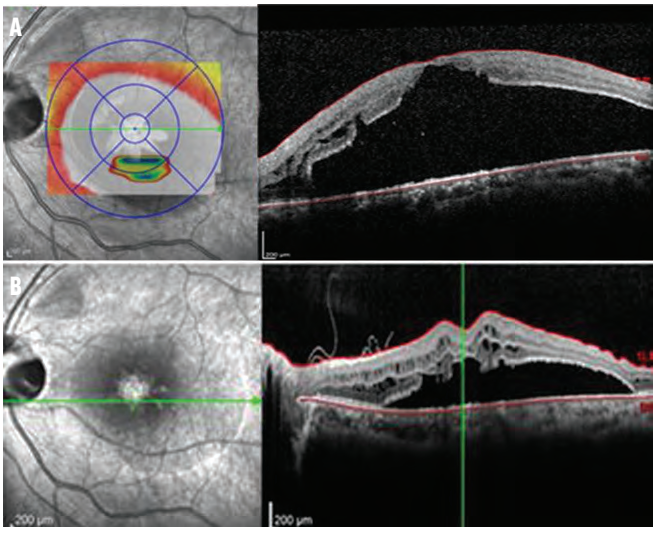

Figure 1. OCT showed an ODP and serous macular detachment in the left eye (A). Subretinal fluid was partially absorbed after PPV with ILM peeling (B).

DISCUSSION

As a rare congenital anomaly, ODP can cause progressive vision loss through serous macular detachment known

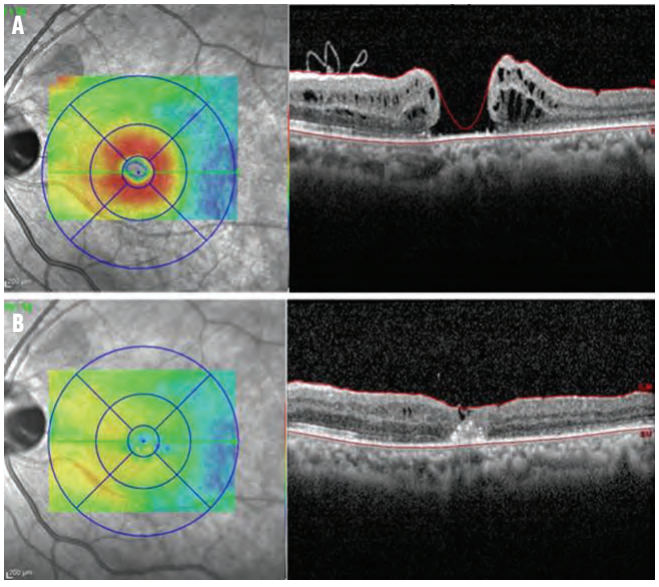

Figure 2. Macular hole formation was confirmed on OCT as the cause of our patient's sudden visual loss on postoperative day 45 (A). Imaging 30 days later revealed complete closure of the macular hole (B).

as ODP-M. Subretinal fluid has three types: intravascular, cerebrospinal, and vitreous. In our patient, fluorescein angiography ruled out intravascular leakage into the subretinal space; nevertheless, both cerebrospinal fluid and vitreous fluid can cause the accumulation of subretinal fluid.[1] ODP alone is not adequately symptomatic and is often diagnosed only after developing maculopathy, typically in the fourth or fifth decades of life.[2] A decrease in VA to between 20/25 and counting fingers is the main symptom of ODP-M.[1]

The age of our patient was within the typical age range for developing ODP-M, and vision loss was her only symptom. A small hypopigmented grayish depression in the optic nerve, detected during careful ophthalmic examination, suggested ODP. Macular changes in ODP-M include retinal holes, mottled retinal pigment epithelium, and macular elevation.[5] The origin of the fluid remains unknown, and the exact pathogenesis of the maculopathy is not fully understood. Although some cases have been reported to resolve spontaneously, most cases require surgical intervention to treat ODP-M and prevent loss of vision.

Currently, there is no definite treatment for these patients, and several surgical methods have been described, including PPV (temporal ODP), and macular elevation was reported in the present case. The ultimate diagnosis was made using SD-OCT, in which retinal schisis expanded from the pit to the macula.[1]

None of the interventions proposed to manage ODP-M have been reported to be a definitive strategy, owing to the disadvantages associated with each.[5] For example, the drawbacks of laser photocoagulation include variable and often prolonged time to improved visual acuity and significant visual field defects caused by laser scars.[2] A case series on intravitreal gas tamponade reported visual acuity improvements in only half of the participants, which is not a convincing outcome.[6]

Nowadays, PPV is considered integral to combination therapies, and surgeons incorporate laser photocoagulation, gas tamponade, or ILM peeling with PPV to enhance the outcomes.[2] PPV with ILM peeling is thought to be useful for resolving the vitreoretinal traction; however, ILM peeling appears to be a risk factor for splitting retinal layers.[1] Shukla et al reported a case series in which four of seven participants developed full-thickness macular holes 1 month after PPV with ILM peeling, laser photocoagulation, and gas tamponade.[3] Our patient underwent PPV with ILM peeling and gas tamponade, and a full-thickness macular hole was similarly observed on postoperative day 45, which required additional surgical management.

UNDERSTAND THE RISKS

Although PPV with ILM peeling and gas tamponade is a common surgical combination for managing ODP-M, in our case, macular hole formation proved to be a serious postoperative complication. ■

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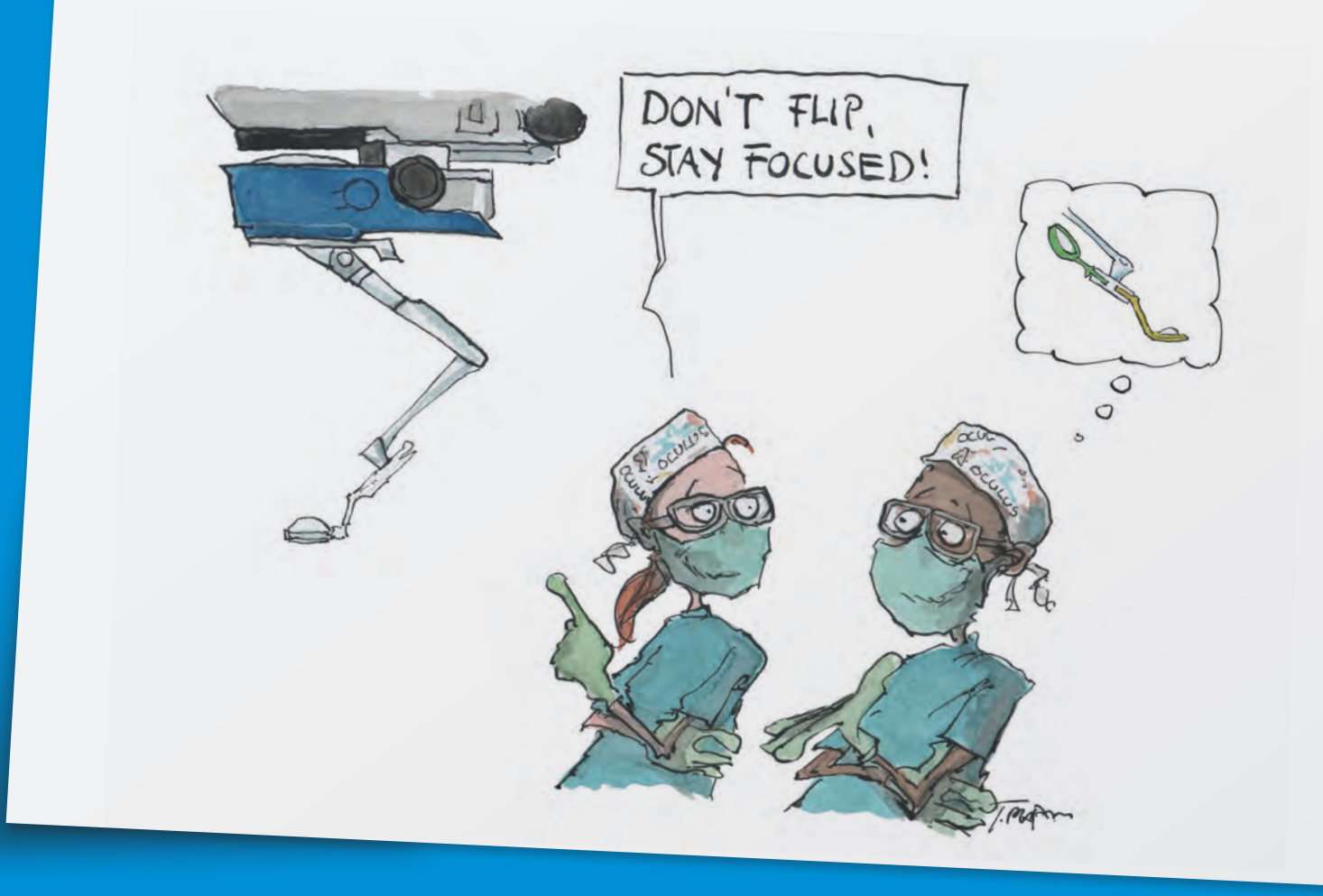

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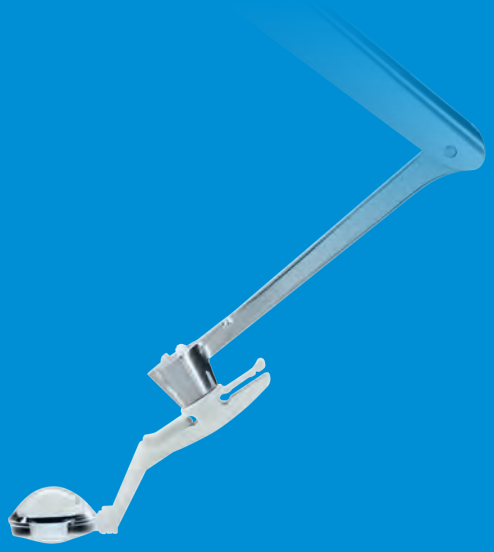

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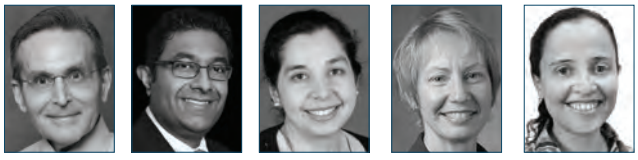
USING OCTA IN YOUR CLINIC

Experts discuss the benefits of this new imaging modality, as well as pitfalls to avoid.

A conversation with Philip J. Rosenfeld, MD, PhD; SriniVas Sadda, MD; and Nadia K. Waheed, MD, MPH
Moderated by Cynthia A. Toth, MD, and Amani A. Fawzi, MD



OCT angiography (OCTA), invented in the mid 2000s, has made its way to the clinic already, yet much debate exists on whether it provides reproducible standardized imaging. For example, if a vessel isn't visible on OCTA, is it a problem with the imaging system or is it indeed missing? To address some of these concerns and help parse out where OCTA fits into our retina imaging armamentarium, we sat down with experts in the field. Here's what they had to say.

– Cynthia A. Toth, MD, and Amani A. Fawzi, MD

DR. TOTH: HOW DOES OCTA FIT INTO THE OVERALL IMAGING PICTURE IN THE RETINA CLINIC?

Philip J. Rosenfeld, MD, PhD: I think of OCTA in two different realms: clinical care and research. The research realm is exciting, but we need to focus more on how the clinician benefits from using this technology. I used to think of it as purely an angiographic tool, but now I think of it as one-stop shopping because an OCTA scan combines both structural and angiographic information.

For angiographic assessment of a patient with AMD, diabetic retinopathy, or a retinal vein occlusion, I use OCTA scans. I can't remember the last time I performed fluorescein angiography (FA) or ICG angiography (ICGA) on a patient with a macular or retinal vascular disease. That's where wide-field swept-source and spectral-domain OCTA imaging are so valuable. I think of OCTA as a single imaging modality from which we can extract multimodal images. While I may not look at the angiographic component right away, I often go back and look at it later.

DR. FAWZI: ARE THERE SPECIFIC PATIENTS FOR WHOM YOU GET AN OCTA?

SriniVas Sadda, MD: I almost never get an OCTA for a patient with a posterior vitreous detachment, but just

Want to hear the conversation as a podcast? Scan the QR code or visit ***New Retina Radio*** on Eyetube at eyetube.net/podcasts.

AT A GLANCE

- OCT angiography (OCTA) may not be multimodal imaging per se, but it does provide different modes of visualization—an angiogram, a structural image, and en face imaging with boundary specific segmentation—from one scan.
- OCTA can help clinicians explain the need for frequent follow-up to patients with geographic atrophy who are at risk for developing exudation.
- By assessing the OCTA cross-section with flow overlay, clinicians can rule out artifacts. If the flow is in the wrong location for the disease, it is most likely an artifact.

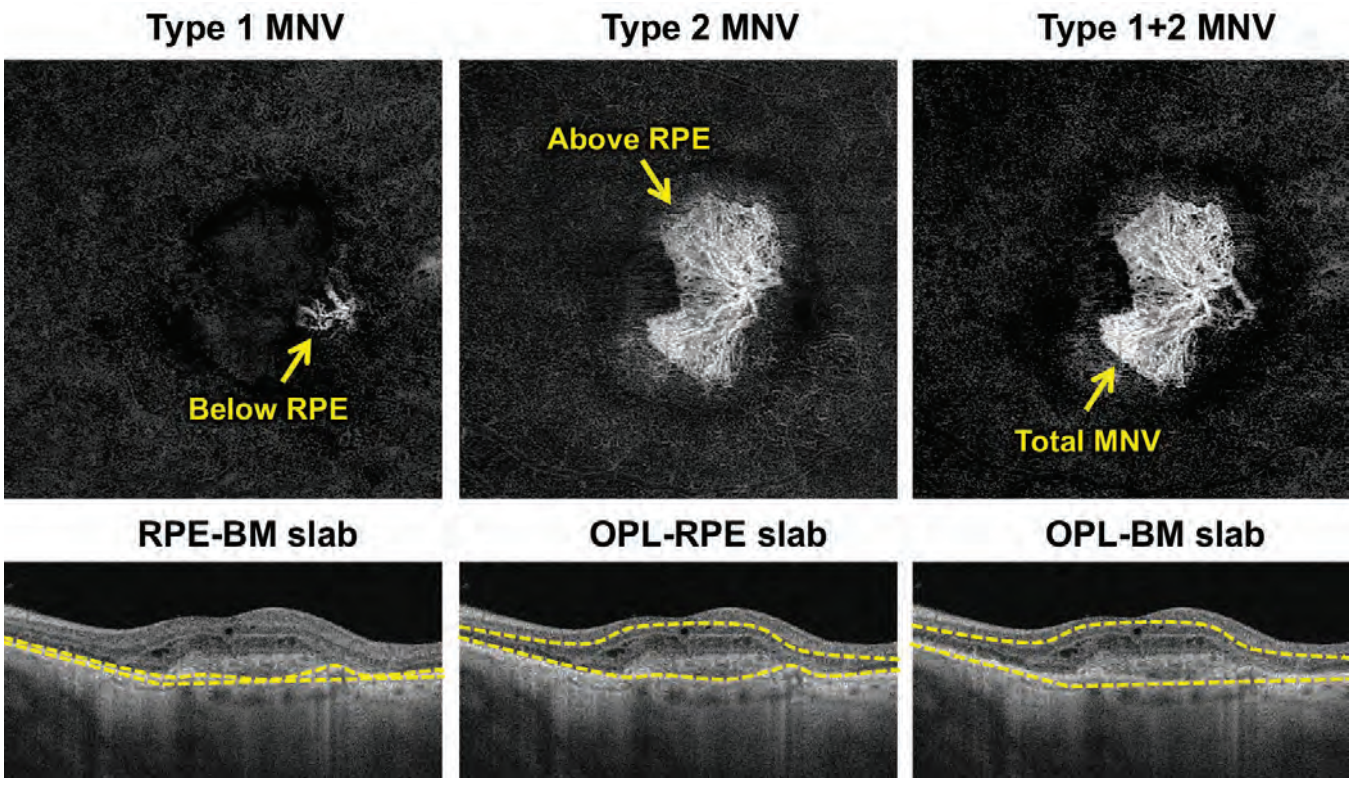


Figure. The use of boundary specific segmentation in OCTA imaging allows for the detection of different components of a macular neovascular lesion. The outer plexiform layer (OPL) to Bruch membrane (BM) slab detects the entire lesion, while the RPE to BM slab detects the type 1 component and the OPL to RPE slab detects the type 2 component.

about everyone else could benefit from OCTA. Still, there are certain patients for whom we get one every time. This really is a clinical tool now, and its utility extends beyond AMD. I use it for any patient who may have macular neovascularization (MNV), and not just high-risk drusen and pigment epithelial detachments (PEDs) with double-layer signs of AMD; it's also useful for other diseases such as myopia and pachychoroid spectrum disorders. In some of those conditions, dye-based angiography is challenging to interpret, and OCTA has been a transformative addition.

I also use it routinely for patients with retinal vascular diseases, such as diabetic retinopathy, to assess macular perfusion. OCTA is clearly better than FA for assessing macular ischemia. It's also a great tool for identifying and monitoring neovascularization, and it can help to distinguish intraretinal microvascular abnormalities from areas of flat neovascularization. In the context of anti-VEGF therapy, especially with montage OCTA scans, I can monitor for the response to treatment.

Another condition for which I obtain OCTA routinely is suspected macular telangiectasia. The structural OCT and OCTA images are really all you need to make this diagnosis.

Lastly, I use it routinely in inflammatory diseases. In placoid chorioretinopathies, for example, OCTA can show significant choriocapillaris abnormalities, a finding that can be helpful with patient management because you can observe some recovery of the choriocapillaris during the course of treatment. In one of our offices, almost every patient gets an OCTA because we anticipate that it might be useful later. Since I can capture OCTA at the same time as a structural OCT, it fits nicely into the workflow.

DR. TOTH: GEOGRAPHIC ATROPHY (GA) IS A HOT TOPIC BECAUSE OF THE NEWLY FDA-APPROVED THERAPY. DO YOU USE OCTA IN THE SETTING OF GA?

Nadia K. Waheed, MD, MPH: We know that patients with dry AMD may have nonexudative MNV on OCTA but may not necessarily have fluid. Their OCT may show low-lying PEDs, and OCTA can help us visualize the network of vasculature that underlies these low-lying detachments. This is a very important feature in patients who phenotypically appear dry because they are at a much higher risk of developing exudation.

I like to do an OCTA scan for my dry AMD patients. While looking for a low-lying PED on the OCT can help, it can be challenging to tell if a patient has MNV at the margins of the lesions, particularly in patients with GA who have basal laminar deposits that often mimic a low-lying PED. It is useful to obtain an OCTA to definitively ascertain if there is neovascularization because it helps me determine how frequently I need to follow these patients.

All of this, of course, will become even more important

as we start using anticomplement therapies for GA. Many of the upcoming new therapies have been associated with a higher risk of conversion to exudation. Now we must question whether this already high risk is even higher in patients who have pre-existing nonexudative lesions. I anticipate using OCTA to look for these lesions and track if they are growing and, eventually, watch for exudation more carefully over time. Additionally, OCTA will be important to either diagnose or rule out conversion to exudation in these patients.

Dr. Rosenfeld: In nonexudative AMD, I really depend on en face OCTA images for the detection of soft drusen, reticular pseudodrusen, calcified drusen, hyperpigmentation, and, most importantly, persistent hypertransmission defects, also known as complete retinal pigment epithelium (RPE) and outer retinal atrophy, or cRORA. These are bright areas on the sub-RPE slab. I can see where the light is beginning to penetrate through the attenuated or absent RPE. The appearance and growth of these persistent hypertransmission defects are synonymous in my mind with the appearance and growth of GA. That's how I'm going to diagnose and follow patients who are candidates for treatment with a complement inhibitor.

Using the same scan pattern but with a different boundary specific slab, I can see a thin double-layer sign or basal laminar deposits around the atrophy, which is a good indication that the lesion is going to grow quickly. Looking at a slab above the RPE, I can identify the reticular pseudodrusen, and with the choriocapillaris slab, I can see flow deficits around the lesion.

Sometimes this double-layer sign in nonexudative AMD corresponds to MNV, and this is where OCTA is so valuable. OCTA can distinguish between basal laminar deposits and MNV. I also make the distinction between macular atrophy that is adjacent to, versus within, the neovascularization. I interpret the prognosis of these cases differently because the atrophy tends to grow slowly when it forms within the lesion. But, when the atrophy is adjacent to the lesion, the GA tends to grow at the same pace as other atrophic lesions.

DR. FAWZI: HOW MUCH TIME DOES THIS TAKE, AND HOW MUCH INFORMATION ABOUT OCTA DO CLINICIANS NEED TO USE IT PROPERLY?

Dr. Rosenfeld: Clinicians can spend a lot of time slicing and dicing these OCTA scans, but in clinic, you just need the basic information, which can be obtained with a retinal thickness map and the sub-RPE slab. The sub-RPE slab is important for detecting the areas of atrophy. Initially, I want to know the answer to two important questions: Is there atrophy, and is there exudation? Everything else can be analyzed later.

Dr. Sadda: The most critical application for most clinicians is identifying neovascularization and patients who may be at high risk for the development of neovascularization.

The beauty of OCTA is that you know for sure because you can see the vasculature. If you are going to treat a patient with a complement inhibitor who already has an area of nonexudative neovascularization, the OCTA is a good discussion point for that patient to help explain why you need to monitor them more frequently for the development of exudation.

Dr. Fawzi: The biggest question that we always face is what about the artifact and how do you deal with them? Some of my colleagues use OCTA and they're sure a patient has MNV, but because the signal strength is weak or the patient has a cataract, they can't find that neovascularization, and they end up throwing the baby out with the bath water, so to speak.

DR. FAWZI: WHAT ADVICE CAN YOU OFFER TO HELP CLINICIANS AVOID ARTIFACTS WHEN STARTING WITH OCTA IMAGING?

Dr. Waheed: There are a few critical pieces to integrating OCTA into clinic. The first is having well-trained photographers. There is a steep learning curve to OCTA, and much of that is photographer dependent. A good OCTA image depends on proper image acquisition much more than a structural OCT alone, and you need people who know how to acquire good images. It does take a little longer than your standard OCT, and standard OCTs tend to be very forgiving of operators.

The second is choosing the right patients. The more I use OCTA, and the better the technology, software, and tracking gets, the easier it is to apply to a broader swath of patients.

The third piece is understanding that the structural information always comes cross-registered with the vascular information. Perhaps the most useful scans are the structural B scans with the flow overlay because they help you correlate the structure and function. For example, if you see an area that has vessels on the OCTA and you think that it might be neovascularization, you can correlate the structure and the function to tell if it is a projection artifact from overlying blood vessels or if it's an area that has a PED or subretinal hyperreflective material associated with the vessels.

OCTA is not multimodal imaging per se, but it does provide multiple different modes of visualization—an angiogram, a structural image, and an en face image—from one scan.

Dr. Fawzi: The cross-section with flow overlay is the most useful scan because you can rule out the artifacts. You can see where that flow is happening and if it's in the wrong location for your disease, it is most likely an artifact.

Dr. Rosenfeld: Artifacts are an issue, but it's rare that they prevent you from appropriately interpreting the data. Artifacts on OCTA, and motion artifacts in particular, tend to arise with the more difficult cases, and dye-based angiography isn't going to provide you any more information anyway. For example, you can't always see the lesion well in patients who have large PEDs associated with type 1 MNV, but these are the same types of lesions that FA and ICGA imaging would yield ambiguous results as well. The more clinicians use OCTA, the more comfortable they will become with processing the images. If you really want to learn as much as possible, these more difficult cases do take time.

Dr. Fawzi: The worst offenders are patients for whom the signal strength is very low; then, you start to see many artifacts, and people are unfortunately misinterpreting them as flow in the wrong places. I usually teach my fellows that if the signal strength is below a certain level, they should ignore that scan because it's full of artifacts and they shouldn't try to extract information that isn't there.

Dr. Rosenfeld: I always teach my fellows to look at the flow but also look at the structural image, particularly the en face image. If you don't have a good structural image, you're never going to be able to extract a useful flow image. Always look at the structure and the flow together.

DR. TOTH: WHAT TYPE OF PATIENTS SHOULD CLINICIANS CHOOSE TO IMAGE WITH OCTA WHEN THEY ARE FIRST LEARNING TO USE THE DEVICE?

Dr. Sadda: Choosing patients with clear media, and maybe patients with good vision and good fixation, can give you a positive experience. You're just asking for problems with signal attenuation and motion artifacts with patients who have substantial media opacity and can't fixate. You want to get off to a good start so that you don't give up because you are frustrated.

OCTA is an incredibly powerful tool, but with great power comes great responsibility. You really must understand the technology to use it wisely. As with all our ophthalmic imaging technology, you must get into the weeds a bit as a responsible clinician to understand how the information from OCTA is actually generated. That can help you make sense of some of the limitations and pitfalls.

We should all look at the en face OCTA imaging with its companion structural image (the same is true of the OCT B scans) to help us recognize various problems, such as motion artifacts.

Similarly, when things disappear in and out of the en face image, be wary of segmentation artifacts. We are used to looking for segmentation artifacts in OCT thickness maps, and we can apply those same lessons to OCTA.

Finally, it is important to recognize projection artifacts. All OCTA devices come with projection removal software, but it's not perfect. Again, using the structural OCT is helpful because the more hyperreflective an object is on the structural OCT, the more likely that it's a projection artifact from an overlying vascular structure.

Dr. Waheed: As you're starting out, some of the interesting cases to look at are either patients who have conditions like central serous chorioretinopathy or those along the pachychoroid spectrum where you're wondering if its neovascularization or fluid in the absence of neovascularization. I'm not a great fluorescein interpreter and always questioned whether something was neovascularization or leakage from a hotspot or small RPE punctures. I've always liked ICG in these ambiguous cases. Now with OCTA, I can tell right away whether there is neovascularization.

OCTA is also useful to image patients with retinal vascular disease, such as diabetic eye disease, especially if you have widefield OCTA. Looking for areas of peripheral ischemia can help you risk stratify these patients. In addition, looking at patients with branch retinal vein occlusions can give you a good idea of how ischemic the retina is and can help you think forward.

For example, if a patient has a branch retinal vein occlusion and macular edema, assessing the level of ischemia can tell you how responsive these patients may be to anti-VEGF therapy. Similarly, for patients with diabetes and macular ischemia, OCTA can help you understand what kind of vision these patients will have after treatment. I find it really gratifying to use OCTA in my retinal vascular disease patients because the images are beautiful, and they tell a story beyond what you can see with structural OCT scans.

Dr. Rosenfeld: A good imaging technician who can acquire OCTA images is worth their weight in gold. They are so valuable because you get good images time and time again.

The more time you spend with OCTA, the better your ability to interpret structural OCT gets. Once you challenge yourself looking at structural OCTs, you can identify the location of both exudative and nonexudative neovascular lesions, polypoidal choroidal vasculopathy lesions, and RPE tears. You will improve your structural OCT interpretations by learning how to interpret the OCTA scan (Figure).

Dr. Fawzi: Know your OCTA machine and get as many OCTAs as you can during the day. But you must sit down at the end of the day with your fellows and go through them. You will get more out of it if you do it after hours. Don't throw the baby out with the bath water when it comes to interpreting OCTA in your clinic; instead, wait until

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IMAGING ADVANCES AND APPLICATIONS FOR ROP

Novel approaches are helping researchers and clinicians better diagnose and monitor infants with retinopathy of prematurity.

By Benjamin K. Young, MD, MS, and J. Peter Campbell, MD, MPH


Screening for retinopathy of prematurity (ROP) is a high-stakes endeavor, with decisions that can determine a lifetime with either functional vision or blindness; thus, a timely and accurate diagnosis is essential. Current management is guided by the landmark Early Treatment of ROP study, which provided the modern definition of treatment-requiring ROP, and most infants who are treated on time do well.[1] However, imaging advances have exposed challenges to consistently and accurately determining a diagnosis based on the clinical examination alone, whether via ophthalmoscopy or digital imaging.

Despite standardized published photographs of plus disease, research shows differences in diagnosis between individuals and groups of individuals across geographic boundaries; over time, this has led to real-world treatment differences.[2-4] Although the International Classification of ROP seeks to be a relevant and applicable resource for clinicians at the bedside without any additional imaging techniques,[2] several newer modalities and approaches may lead to changes not only in disease diagnosis and management but also classification.

ADVANTAGES OF IMAGING

While the ophthalmoscopic examination has long been considered the standard, with certain advantages over available imaging devices, traditional contact-based widefield fundus photography offers several advantages. For one, disease severity may be more easily tracked and monitored with the superior accuracy of imaging versus retina drawings.[4] Clinicians are far better at determining changes in relative disease severity than they are at determining the disease category at a single point in time. Photodocumentation facilitates the direct comparison of prior disease severity in the same eye, which may be most important for aggressive ROP. Although the term implies rapid progression, this has yet to be formally included in the diagnostic criteria.[2]

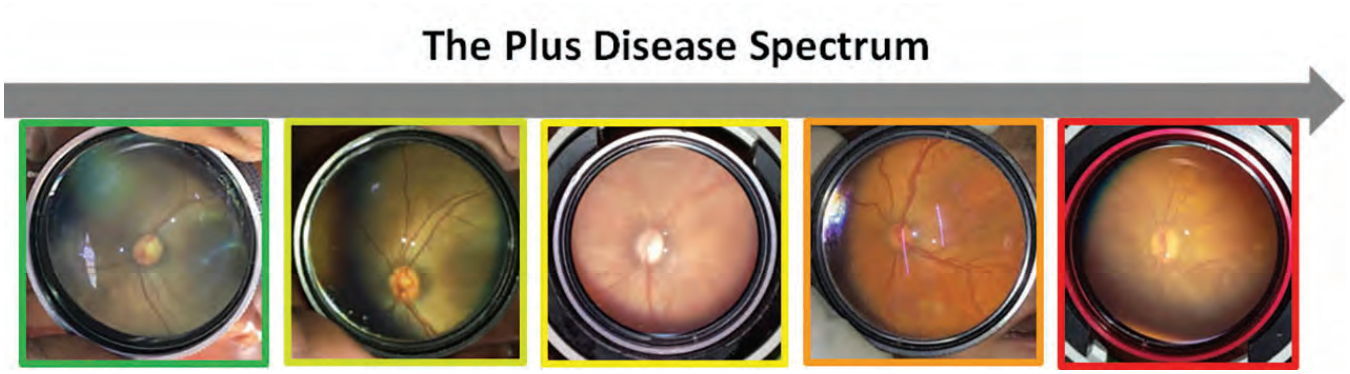
Aggressive ROP is defined by plus disease out of proportion to the typical peripheral stage and a preponderance of flat neovascularization that may be difficult to notice without high magnification but can rapidly progress to retinal detachment.[2] Comparing progression using retina drawings or clinician memory is notoriously impractical, especially when different clinicians examine the same infant over time. This may contribute to missing these important clinical signs of disease progression and risk.

PLUS DISEASE SPECTRUM

The recently updated International Classification of ROP introduced the concept of a plus disease spectrum to the vernacular (Figure 1)[2]; this classification recognizes that there is good agreement at the ends of the spectrum, but clinicians must factor in other features for presentations that are in the middle of the spectrum to determine if treatment is needed. While this presents some challenges to the application of evidence-based treatment guidelines from the Early Treatment of ROP study, the classification acknowledges the current state of practice and opens the door for quantitative approaches to the diagnosis and monitoring of ROP.

AT A GLANCE

- Research shows differences in the diagnosis of plus disease, leading to real-world treatment differences.
- Disease severity is more easily tracked and monitored with the superior accuracy of imaging versus retina drawings.
- One quantitative approach to the diagnosis and monitoring of retinopathy of prematurity is to measure the plus disease spectrum using a vascular severity score.



Images courtesy of Parag Shah, MD

Figure. These fundus photographs of neonates undergoing ROP screening (as viewed through a standard 28 D lens) are representative samples of patients who span from no plus (left) to plus (right), with intermediaries along the spectrum of disease.

One such quantitative approach is to measure the plus disease spectrum using a vascular severity score (VSS), which either the clinician or, in the future, artificial intelligence (AI) algorithms can assign.[5,6] Research demonstrates that higher VSS is associated with more posterior disease and a higher stage and extent of stage 3 disease, providing a measurable biomarker for overall disease severity.[7] The VSS concept does not solve the problem of determining when treatment is needed consistently, but it provides an objective framework to help do so in the future. Moreover, it facilitates objective monitoring of disease progression, which may help identify infants who are already progressing toward treatment-requiring ROP before diagnosis. Conversely, the VSS may help clinicians identify treatment failure and disease reactivation after anti-VEGF therapy. The strong connection between posterior vascular features and peripheral pathology is an active area of investigation that may significantly improve how we screen and decide to treat ROP.

TELEMEDICINE

Objective diagnosis through ophthalmic imaging and AI also facilitates AI-assisted telemedicine. Globally, we are experiencing a third epidemic of ROP, where very premature neonates in low- and middle-income countries have improved survival, leading to higher rates of ROP.[7] However, there is a shortage of trained clinicians globally to perform clinical examinations on all neonates in need, making telemedicine with widefield fundus photography the only solution in many settings.

Studies suggest that AI-assessed disease severity early in the disease course may be used in a predictive model to rule out a high-risk disease with 100% negative predictive value.[7] This may, in turn, reduce the need for repeated examinations in lower-risk infants, both in high-income and, importantly, low- and middle-income populations.

AI models that work on lower-cost imaging devices are critical to enabling us to scale these technologies globally to the areas of greatest need. Although many of these devices have a lower field of view, with further validation, the VSS concept may complement lower field of view imaging systems to enhance the sensitivity and specificity of ROP screening where widefield imaging is not available.[6,7]

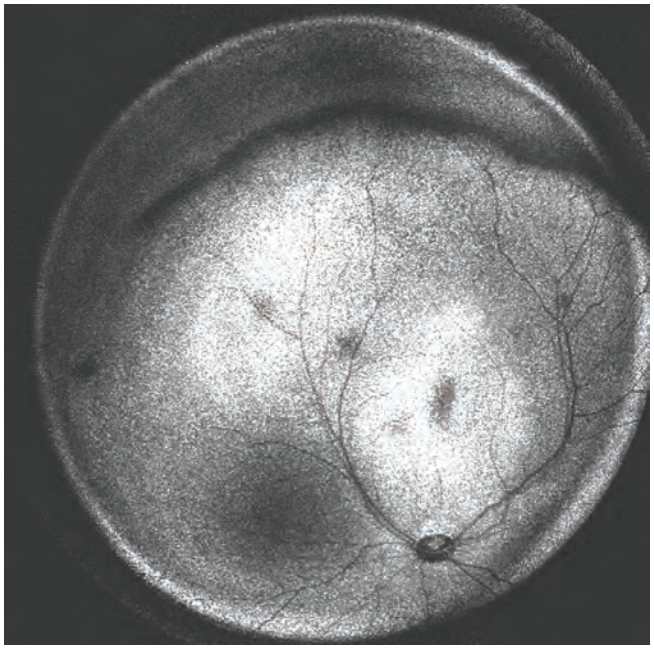


Image courtesy of Yifan Jian, PhD, and Mani Woodward

Figure 2. En face ultra-widefield OCT clearly demonstrates the ridge in a neonate with stage 2 ROP.

ULTRA-WIDEFIELD OCT

Ultra-widefield (UWF) OCT, still in the research setting for ROP, is offering new insights, including the understanding that stage exists along a spectrum (Figure 2).[8] Specifically, UWF OCT can detect the thickness of the ridge and show that it correlates continuously with the clinical diagnosis of stage.[8] Further, UWF OCT may be able to detect the progression of the stage earlier than a clinical examination or traditional fundus photography.[8] Quantitative and objective biomarkers, such as ridge thickness, have the potential to eliminate the problems with interrater reliability.

This technology, if brought to market, could have tremendous utility in creating objective markers for staging disease,

tracking progression earlier, and determining the incidence of neovascularization.

PERSISTENT AVASCULAR RETINA

Persistent avascular retina is an increasingly recognized phenomenon in many infants who were screened for but never diagnosed with ROP.[9] UWF fundus photography and fluorescein angiography have demonstrated that the rate of persistent avascular retina is very high in patients with a history of ROP. These patients often develop severe vitreoretinal complications such as retinal breaks, vitreous hemorrhages, and tractional, rhegmatogenous, exudative, or combination retinal detachments at a young age. There is still insufficient evidence on whether laser photocoagulation is indicated for these patients because many may have no clinical sequelae; still, monitoring and future study will be important to observe for vision-threatening complications.

NEXT STEPS

As imaging technology advances, we will learn more about the natural history of ROP, fine-tune our ability to predict patients who are at risk for the development of this treatment-requiring disease, and achieve the goal of preventing blindness in this vulnerable population. ■

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the patients are gone, then discuss the difficult cases and challenge each other. Over time, you and your fellows will get better at it. ■

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LEVERAGING AI TO ALLEVIATE DIABETIC VISION LOSS

New tools may help clinicians screen, diagnose, and monitor patients with diabetic eye disease.

By Sanya Yadav, MD, and Tayyeba K. Ali, MD


In less than a decade, the number of individuals diagnosed with diabetic retinopathy (DR) is projected to surpass 24 million.[1] While 90% of vision loss due to DR can be prevented by early detection, 40% to 60% of Americans are unable to obtain regular eye examinations.[2,3]

Although high-resolution fundus imaging is available across the nation, interpretation of images by skilled eye care providers continues to be a rate-limiting and costly step. Even when employing expert graders, effective end-to-end screening that leads to the preservation of a patient's vision is difficult to implement and scale. Machine learning-based solutions have the potential to bridge this gap and have garnered significant interest in academia and industry. In this article, we highlight some of the DR screening initiatives.

RECENT ADVANCES

In 2016, Gulshan et al presented a deep-learning algorithm capable of detecting referable DR using color fundus photographs (CFP) with remarkable speed and accuracy. The model predicted the disease severity in each CFP based on pixel intensities and made binary predictions on whether the disease was referable or not. This network was trained on more than 128,000 images and validated on 12,000 images. The reference standard was the majority vote of a panel of seven to eight expert ophthalmologists. The model's performance was noted to be on par with that of the expert panel, with F-scores of 0.95 and 0.91 (a measure of the model's accuracy calculated as a geometric mean of the precision and recall) for the model and expert physician panel, respectively, as demonstrated by the area under the curves.[4]

In 2018, Krause et al published a more robust network for automated grading of DR. The model made more granular predictions of the five-point severity grading scale as opposed to the two-point output in the prior version. In addition, the reference standard included an adjudication process in which a panel of expert retina specialists discussed each case until reaching a consensus on the final grade. Even using a small set of adjudicated DR grades led to enhanced identification of subtle findings, such as microaneurysms, and significantly improved the model's performance. Using a subset of 0.22% of images as a tuning set, the model's hyper-parameters yielded a kappa score (measurement of agreement that ranges from 0 [random] to 1 [perfect agreement]) of 0.84, which was similar to that of ophthalmologists (range: 0.80–0.84) and retina specialists (range: 0.82–0.91).[5]

In another study, a deep-learning system was trained to predict diabetic macular edema (DME) from 2D CFPs with the help of retinal thickness and fluid labels identified in the paired OCT images.[6] The network performed better when predicting DME with OCT-derived parameters as reference standards as opposed to expert CFP labels alone. The model generalized data from multiple international populations (ie, Australia, India, and Thailand) and exceeded the performance accuracy of experts with higher specificity—80% for the network versus 59% for human experts ($P = .008$)—and noninferior sensitivity—81% for the network versus 70% for human experts ($P < .001$).

AT A GLANCE

- Artificial intelligence-based solutions for diabetic retinopathy (DR) screening promise to improve access to and delivery of care for patients.
- Although high-resolution fundus imaging is available for remote screening, interpretation by skilled providers is a rate-limiting and costly step.
- In addition to DR grade, deep-learning systems can be trained to predict diabetic macular edema from fundus images with the help of OCT images that can provide retinal thickness and fluid measures.

IMPLEMENTATION HURDLES

A long-standing limitation of deep-learning models has been the *black box effect*: the model takes inputs and provides prediction scores with no insight into the inner workings of the process. This lack of understanding has led to mistrust among the scientific community, thereby limiting the widespread adoption and use of deep-learning models, especially in clinical care.

To overcome this, Sayers et al showed the final disease predictions as well as the model's decision process; along with the DR severity scores, physicians could view heatmaps that highlighted the regions of the CFPs that most strongly drove the predictions. Having overcome some of the black box effect, more clinicians began to use these deep-learning models to help improve their diagnostic accuracy and confidence in CFP interpretations.[7]

Although OCT has become ubiquitous in retina clinics, it still presents a challenge to the successful implementation of artificial intelligence (AI)-based solutions due to a dearth of annotated training images, hundreds of thousands of which are needed to train neural networks. In 2018, De Fauw et al published a novel deep-learning architecture to address this issue. This model used autosegmented OCT scans to create device-independent tissue-segmentation maps.[8] These features were then combined with clinical labels to detect retinal diseases and determine the need for *urgent*, *semi-urgent*, or *routine and observation-only* referrals to ophthalmologists. The creation of device-independent segmentation of OCT scans eliminated interdevice heterogeneity and standardized the images for more accurate analysis.[8]

In addition, this model created a report that was readily viewable by clinical experts, thereby alleviating part of the black box effect. This technique allowed for the detection of a range of retinal diseases, including rare diseases, and was not limited to DR. With this robust architecture and after training on more than 14,000 scans, the model's performance was on par with expert physicians. The expert performance of the network was achieved without missing clinically important, sight-threatening diseases.[8]

NOVEL APPROACHES

Despite the advanced tools, patient adherence to screening appointments remains challenging because people often trivialize the importance of routine diabetic examinations when their vision is still adequate. To address this, Google partnered with Verily to create the Verily Retinal Service, which combines a fundus camera (Verily Retinal Camera) with end-to-end workflow software (Verily Retinal Platform) to provide seamless integration into clinical workflows with minimal operator training.[9]

Telemedicine, which has been successfully used in other medical specialties for routine visits, especially during the COVID-19 pandemic, also has the potential to address this issue. The need for specialized eye equipment has made it difficult to translate well to an ophthalmic telemedicine platform. Babenko et al showed that one can detect diabetic eye disease by looking at external eye photos alone.[10] Thus, the use of AI and deep-learning algorithms on photos taken by a patient at their home using their smartphone, particularly when paired with telemedicine, may enable and scale real-time screening and prevent vision loss.

When assessing the utility of AI to minimize the burden of vision-threatening disease, detecting referable DR is only the tip of the iceberg. This technology may one day help physicians determine the best treatment approach (eg, steroids vs anti-VEGF therapy) for a particular patient, as well as determine appropriate treatment intervals to maintain good vision.[11] Such personalized care may not be limited to DR, as researchers work to expand the indications to other conditions such as AMD and glaucoma.[11]

In short, AI-based solutions for DR screening promise to improve access to and delivery of care to patients with diabetes. As clinicians, we are eager to see the diagnostic and therapeutic implications of any given intervention. Still, we must also focus on how we can leverage this technology to provide safe and equitable care, especially to those who have the most limited access to timely, accurate, and quality health care. ■

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RETINAL DISPLACEMENT ON FAF: THE TIP OF THE ICEBERG

Insights from OCT homography may help clinicians better understand the implications of this novel finding.

By Koby Brosh, MD; Eduardo Roditi, MD; and Rajeev H. Muni, MD, MSc



There has been recent interest in improving the integrity of anatomic outcomes following rhegmatogenous retinal detachment (RRD) repair to optimize postoperative functional outcomes. This is of critical importance because a substantial proportion of patients with an RRD complain of postoperative aniseikonia and metamorphopsia with current surgical repair techniques.[1-4]

Postoperative retinal displacement, also known as a *low-integrity retinal attachment* (LIRA), is a common and unwanted outcome following RRD repair. One post-hoc study found that 75% of patients had subjective distortion 2 months following macula-off RRD repair.[4] There is increasing evidence that modifications to our treatment paradigms and variations in surgical technique can influence both the incidence and the extent of postoperative retinal displacement, leading to better anatomical and functional outcomes.[5-9] For example, research suggests that pars plana vitrectomy (PPV) is associated with a higher risk of LIRA compared with pneumatic retinopexy.[5,10] Studies have found that LIRA is associated with greater risk of postoperative metamorphopsia and aniseikonia.[4,5,10] Moreover, an association was found between the amplitude of retinal displacement and some of these outcomes.[4]

Finding ways to minimize LIRA may lower the incidence and severity of postoperative visual distortion.

DISPLACEMENT ORIGINS

Retinal displacement was first detected and described by Shiragami et al in 2010 using fundus autofluorescence (FAF) imaging.[11] The researchers identified hyperautofluorescent lines that were adjacent to and followed the contour of retinal vessels. They hypothesized that these retinal vessel printings (RVPs) were hyperautofluorecent because retinal displacement had uncovered retinal pigment epithelium (RPE) cells that were previously naive to light.[12] This likely results in a different composition of fluorophores or differences in metabolic activity that lead to increased autofluorescence on FAF.[11-13]

IMAGING UPDATES

Currently, FAF imaging is the only method to detect postoperative retinal displacement, although grading FAF images for LIRA can be challenging. For example, in some patients, the displacement is less than a full vessel width or there are other abnormal RPE cells in the same vicinity. In other situations, there may be RPE atrophy, high myopia, or generally reduced image quality preventing the detection of RVPs. In addition, RVPs on FAF imaging are almost exclusively detected along major arcades and are often not visible adjacent to smaller retinal blood vessels, such as those in the macular region, where displacement is most relevant.

To assess the true extent of retinal displacement, clinicians must evaluate the location of retinal blood vessels before the occurrence of the RRD and compare this to the location of the retinal vessels postoperatively. Such a study is only possible if pre-RRD imaging is available.

AT A GLANCE

- Postoperative retinal displacement is a common and unwanted outcome following RRD repair.
- The authors' study found that assessment of retinal displacement using a novel homography-based overlay method was superior to fundus autofluorescence imaging.
- Treatment modifications and varied surgical techniques can influence and reduce postoperative retinal displacement, leading to better anatomical and functional outcomes.

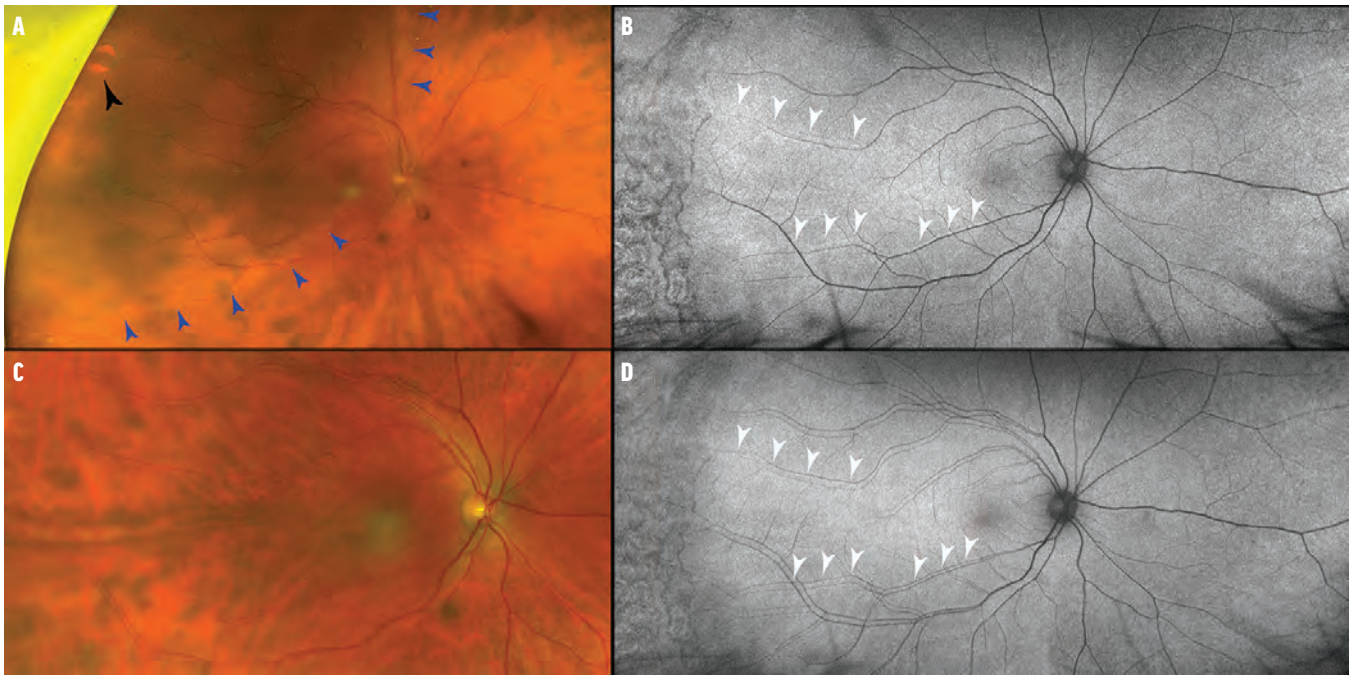


Figure 1. This patient presented with a superotemporal macula-off RRD and was treated with vitrectomy (A). Postoperative FAF demonstrated fine RVPs adjacent to both the superior and inferior arcades (B, arrows). Overlay of ultra-widefield retina images (C) and FAF (D) show that the RVPs correspond to the location of pre-RRD blood vessels.

Our group encountered one patient with available ultra-widefield imaging before the occurrence of an RRD. Using a novel overlay technique with ultra-widefield FAF, we found that the RVPs corresponded to the location of retinal vessels before the RRD (Figure 1)—proving Shirigami's hypothesis.[14] What was most surprising was that the retinal displacement was much more extensive than what was seen when only assessing the RVPs on FAF.

Therefore, we retrospectively reviewed RRD patients to find cases where we had imaging before an RRD. We used the infrared en face spectral-domain (SD) OCT imaging of the macula before the occurrence of RRD to assess postoperative LIRA using the overlay technique.

To perform the overlay, at least four corresponding landmarks of the optic nerve head (ONH)/RPE/choroid were manually selected on both pre- and post-RRD infrared SD-OCT imaging (Video). An ONH marking was mandatory and combined with, ideally, one mark in each quadrant on RPE or choroidal landmarks. A computer code for homography was used to perform the overlay based on the provided markings. Red and green color channels were used to allow for better visualization of the retinal vessels pre- and post-RRD repair, respectively (Figure 2).

To validate this novel approach, we performed the technique in eight contralateral normal eyes and another 12 healthy eyes with no displacement. We also confirmed stationary ONH, RPE, and choroidal vessel landmarks using the "flipping mode," which consisted of rapid visualization between aligned pre- and post-RRD repair infrared SD-OCT images to confirm that the landmarks were fixed.

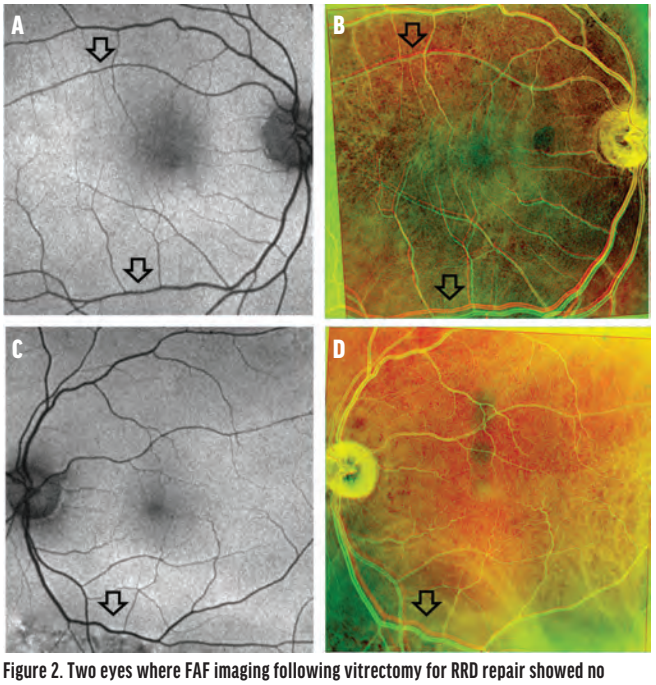
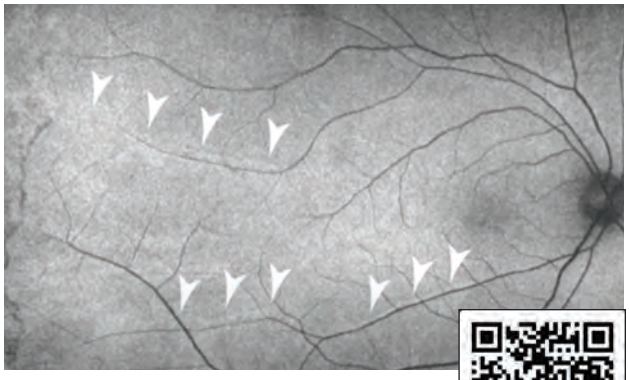


Figure 2. Two eyes where FAF imaging following vitrectomy for RRD repair showed no evidence of retinal displacement (A, C; arrows). However, OCT overlays demonstrated obvious inferior displacement (B, D; arrows).

We found 16 eyes of 15 patients that were eligible for the study. All patients underwent PPV for RRD repair except one, who had pneumatic retinopexy. Two independent and masked graders assessed both the overlays and FAFs

WATCH IT NOW



Video. Retinal Displacement on FAF Imaging: The Tip of the Iceberg

for retinal displacement; 46.6% of FAFs were found to be positive for retinal displacement compared with 100% of the overlays after PPV.

The mean number of displaced macular vessels detected by FAF and overlay techniques were 1.0 ± 0.8 and 2.6 ± 0.9, respectively (P = .001). In 93.3% (14/15) of cases, the infrared overlay images revealed a greater number of major arcade vessels displaced than the FAF images. Additionally, the infrared overlay demonstrated more definitive displacement, graded as obvious in 53.3% (8/15) of images, whereas RVPs on FAF were never graded as obvious (0/7).

Our results demonstrated that FAF underestimates the presence and extent of LIRA, which may explain the variability in displacement rates among previous studies.[5,13,15-18] Our data suggest that FAF images should be very carefully assessed for the presence of retinal displacement, as there is a high risk of false negatives.

A major limitation of the overlay technique is that pre-RRD imaging is needed to produce the homography. The small number of patients in our cohort, and the fact that this was a novel technique with the possibility of small errors in the manual markings, are also limitations.

KEY TAKEAWAYS

RRD repair has undergone a significant shift in the last few decades toward PPV. However, research suggests that functional and structural outcomes may be better with alternative techniques. It is important that we continuously evaluate our RRD repair techniques to maximize the integrity of retinal attachment and functional outcomes.

Our findings demonstrate that assessment of retinal displacement using a novel homography-based overlay method was superior to FAF imaging, which can miss or underestimate the true extent of LIRA. FAF has limited sensitivity and is likely showing only the tip of the iceberg when it comes to retinal displacement. Further research is needed to reveal what lies beneath the water and detect the true extent of retinal displacement after RRD repair. ■

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FUNDUS AUTOFLUORESCENCE FOR IRDS

Don't overlook this tried-and-true tool when evaluating patients suspicious for inherited diseases.

By Nita Valikodath, MD, MS, and Ramiro Maldonado, MD


Fundus autofluorescence (FAF) is a noninvasive imaging technique that predominantly highlights the distribution of fluorophores in the retinal pigment epithelium (RPE), such as lipofuscin.[1] Other fluorophores, such as rhodopsin, melanin, N-retinylidene-N-retinylethanolamine (A2E), or optic disc drusen, also produce changes in autofluorescence and have various excitation and emission wavelengths (Table).

FAF can be useful in the diagnosis and monitoring of inherited retinal diseases (IRDs). For example, in the early stages of these diseases, FAF can show abnormalities when the dilated fundus examination and OCT are unremarkable. FAF is also a useful tool for monitoring disease progression or stability in patients with an IRD, such as tracking the progression of atrophic noncentral lesions in Stargardt disease. In addition, clinical trials use FAF findings as outcome measures in response to investigational therapies.

In this article, we provide an overview of the use of FAF imaging in various IRDs.

MACULAR DYSTROPHIES

***ABCA4*-related diseases.** Stargardt disease is most commonly an autosomal recessive condition caused by a pathogenic *ABCA4* gene variant. The condition leads to outer segment degradation, lipofuscin accumulation, and damage to the RPE and photoreceptor layer. In the early stages of the disease, FAF shows a hyperautofluorescence, indicating an accumulation of lipofuscin. As the disease progresses, FAF shows macular hypoautofluorescence surrounded by pisciform flecks of hyperautofluorescence with peripapillary sparing (Figure 1). In advanced disease, FAF shows hypoautofluorescence from diffuse atrophy of RPE cells and photoreceptor death.[2]

FAF seems to correlate with visual function based on visual acuity and electroretinography findings,[3] which can help with the timely identification of progression. Klufas et al described three ultra-widefield FAF patterns in this disease[4]: type I (lesions are localized to the macula); type II (macular atrophy with variable peripheral FAF flecks and atrophy); and type III (macular and peripheral atrophy, which is further divided based on the extent of atrophy).

***BEST1*-related maculopathies and retinopathies.** Best disease, an autosomal dominant condition, is caused by mutations in the *BEST1* gene and leads to accumulation of lipofuscin and photoreceptor material in the subretinal space. There are five stages of disease, according to the Gass classification, each presenting with different FAF patterns[5]:

- **Stage 1:** The previtelliform stage shows minimal to no change in hyperautofluorescence.
- **Stage 2:** The vitelliform stage demonstrates a homogenous hyperautofluorescent lesion in the macula.
- **Stage 3:** The pseudohypopyon stage shows isoautofluorescent fluid on top of a hyperautofluorescent layer.
- **Stage 4:** The vitelliruptive stage shows a hypoautofluorescent lesion bordered by hyperautofluorescence.
- **Stage 5:** The atrophic stage shows diffuse hypoautofluorescence due to chorioretinal atrophy.

A study by Parodi et al identified six qualitative patterns on FAF in various stages of Best disease: normal, hyperautofluorescent, hypoautofluorescent, patchy, spoke-like, and multifocal.[6] In autosomal recessive bestrophinopathy, FAF can show the extent of abnormal lipofuscin

AT A GLANCE

- Fundus autofluorescence (FAF) is key in the evaluation of patients with inherited retinal diseases.
- Certain FAF patterns can narrow the diagnosis to a specific type of inherited retinal disease.
- Widefield FAF can provide an estimate of the amount of retina affected, and its findings can correlate with visual field defects.

TABLE. EXCITATION AND EMISSION WAVELENGTHS OF FLUOROPHORES

Fluorophore	Excitation wavelength (nm)	Emission wavelength (nm)
A2E	430–450	560–575
Rhodopsin	470	540
Lipofuscin	470 (blue)	600–610 (yellow-green)
Melanin[1]	787 (near-infrared)	870–900 (near-infrared)

1. Keilhauer CN, Delori FC. Near-infrared autofluorescence imaging of the fundus: visualization of ocular melanin. *Invest Ophthalmol Vis Sci.* 2006;47(8):3556-3564.

accumulation in a pattern that appears pathognomonic.[7] Autosomal recessive bestrophinopathy shows more extensive and variable FAF findings that can include hyperautofluorescence in areas of vitelliform deposition, zonal areas of hyperautofluorescence and mottled hypoautofluorescence, or a combination of these patterns. Acute exudative polymorphous vitelliform maculopathy is characterized by exudative retinal detachment with subretinal lesions. On FAF, the subretinal material initially appears hyperfluorescent and, as lesions resolve, there is a decrease in autofluorescence.[8]

Pattern dystrophies. These are commonly caused by mutations of the *PRPH2* gene, which encodes a membrane protein responsible for the function of photoreceptor outer segments. This group includes adult-onset vitelliform macular dystrophy, multifocal pattern dystrophy, butterfly pigment dystrophy, reticular pattern dystrophy, and fundus pulverulentus. These dystrophies typically have a clinically stable and benign course. Adult-onset vitelliform macular dystrophy is characterized by yellow-white subfoveal lesions and variable FAF patterns. Parodi et al described normal, focal hyperautofluorescent, or patchy autofluorescent patterns, while Furino et al described three FAF patterns, including patchy, ring-like focal, and linear.[6,9] All these patterns are likely representations of different disease stages.

Cone dystrophies. These are part of a heterogeneous group of IRDs that affect the cone cells and include achromatopsia, incomplete achromatopsia, blue cone monochromatism, and X-linked progressive cone dystrophy. They are divided into stationary and progressive forms, and some are inherited while others occur sporadically. Affected patients experience photophobia, reduced visual acuity, and color perception deficiencies. From the stationary group, achromatopsia classically has a normal fundus, but FAF can detect photoreceptor disease at the fovea by demonstrating abnormal hyperautofluorescence (Figure 2).[10,11]

Panretinal photoreceptor dystrophies. Autosomal dominant retinitis pigmentosa (RP) is commonly caused by mutations in the *rhodopsin* gene, autosomal recessive RP is caused by *USH2A* gene mutations, and X-linked RP is due to *RPGR* and *RP2* gene mutations. While electroretinography is the standard for diagnosis and monitoring of this disease, FAF

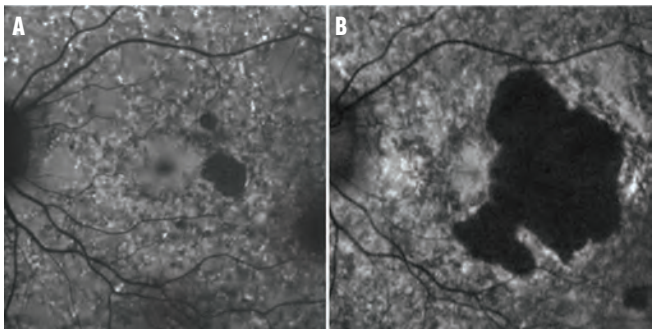

Figure 1. Baseline FAF imaging of a patient with Stargardt disease who has two pathogenic *ABCA4* variants shows small patches of hypoautofluorescence (A). Seven years later, FAF shows that the hypoautofluorescent areas have significantly increased in size (B).

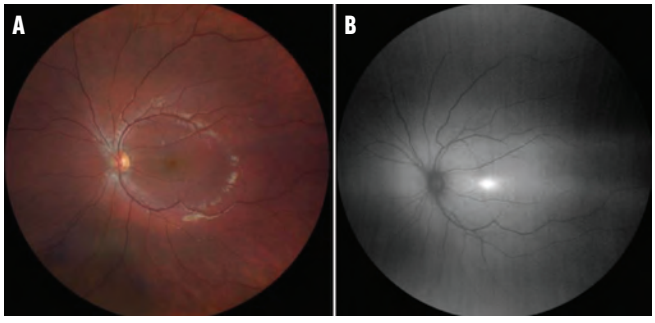

Figure 2. Widefield fundus photography does not show any abnormalities in a patient with achromatopsia (A). Widefield FAF shows subclinical findings, demonstrating hyperautofluorescence at the foveal center (B).

can be helpful in phenotype-genotype correlation. On FAF, a hyperautofluorescent parafoveal ring known as a Robson-Holder ring can be seen.[12] The ring corresponds to outer segment dysfunction and lipofuscin production. In addition to RP, an autofluorescent ring can also be seen in Leber congenital amaurosis,[13] Best disease, cone–rod dystrophies, and X-linked retinoschisis—suggesting a common mechanism.[14] Monitoring changes in the size of the ring could be a good outcome marker for rod–cone dystrophies. Outside of this ring, retinal sensitivity is affected, and photoreceptor loss can be seen on OCT; inside the ring, the retina may be normal. Visual fields correlate to the size of the ring.[15] Progression of disease may be marked by constriction of the ring, although the ring may expand in cone–rod dystrophy.[16] Peripheral hypoautofluorescent changes can be seen in rod–cone dystrophies and are best visualized on ultra-widefield FAF (Figure 3). These changes correlate with visual field constriction and can be used to monitor progression over time.

Choroideremia. This condition has an X-linked recessive inheritance pattern and is caused by a mutation in the CHM protein. FAF patterns are characterized by bilateral, midperipheral areas of hypoautofluorescence representing areas of RPE atrophy with scalloped edges. Usually, there is an area of central stellate autofluorescence that is preserved.[17] With the progression of the disease, the areas of hyperautofluorescence expand and involve the fovea. FAF

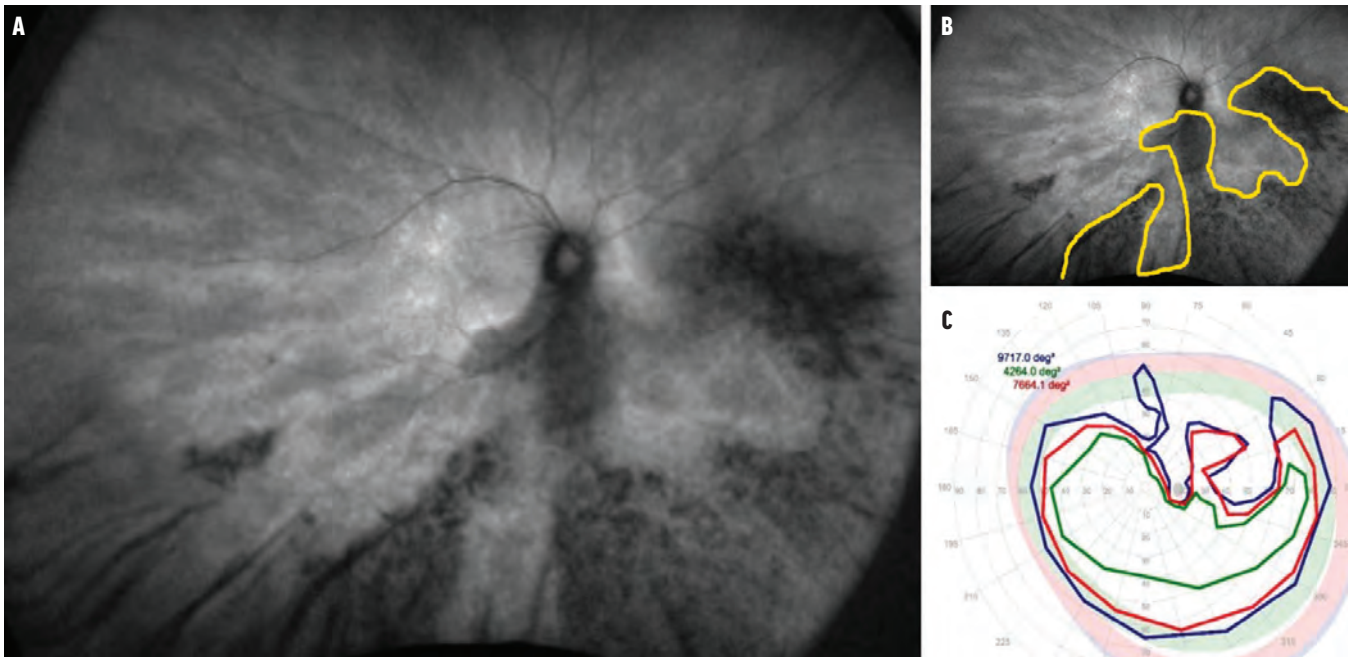

Figure 3. Ultra-widefield FAF imaging in a patient who is a carrier of an *RPGR* pathogenic variant (A) shows hypoautofluorescence in the inferonasal retina (B, yellow border), which correlates with Goldmann perimetry that demonstrates superotemporal visual field constriction in all isopters (C).

can be used to monitor disease as it correlates with vision and age. Female carriers also show FAF changes, such as a peripheral speckled pattern of hyperautofluorescence and hypoautofluorescence.[18]

FUTURE DIRECTIONS

Deep-learning algorithms evaluating FAF images in IRD patients are being explored. Miere et al developed a deep convolutional neural network that classified IRDs, including RP, Best disease, and Stargardt disease, using FAF images, and it performed well.[19] In another study, a deep-learning algorithm used FAF and fundus images to predict causative genes in IRDs and showed a mean overall sensitivity of 81.3% and 81.8% when using FAF alone and both imaging tools, respectively.[20] In addition, artificial intelligence has been employed to evaluate structural changes seen on FAF. For example, Charng et al used a deep-learning algorithm to segment hyperautofluorescent fleck lesions in Stargardt disease to evaluate fleck count and area. This may one day affect disease monitoring and clinical trial endopoints.[21] ■

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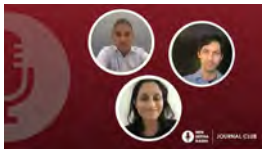

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3D HEADS-UP DISPLAY: PEARLS FOR NEW USERS

Preoperative planning, OR layout, and system parameters are just a few considerations when starting out with this new technology.

By Reem Amine, MD; Leanne Clevenger, MD; and Justis P. Ehlers, MD



One of the most interesting advances in ophthalmic surgery is the advent of the 3D heads-up display (HUD; Figures 1–3). Commercially available systems include the Ngenuity (Alcon), Artevo 800 (Carl Zeiss Meditec), and Beyeonics One (Beyeonics).

While the use of 3D HUD certainly has an important learning curve, and although some studies suggest that surgical time may be longer, the technology provides better depth of field/focus, enhanced resolution, customizable visualization palates (ie, color filters and task-specific visualization modes), and potential enhancements to ergonomics.[1-9] It holds tremendous utility as a teaching tool, as everyone in the OR has the same high-resolution view of the surgery.

As more platforms become available, these systems are likely to become integrated into more retina ORs. In this article, we review ways to improve the learning curve, surgeon experience, and overall success in adopting 3D HUD.

PREOPERATIVE PREPAREDNESS

Surgeons must familiarize themselves with the 3D HUD prior to the day of surgery. It may be helpful to simulate a case to evaluate room layout, display and lighting settings, focus, and intraoperative maneuvering. Working with the device prior to incorporating it into patient care allows uninhibited one-on-one instruction and boosts confidence. Surgeons should develop a preoperative game plan regarding which functionalities to use during surgery to maximize the experience and expectations. Instruction from experienced surgeons regarding the 3D HUD can also help new users become acquainted with the system.

CASE SELECTION AND DURATION

Case selection is an important consideration with 3D HUD. When first learning to use this technology, some surgeons prefer to start with less complex surgical cases that require fewer maneuvers, such as non-clearing vitreous hemorrhage or macular cases. Because macular visualization is particularly good with this technology, vitreomacular interface disorders may be good first choices. Cases requiring more significant anterior segment manipulation, such as sutured IOLs, can have a steeper learning curve depending on the surgeon and the system. New users should be highly comfortable with the selected procedure to avoid adding a significant variable when becoming familiar with 3D HUD.

Scheduling extra surgical time will be necessary, at least for the first surgical day. Scheduling appropriately reduces stress, provides more opportunities for system set-up and modifications, and removes time as an additional stressor. In our experience, surgical time rapidly improves as new users become more familiar and efficient with the 3D HUD.

Finally, new users should consider having a visualization back-up in place during the surgical procedure, in the unlikely event that it is necessary during the surgical case.

ROOM LAYOUT

Almost all HUD systems require a varied room layout compared with traditional microscopes. Identifying your

AT A GLANCE

- When incorporating 3D heads-up display (HUD), simulate a case to evaluate the room layout, system settings, and intraoperative maneuvering.
- With 3D HUD systems, coaxial illumination with an endolaser probe can significantly reduce the visualization of the laser beam and, potentially, visualization of laser uptake.
- Placing the 3D HUD approximately 1.5 m from the surgeon can maximize the viewing experience.

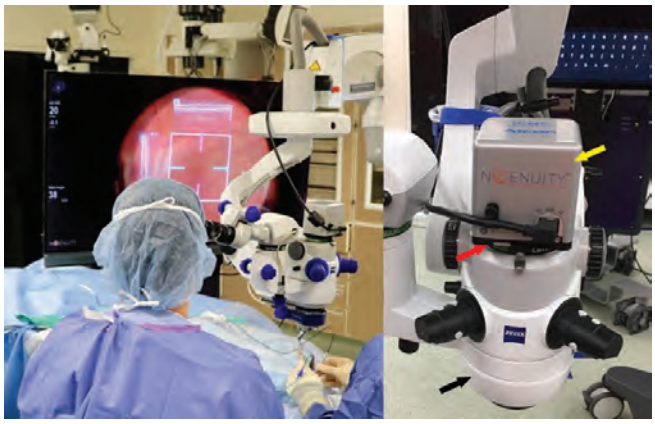

Figure 1. The Ngenuity 3D system uses a high-performance digital camera to provide the 3D visualization on an HD external monitor. This approach leverages the internal optics of the surgical microscope and can be used across microscope platforms.

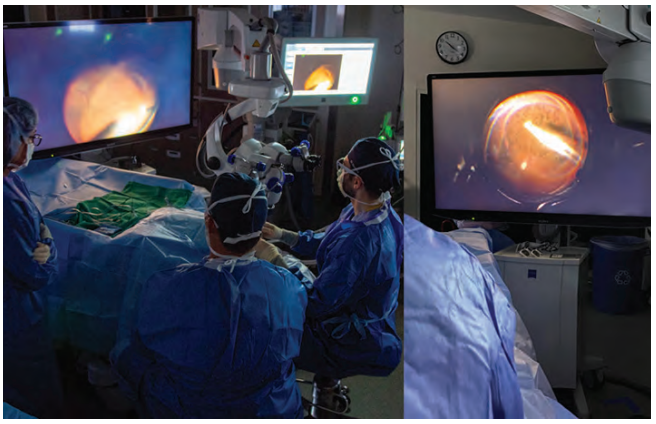

Figure 2. The Artevo 800 uses a hybrid system that includes both the optics and digital camera system within the head of the microscope. The digital signal is then directed to an external HD monitor.

Figure 3. The Beyeonics One system uses a surgical visor that receives the digital signal from a completely digital microscope.

Figure 4. An example of the OR layout demonstrating the microscope location and 3D HUD relative to the surgical field.

preferences for screen location, screen angle, and microscope location are all keys to success (Figure 4). Surgeons should create a reproducible OR layout by adding floor markings of where the scope and the display screen should be placed relative to the surgical bed to ensure consistency, provide maximal visualization, and increase surgeon comfort (Figure 5). Studies demonstrate that placing the 3D screen approximately 1.5 m from the surgeon can maximize the view, including lateral resolution and depth of field.[6]

Our experience is that surgeons vary significantly on their room layout preferences. Thus, identifying each surgeon's specific preferences and ensuring those settings are reproduced for each operation can significantly affect the experience with 3D HUD.

TESTING FUNCTIONALITY

Surgical teams must make time to test the system—including the foot control pedal, screen display, and flexible scope mobilization—on the day of surgery to secure functionality before the start of the operation. This may also include camera/system optimization, such as white balancing. Any additional integrated systems, such as vitrectomy settings or intraoperative OCT (iOCT), should be tested as well. Any necessary troubleshooting should happen prior to the start of the actual procedure.

LIGHTING CONCERNS

Choosing the right light intensity for the screen display is vital for proper 3D visualization of the retina and associated pathologies. In many situations, surgeons may be able to reduce the overall light level during the surgical procedure. Surgeons should explore various approaches to lighting based on the surgical task. In some cases, pathology and adjuvant staining may be better visualized with slight indirect light compared with direct focus from the endoilluminator.[7] Light settings may be highly variable and should be adjusted if the surgical field appears washed-out or if there is limited visibility of the adjuvant staining.

One unique challenge with HUD technology is that coaxial illumination with an endolaser probe can significantly reduce the visualization of the laser beam and, potentially, visualization of laser uptake. This can vary from system to system, but our experience is that illuminated laser use is often unnecessary with HUD compared with a traditional microscope. Optimal laser uptake is generally evaluated based on the overall appearance of the laser in areas of application.

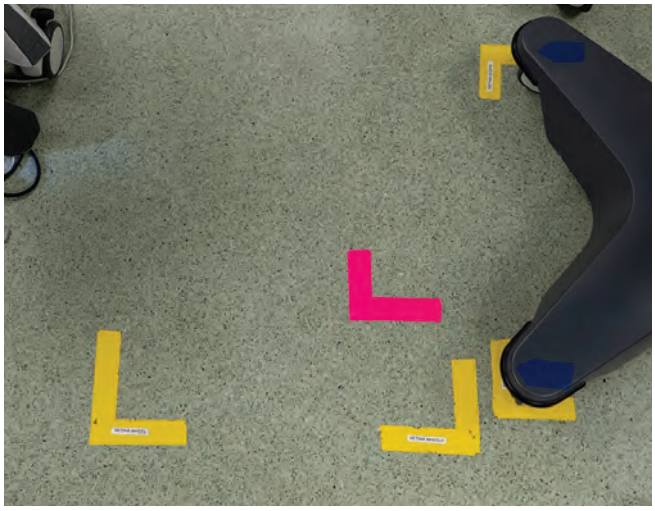

Figure 5. OR floor markings ensure the same room layout and microscope positioning relative to the surgical bed.

In digital systems the overall "whiteness" of the laser uptake may be different than what the surgeon is accustomed to seeing with traditional microscopes.

POSTOPERATIVE DEBRIEF

To maximize the surgical experience with 3D systems, the team—including the scrub nurse/tech, circulator, surgical assistant, and anesthesia team—should have a post-surgery debriefing to discuss the workflow. The surgeon should note any pitfalls that could have been avoided or steps to improve upon for future cases. Key points to discuss include any required troubleshooting, feedback on visualization, and variations in technique when using the technology.

NEW TECH IN THE OR

3D HUD provides a unique opportunity for incorporating multimodal information into the surgical field. Examples include surgical alignment overlays (eg, toric markers), surgical system parameters (eg, vacuum, surgical modes), and iOCT (Figure 6). These tools can help the surgeon focus on the surgical field while accessing additional information without having to look away from the posterior segment.[3,4]

To maximize the initial experience when integrating iOCT, surgeons should consider assigning a trained assistant to manage the iOCT image acquisition. Doing so can improve workflow and image quality and ensure that troubleshooting is performed in a timely manner. In our experience, the parfocality of the OCT and 3D HUD surgical view facilitates enhanced image quality during OCT acquisition. Integration with 3D HUD provides a larger image size for review and minimizes the need to review through a separate display.[3]

NEXT STEPS

The right preparation and intraoperative attention can help facilitate successful incorporation of 3D HUD systems into surgical practice. More investigation is needed to determine the overall effect this technology has on surgical outcomes and to better understand the role of integrative technologies in the future of vitreoretinal surgery. ■

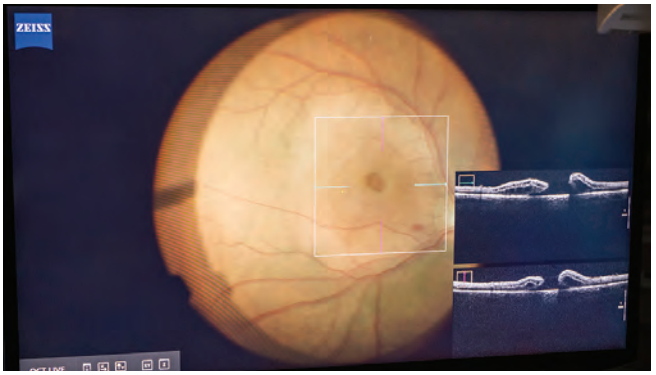

Figure 6. iOCT can provide additional information during surgery, particularly when integrated with 3D HUD.

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NO supplemental treatment needed to maintain anesthesia*†[1]

NO serious adverse events with an established safety profile[2]

NO patients reported experiencing pain[2]

*In the clinical trial, no patient undergoing routine cataract surgery receiving IHEEZO required supplemental treatment to maintain anesthesia; this was not the case for patients receiving tetracaine. Supplemental treatment was defined as general anesthesia, intraoperative systemic analgesia, or local anesthesia. Though supplemental administration was not required by any patient in the clinical trial, IHEEZO may be reapplied as needed to maintain anesthesia.[1,2]

†Sufficient anesthesia with IHEEZO lasted an average of 21.5 minutes in the clinical trial, while mean total surgical time was 13.9 minutes.[2]

APPROVED USE

IHEEZO is indicated for ocular surface anesthesia.

IMPORTANT SAFETY INFORMATION

IHEEZO is contraindicated in patients with a history of hypersensitivity to any component of this preparation.

IHEEZO should not be injected or intraocularly administered.

Patients should not touch the eye for at least 10 to 20 minutes after using anesthetic as accidental injuries can occur due to insensitivity of the eye.

Prolonged use of a topical ocular anesthetic may produce permanent corneal opacification and ulceration with accompanying visual loss.

Do not touch the dropper tip to any surface as this may contaminate the gel.

IHEEZO is indicated for administration under the direct supervision of a healthcare provider. IHEEZO is not intended for patient self-administration.

The most common adverse reactions in studies following IHEEZO administration (incidence greater than or equal to 5%) were mydriasis, conjunctival hyperemia, and eye irritation.

You are encouraged to report suspected adverse reactions to the FDA. Visit **www.fda.gov/medwatch**, or call **1-800-FDA-1088**.

Please see Brief Summary of Full Prescribing Information for IHEEZO on adjacent page.

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References: 1. Iheezo. Prescribing information. Harrow IP, LLC; 2022. **2.** Data on File. Harrow IP, LLC; 2023.

IHEEZO™

(chloroprocaine HCl ophthalmic gel) 3%

BRIEF SUMMARY OF PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

IHEEZO™ (chloroprocaine hydrochloride ophthalmic gel) 3% is a preservative-free ester anesthetic indicated for ocular surface anesthesia.

4 CONTRAINDICATIONS

IHEEZO is contraindicated in patients with a history of hypersensitivity to any component of this preparation.

5 WARNINGS AND PRECAUTIONS

5.1 Not for Injection or Intraocular Administration

IHEEZO should not be injected or intraocularly administered.

5.2 Corneal Injury Due to Insensitivity

Patients should not touch the eye for at least 10 to 20 minutes after using anesthetic as accidental injuries can occur due to insensitivity of the eye.

5.3 Corneal Opacification

Prolonged use of a topical ocular anesthetic may produce permanent corneal opacification and ulceration with accompanying visual loss.

5.4 Risk of Contamination

Do not touch the dropper tip to any surface as this may contaminate the gel.

5.5 For Administration by Healthcare Provider

IHEEZO is indicated for administration under the direct supervision of a healthcare provider. IHEEZO is not intended for patient self-administration.

6 ADVERSE REACTIONS

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 data described below reflect 201 patients undergoing various surgical ocular procedures in two placebo-controlled trials (Study 1 and Study 2). Patients in Study 1 were randomized to receive a single instillation of 3 drops of IHEEZO or placebo. Patients in Study 2 were randomized to receive a single or multiple instillations of 1, 3, or 3+3 drops of IHEEZO or placebo.

The most common adverse reactions in these studies (incidence greater than or equal to 5%) following IHEEZO administration were mydriasis, conjunctival hyperemia, and eye irritation.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate and well-controlled studies of IHEEZO use in pregnant women to inform a drug-associated risk. There are no animal reproduction studies for chloroprocaine.

8.2 Lactation

Risk Summary

There are no data on the presence of chloroprocaine in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for IHEEZO and any potential adverse effects on the breastfed infant from IHEEZO.

8.4 Pediatric Use

The safety and effectiveness of IHEEZO have not been established in pediatric patients.

8.5 Geriatric Use

No overall differences in safety or effectiveness of IHEEZO have been observed between elderly and younger patients.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Chloroprocaine, like other local anesthetics, blocks the generation and the conduction of nerve impulses, presumably by increasing the threshold for electrical excitation in the nerve, slowing the propagation of the nerve impulse, and reducing the rate of rise of the action potential. In general, the progression of anesthesia is related to the diameter, myelination, and conduction velocity of affected nerve fibers. Clinically, the order of loss of nerve function is as follows: (1) pain, (2) temperature, (3) touch, (4) proprioception, and (5) skeletal muscle tone.

12.3 Pharmacokinetics

The systemic exposure to chloroprocaine following topical ocular administration of IHEEZO has not been studied.

Elimination

Metabolism

Chloroprocaine is metabolized by plasma pseudocholinesterases and nonspecific esterases in ocular tissues. Chloroprocaine is rapidly metabolized in plasma by hydrolysis of the ester linkage by pseudocholinesterase. The hydrolysis of chloroprocaine results in the production of ß-diethylaminoethanol and 2-chloro-4-aminobenzoic acid, which inhibits the action of the sulfonamides.

Excretion

Chloroprocaine plasma half-life in vitro is approximately 25 seconds in adults and approximately 43 seconds in neonates. The kidney is the main excretory organ for most local anesthetics and their metabolites. Urinary excretion is affected by urinary perfusion and factors affecting urinary pH.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long-term studies in animals to evaluate carcinogenic potential of chloroprocaine have not been conducted.

Mutagenesis

2-chloroprocaine and the main metabolite, ACBA, were negative in the in vitro bacterial reverse mutation test (Ames assay) and the in vitro chromosome aberrations assay.

Impairment of Fertility

Studies in animals to evaluate the impairment of fertility have not been conducted with chloroprocaine.

14 CLINICAL STUDIES

14.1 Study 1 and Study 2

Study 1 (NCT04779606) and Study 2 (NCT04753710) were randomized, double-blinded, placebo-controlled studies conducted to evaluate the efficacy, safety, and local tolerability of IHEEZO in 145 healthy volunteers.

In Study 1, 85 healthy males and females were randomized in a 4:1 ratio to receive a single ocular instillation of IHEEZO (n=68) or placebo (n=17). The double-blinded treatment included an IHEEZO or a placebo dose of 3 drops instilled at 1-minute (±15 seconds) intervals in the right eye of each volunteer. The median age was 39 years (range 19 to 55 years); 59% female and 41% male.

In Study 2, 60 healthy males and females were randomized (40:20) to receive single or multiple ocular instillations of an IHEEZO dose of 3 drops in the right eye. The median age was 25 years (range 18 to 59 years); 54% female and 46% male.

The efficacy in Study 1 and Study 2 was determined by proportion of patients achieving full conjunctival anesthesia evaluated by conjunctival pinching 5 minutes after administration.

Efficacy results of Study 1

The proportion of subjects with successful anesthesia was 90% in the IHEEZO group and 12% in the placebo group (P<0.01). The median time for the IHEEZO group achieving anesthesia was 0.67 minutes. The median duration of anesthesia was 14.3 minutes.

Efficacy results of Study 2

The proportion of subjects with successful anesthesia was 95% in the IHEEZO group and 20% in the placebo group (P<0.01). The median time for the IHEEZO group achieving anesthesia was 0.67 minutes. The median duration of anesthesia was 19.3 minutes.

14.2 Study 3

Study 3 (NCT04685538) was a randomized, prospective, multicenter, active-controlled, observer-masked study conducted to evaluate the efficacy and safety of IHEEZO (n=166) versus tetracaine ophthalmic solution 0.5% (n=172) in patients undergoing cataract surgery.

The primary endpoint was defined as the proportion of patients in each treatment group gaining successful anesthesia without any supplementation. On average, patients needed 1 to 1.5 minutes to obtain sufficient anesthesia to successfully perform the surgical procedure, which lasted on average 22 minutes.

No patient treated with IHEEZO required supplemental treatment to complete the intended surgical procedure.

17 PATIENT COUNSELING INFORMATION

Eye Care Precaution

Do not touch the dropper tip to any surface as this may contaminate the gel. Advise patients that their eyes will be insensitive for up to 20 minutes due to the effect of the anesthetic, and that care should be taken to avoid accidental injuries.

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A MELANOMA MASQUERADER: CHOROIDAL VORTEX VEIN VARIX

Imaging and diagnostic pearls to help you distinguish a rare type of benign choroidal mass.

BY LAWRENCE CHIANG, BA; G. BRANDON CAUDILL, MD; AND CAROL L. SHIELDS, MD

The differential diagnosis for bilateral choroidal tumors includes several life-threatening conditions, such as choroidal metastasis, lymphoma, and melanoma.[1] However, there are benign choroidal lesions that can present bilaterally, including choroidal nevus and, rarely, vortex vein varix (VVV). This finding carries little to no risk for thrombosis but can simulate other choroidal tumors with serious clinical implications, including choroidal metastasis and melanoma.[1] Therefore, it is important to understand the imaging features of VVV to clearly differentiate this condition from potentially malignant lesions.[1]

Herein, we describe a rare case of bilateral VVV and discuss the imaging features that helped to characterize it.

CASE REPORT

A 46-year-old White female was referred to our ocular oncology service for evaluation of pigmented choroidal lesions with suspicion for choroidal melanoma or metastasis in each eye. Her family history and past medical history were noncontributory. On examination, her BCVA was 20/25 OD and 20/30 OS. IOP was within normal limits in each eye. Dilated fundus examination of the right eye revealed a subtle, superonasal, brown-red mass at the vortex vein ampulla measuring 3 x 3 mm in basal diameter and an estimated 2 mm in thickness (Figure 1A). Examination of the left eye revealed a similar brown-red mass at the superonasal vortex vein ampulla measuring 5 x 5 mm in basal dimension and an estimated 2 mm in thickness (Figure 1B). The mass became more apparent and appeared thicker when the patient's gaze was directed superonasally towards the lesion in each eye.

Ultrasonography confirmed the presence of an expansile mass with low internal reflectivity. The mass in the left eye demonstrated fluctuations in thickness ranging from 1.12 mm to 2.06 mm (Figure 2). The lesion spontaneously deflated in primary gaze and disappeared when digital pressure was applied to the eyelid onto the globe.

A pigmented choroidal mass that fluctuates in thickness or appearance with changes in gaze or with digital pressure is suggestive of VVV. Thus, a diagnosis of bilateral VVV was rendered, and the patient returned for 1- and 5-year follow-up appointments without change in the appearance of the vascular lesions in either eye.

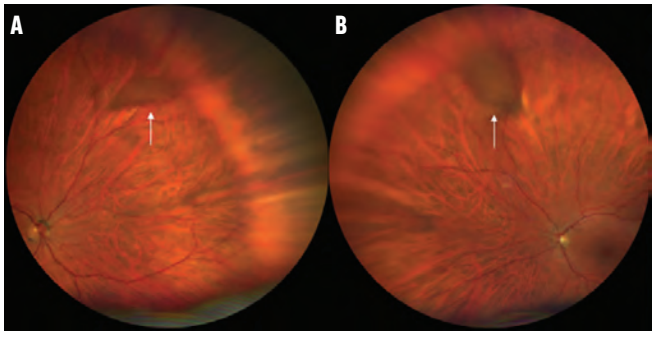

Figure 1. The fundus photograph at presentation showed brown-red subtle VVV in the superonasal quadrant (arrows) of both the right (A) and left (B) eyes, simulating choroidal melanoma.

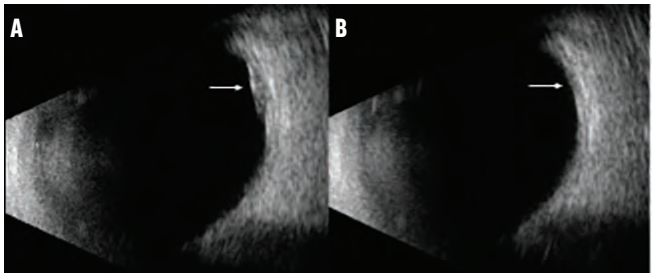

Figure 2. Ultrasonography showed dynamic fluctuations of the VVV in the left eye (arrows) with the lesion filling with blood up to 2.06 mm in thickness when the eye was positioned in the direction of the lesion (A) and draining down to 1.12 mm upon primary gaze (B).

DISCUSSION

VVV is almost always unilateral, making this bilateral case particularly unusual. The patient was referred for possible choroidal melanoma, but melanoma is rarely bilateral, estimated to occur in only 1 in 50 million people.[2] However, underlying conditions, such as oculodermal melanocytosis and BAP-1 cancer predisposition syndrome, can

promote bilateral choroidal melanoma.[3,4] Clinicians must also consider other bilateral pigmentary conditions in the differential diagnosis, such as choroidal nevi, choroidal freckling in neurofibromatosis type 1, choroidal hemorrhage in the elderly population, cutaneous melanoma metastasis to the choroid, and bilateral diffuse uveal melanocytic proliferation.

Literature Review

A PubMed search of keywords *bilateral* and *vortex vein varix* yielded few cases of bilateral VVV. One case by Osher et al described a 69-year-old male patient with dome-shaped, elevated VVV at the superonasal vortex ampulla in each eye.[5] Another case by Higham et al described a 7-month-old infant with Donnai Barrow syndrome who had giant vortex veins at the posterior pole.[6] The presence of multiple VVV within a single eye has been rarely observed.[1]

VVV is believed to be related to an aneurysmal dilation of the choroidal venous system, specifically the vortex vein ampulla, particularly if the episcleral vortex vein is kinked when the patient gazes in the direction of the ampulla.[1] This mass is usually seen in adults 45 years of age and older, and it occurs most frequently in the superonasal quadrant of the eye and near the globe equator, the anatomic location of the vortex vein ampulla.[1,5,7-9]

The specific etiology of VVV is not completely understood; however, there is a reported case in which VVV spontaneously resolved, leading to the hypothesis that venous congestion and venous collateralization could be the respective initiator and alleviator of this condition.[10] Fortunately, there are no known ocular complications, such as thrombosis or hemorrhage, or systemic conditions associated with VVV.[11] Thus, management involves annual monitoring.[12]

Distinguishing Features

The most important clinical implication of a bilateral VVV case is that it can resemble serious bilateral choroidal lesions, such as small choroidal metastasis, melanoma, nevus, and, rarely, circumscribed hemangioma.[13] On fundus examination, VVV presents as a brown-red nodule elevating the retina, reaching up to 6 mm in basal diameter and 2.5 mm to 3 mm in thickness.[1] On ultrasonography, the lesion may appear solid with medium internal reflectivity; the fluctuating nature is suggestive of a vascular, not solid, mass.[7] OCT of VVV typically demonstrates dilation of a choroidal vessel with a low reflectivity, suggestive of an ectatic vessel rather than a solid mass.[13] ICG angiography (ICGA) of VVV shows early hyperfluorescence with slow pooling of dye over 40 seconds.[1,8]

The most important differentiating feature of VVV is the unique tendency to fluctuate in size when filling with and draining blood, suggestive of a varix.[1] For example, on fundus photography, the VVV can be made to appear more prominent by having the patient look in the direction of the lesion; then, it disappears upon return to primary gaze.[1] Similarly, ICGA of VVV reveals gaze-evoked fluctuation of hyperfluorescence within the mass, and subsequent decreased hyperfluorescence upon return to primary gaze or with application of digital pressure to the globe.[1,7,8] Additionally, B-scan ultrasonography documents the waxing and waning of VVV with ocular movements.[1] Performing a Valsalva breath hold can also inflate the lesion on dynamic ultrasound imaging.[9]

FLUCTUATION IS KEY

VVV is a benign condition that can present bilaterally and may resemble other choroidal lesions, including melanoma. Implementing strategies to differentiate these conditions, including recognizing the fluctuating appearance of VVV, can lead to an accurate diagnosis. ■

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PATH TO THE PODIUM: RETINA

Avni P. Finn, MD, MBA; Yannek Leiderman, MD, PhD; Sarah Parker Read, MD, PhD; Yoshihiro Yonekawa, MD

YoungMD Connect recently hosted a special encore of our popular Path to the Podium Workshop, where we invited a panel of ophthalmic thought leaders to share their journeys of how they became sought-after speakers and consultants. This time we focused on retina, a subspecialty that has witnessed substantial growth in new technologies introduced to the clinic over the last decade, and one in which the pace of innovation only seems to be accelerating.

Our panel's most important message to the audience: New technologies and interventions create an inherent educational need; ophthalmology is unique among medical specialties in the working relationship between industry and physicians; those younger ophthalmologists now establishing their own careers have ample opportunity—if they are interested—to get on the podium and help advance the field.

PEARLS FROM THE PANEL

Preparing a presentation:

- **The more you read, the less you connect: Have structure, but have room to be extemporaneous.**
- **Your nightmare presentation may not be as bad as you think it is in the moment; keep going!**
- **If you are using a slide deck, think through the technical pieces: Avoid large videos, use universal fonts, and keep file sizes small for easy transfer.**

STEPS YOU CAN TAKE IN FELLOWSHIP

Avni P. Finn, MD, MBA

"Although fellowship is your time to hone your clinical skills, it is also a time to broaden your horizons and explore the things that you are passionate about."

- Talk to mentors about opportunities. Investigator initiated trials (IITs) are a great first step.
  - Industry needs feedback from the field 1) when new technologies/drugs are being studied or introduced to market, 2) about safety and efficacy, and 3) about usability and how they fit in real-world practice.
- Three tips for getting started:
  1. Networking is a skill: It comes naturally to some, most have to work at it.
  2. Practice your presenting and speaking skills.
  3. Express interest to people you meet in industry and to mentors who can help create opportunities for you: "The best way to do this is just by voicing your interest."

ESSENTIAL SKILLS THAT HELP SHAPE YOUR JOURNEY

Sarah Parker Read, MD, PhD

"At some point you stop getting grades, and you just have to do things you like to do "

- Several attributes make someone a good speaker, but connection with the audience is up there.
  - Try to present as much of your material as possible without notes. Practice presenting cases from memory during rounds and when talking to faculty.
  - The really good speakers don't talk to their slides; they set up the next one, and they guide listeners through the story their slides convey.
- Is work-life balance an "essential skill" in this regard?
  - I ask myself often: "Is the juice worth the squeeze?" If the reward you're getting out isn't worth the work you're putting in, it's fine to say no—and you're probably better off that way.

NO ONE WALKS ALONE: CONNECTING WITH INDUSTRY

Yannek Leiderman, MD, PhD

"Be genuine and do good work, and by that virtue, industry will want to work with you."

- The wave of innovation in retina creates opportunity for young ophthalmologists:
  - Those on the leading edge have an important role in relaying experiences back to industry and colleagues.
  - Being on the "leading edge" does not necessarily mean being a "first adopter." Don't force change just to study something.
- Top tip for getting noticed by industry:
  - Think about the last time you met a pushy salesman; did you enjoy the interaction? If not, make sure your eagerness doesn't come off the wrong way.

ASKING FOR DIRECTIONS: THE ROLE OF MENTORS AND HOW TO ENGAGE

Yoshihiro Yonekawa, MD

"I have had the great fortune in my career to have trained in several places, giving me exposure to an array of mentors. Equally as important is the variety of colleagues I've been able to collaborate with."

- I've learned from each unique person I've interacted with in training, and in some way, they've all been mentors: "Don't take your mentors for granted, and don't forget the friends you make along the way."
- The people you are in training with will be your peers and hopefully your friends for life. The learning opportunities extend to them, as well.
- Try to say yes when your mentors offer opportunities: "It's a snowball effect—the more you do the little things well, the more you will be trusted to do the big work."

CODING ADVISOR
A Collaboration Between *Retina Today* and AMERICAN ACADEMY™ OF OPHTHALMOLOGY Protecting Sight. Empowering Lives.

CODING AND REIMBURSEMENT FOR NEW DRUGS

Providers must stay up to date on payer policies, HCPCS codes, and more when therapies roll out of the pipeline.

BY JOY WOODKE, COE, OCS, OCSR

As new FDA-approved drugs to treat retinal diseases are introduced, physicians and their staff face increasing challenges to ensure prompt reimbursement. The pathway to consistent payer policies, permanent HCPCS codes, and prior authorization or step-therapy implications can be difficult to navigate.

As with any aspect of health care billing and reimbursement, coding requirements can change frequently, and it is crucial that physicians stay informed to avoid errors and denials. Using a consistent implementation checklist will assist in the process, and referencing the new medications and current coding guidance will provide perspective.

For example, there are currently two FDA-approved ranibizumab biosimilars with the same indications as the brand name ranibizumab (Lucentis, Genentech/Roche). Ranibizumab-nuna (Byooviz, Samsung Bioepis/Biogen) has been approved for the same indications as ranibizumab 0.5 mg/0.05 mL. Alternatively, ranibizumab-eqrn (Cimerli, Coherus Biosciences) offers 0.3 mg/0.05 mL and 0.5 mg/0.05 mL dosages for the same conditions as the brand name drug.

Additionally, the novel dual inhibitor faricimab-svoa (Vabysmo, Genentech/Roche) entered the retina space last year and targets both angiopoietin-2 and VEGF.

To help accurately reference new medications such as these, a modifiable reference guide can be useful for tracking the current coding guidance and any future updates (Table).

STEPS TO SUCCESS

Regardless of the type of new medication, there are essential steps to follow for coding and reimbursement success.

TABLE. NEW DRUGS FOR INTRAVITREAL INJECTION*

Drug (Brand, Company)	HCPCS	Descriptor	Units	NDC in 5-4-2 format
Ranibizumab-nuna 0.5 mg (Byooviz, Samsung Bioepis/Biogen)	Q5124	Injection, ranibizumab-nuna (Byooviz), biosimilar, 0.1 mg	5	64406-0019-07
Ranibizumab-eqrn 0.3 mg (Cimerli, Coherus Biosciences)	Q5128	Injection, ranibizumab-eqrn (Cimerli), biosimilar, 0.1 mg	3	70114-0440-01
Ranibizumab-eqrn 0.5 mg (Cimerli, Coherus Biosciences)	Q5128	Injection, ranibizumab-eqrn (Cimerli), biosimilar, 0.1 mg	5	70114-0441-01
Faricimab-svoa 6 mg (Vabysmo, Genentech/Roche)	J2777	Injection, faricimab-svoa (Vabysmo), 0.1 mg	60	50242-0096-01

*This information is as of April 1, 2023. To monitor changes, visit aao.org/retinapm and access the Table of Common Retina Drugs.

CODING QUICK LINKS

- Medicare Part B Policies
- AAO Intravitreal Injection Documentation Checklist
- Profitable Retina Series: Medication Inventory Management Module
- Retina Coding: Complete Reference Guide
- *Retina Today* Coding Advisor Column

Here are six steps to review and implement in your practice:

1. Review the FDA label and identify the indications for and frequency of the treatments, as this may vary from other medications currently used in the practice. For example, based on the FDA label, when treating diabetic macular edema with brolucizumab-dbll (Beovu, Novartis), the first five doses would be every 6 weeks (approximately 39–45 days) followed by an injection every 8–12 weeks. This is a different interval than anti-VEGF treatments that are often provided every 28 days.

2. Identify any published payer policies for the new drug and any unique documentation guidelines or required HCPCS codes. Some payers may designate a specific "not otherwise classified" NOC HCPCS code to report in their policy. For Medicare Part B policies, visit aao.org/lcds.

3. Audit chart documentation during internal chart reviews and confirm all requirements are included. The best practice would be completing an initial weekly audit to confirm the medical record and the procedure note templates are complete, followed by quarterly audits. You can double-check your work using the AAO's Intravitreal Injection Documentation Checklist.[1]

4. Report new drugs initially with the NOC HCPCS code J3490, J3590 (office setting) or C9399 (facility) until a permanent code is assigned. Faricimab-svoa, for example, was initially reported with an NOC HCPCS code until a permanent HCPCS code was published on October 1, 2022.

5. Confirm that the CMS-1500 includes the required information for the following items:

- Item 19 or EDI equivalent: medication name and dosage in mg/ml and invoice amount.
- Item 24a or EDI loop 2410: the unique national drug code for the medication in 5-4-2 format, proceeded by the "N4" qualifier, and the unit of measure (UOM).

For example, for 0.5 mg ranibizumab-eqrn, the national drug code should be "N470114044101" and the UOM should be "ML0.05." Not appropriately reporting this additional claim information will cause claim denials.

6. Use a quick reference guide for physicians and staff to track the current coding guidance for each drug used. This guide should be a "living document" so that when permanent HCPCS codes are assigned, you can update your internal resources. To watch for changes, visit aao.org/retinapm and access the Table of Common Retina Drugs.

7. Monitor remittance advice for appropriate reimbursement and create audit reports to monitor correct coding and payer allowables. Find case studies and audit reports in the Profitable Retina Series: Medication Inventory Management module.[2]

PRIOR AUTHORIZATION AND STEP THERAPY POLICIES

As new therapeutics are introduced, payers will revise prior authorization requirements. Additionally, step-therapy policies may be updated. For example, instead of just requiring bevacizumab (Avastin, Genentech/Roche) as an initial step—before aflibercept (Eylea, Regeneron Pharmaceuticals), ranibizumab, or faricimab-svoa—payers may add another step and document the failure of a ranibizumab biosimilar.

Missing a crucial update to a prior authorization or step-therapy policy will result in denied claims, often without retroactive resolution or appeal options.

New therapies are a welcome addition to the retina clinic, as they can provide significant hope for patients unhappy with their current treatment plan. At the same time, retina practices must integrate new options carefully to ensure the practice is also happy from a reimbursement standpoint. ■

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RISING STARS IN RETINA

Get to know outstanding retina fellows from the class of 2023.

Grant A. Justin, MD

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

As a medical student, I did an ophthalmology rotation at the Womack Army Medical Center, where the surgeons were doing high-volume refractive surgery, so I thought that I would become a cornea specialist. But once in residency, I was excited by the challenge of complex intraocular trauma. In Iraq and Afghanistan, there was a large increase in ophthalmic injuries compared with prior military conflicts. As a vitreoretinal surgeon, I will have the greatest immediate effect on an injured servicemember's long-term vision potential.

_RT:_ Who do you look to as mentors?

Colonel Marcus Colyer, MD, my mentor in the military, is a true leader and has been an incredible advocate for me.

At Duke, Eric A. Postel, MD, and Sharon Fekrat, MD, nurture your professional and personal growth. Glenn J. Jaffe, MD, has taught me to be precise in everything that I do from positioning a scleral buckle and having the best stool for your posture, to ensuring that the proper pop music is playing. Cynthia A. Toth, MD, and Lejla Vajzovic, MD, push me to always strive to be the best. Xi Chen, MD, PhD, has been the most incredible and patient surgical mentor, and she truly molded me into a vitreoretinal surgeon.

_RT:_ What has been a memorable experience of your fellowship?

Training at Duke, it has been humbling to operate in the same OR as many giants in our field. One of the longstanding traditions at Duke is the skit at the annual Advanced Vitreoretinal Surgery Course, and I enjoyed watching the early videos of Drs. Jaffe, Robert Machemer, and Brooks W. McCuen II, tearing off their shirts to "I'm Too Sexy" in the iconic "Robofellow" videos. Filming this year's skit with my cofellows and attendings has been a unique highlight of fellowship training.

_RT:_ What are you hoping to accomplish once you are in practice?

I'll be in the Army for 10 to 15 years, and I hope to become the residency program director at one of the Army's residency programs. I also plan to pursue my passion for pediatric retina at Children's National Hospital and meld my interests in pediatric retina and ocular trauma.

I would also love to live overseas and train vitreoretinal fellows in a developing country. There's a huge need for competent vitreoretinal surgeons to manage diabetic retinopathy, ocular trauma, and pediatric retinal disease.

FIRST CAREER MILESTONE

Dr. Justin will be returning to Walter Reed National Military Medical Center to serve as a vitreoretinal surgeon and research director.

_RT:_ What advice can you offer to residents who are considering retina?

When graduating from my Basic Officer Leadership Course, the major general giving the speech said, "Blossom where you are planted." My residency program was more clinically focused with less emphasis on academics, but I sought out and completed research opportunities.

Also, glean what you can from every case. The oculoplastics suturing skills help close sclerotomies, complex cataract surgery skills help with IOL repositioning, and looping muscles in pediatric cases is an invaluable tool for scleral buckling.

Lastly, become involved in retina societies, and reach out to giants in the field. It's always surprising who will answer a well-crafted email. ■

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PREVENTION OF POST-VITRECTOMY RETINAL DETACHMENTS


The debate continues on whether to use scleral buckling, vitrectomy, or both.

BY STEVE CHARLES, MD, FACS, FICS, AND ADAM PFLUGRATH, MD

Reducing the development of retinal detachments (RDs) after pars plana vitrectomy (PPV) to treat a variety of vitreoretinal disorders is an ongoing, ever-changing endeavor. The evolution of vitrectomy technology (25- and 27-gauge, high cutting rates, advanced fluidics, and endolaser photocoagulation) has led to additional treatment options and opportunities for improved patient outcomes.

Currently, many surgeons prefer to perform PPV over scleral buckle (SB) procedures for RDs.[1] Others advocate for using a SB or combining SB and PPV.[2] However, studies suggest that PPV/SB may not be efficacious.[3-5] In this article, we discuss risk factors for post-PPV RD and address the growing controversy regarding the best treatment approach for patients at high risk for this postoperative complication.

RD RISK FACTORS

There are several factors that lead to the development of postoperative RD. Eyes at the highest risk of developing post-PPV RD are those in which a posterior vitreous detachment (PVD) is created during vitrectomy. This can include macular hole repair, non-PVD associated detachments (young myopes with round holes), vitreomacular traction, vitreomacular schisis, and inherited collagenopathies, such as Stickler syndrome and Wagner syndrome.[6-8] The interaction between residual vitreous and the air, gas, or silicone bubbles may lead to new inferior retinal breaks.[9] The interaction with the superior aspect of perfluorocarbon liquid in cases of medium-term PFO may cause new superior retinal breaks.[10]

Eyes with a low risk of postoperative RD are those in which a prior PVD has occurred without RD, retinal break, or lattice degeneration; eyes with diabetic tractional RDs; and post-PPV eyes with sufficient vitreous removal accompanied by 360° scleral depression.

TO BUCKLE OR NOT TO BUCKLE

Some surgeons suggest using an SB or combined SB/PPV at the time of RD surgery.[2] Advocates of PPV/SB believe that the buckle reduces postoperative PPV RD compared with vitrectomy alone.[2] However, an argument can be made that it is the degree of retinopexy that provides the benefit.

Other studies have compared SB, PPV, and PPV/SB, and the data suggest that combining PPV with SB doesn't add any benefit. For example, in a meta-analysis comparing PPV with PPV/SB, there is similar single-surgery anatomic success between the approaches.[3] Further, a Cochrane review comparing SBs with PPV found low-certainty evidence favoring PPV.[4] Additionally, a large meta-analysis comparing PPV, SB, and pneumatic retinopexy found similar outcomes with PPV and SB with no added benefit of combined PPV/SB.[5] In Brazitikos et al, a series of vitrectomies without SB produced better RD outcomes than the PRO series of PPV outcomes, which included SBs.[11,12]

SBs are associated with 2.75 D of induced myopia, diplopia, infection, and extrusion.[10,13,14] The practical arguments for PPV alone are that there is no induced myopia or strabismus, and there are fewer ocular surface disorders due to minimal conjunctival and epithelial disruption.[15,16] Further, SBs induce significant tenons and conjunctival scarring, thereby creating challenges for and limiting the efficacy of potential future glaucoma filtering procedures.[17]

LASERS

The use of prophylactic 360° laser retinopexy versus localized laser retinopexy around identified retinal breaks to reduce the risk of post-PPV RD is an area of debate.[18] A large series in Japan noted a significant risk reduction of post-PPV RD with 360° laser retinopexy at the vitreous base.[19] Additionally, there is a threefold reduction in the incidence of postoperative RD with the use of prophylactic 360° laser retinopexy.[20,21] In particular, prophylactic extended vitreous base laser significantly reduces the risk of RD in patients with Stickler syndrome.[22] Thus, adjunct or prophylactic 360° laser retinopexy appears to be advantageous in the prevention of postoperative RD.

Higher laser power has the potential to create retinal breaks at the laser edges, formation of proliferative vitreoretinopathy, and pupillary abnormalities due to ciliary nerve

damage. However, the application of a low-intensity, nearly confluent laser to the vitreous base should reduce the risks.

Intraoperatively, endolaser photocoagulation is preferred to a laser indirect ophthalmoscope, as it improves surgeon ergonomics and prevents direct iris damage.

KEY TAKEAWAYS

SB combined with PPV may not be an efficacious approach to reduce the risk of post-vitrectomy RD.

Prophylactic 360° low-intensity endolaser photocoagulation at the vitreous base reduces postoperative RD and should be used in high-risk cases. ■

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(Continued from page 20)

papillopathy, and cataracts.[9] However, these are usually outweighed by the benefit of maintaining vision in patients who often have limited life expectancy.[9,10] The overall survival rate for patients with choroidal metastases is 57% at 1 year and 24% at 5 years, with a mean survival time of 17.2 months.[1]

FINAL PEARLS

Serous retinal detachment in the setting of multifocal choroidal lesions should be highly concerning for a metastatic process. In cases of bilateral and multifocal lesions, systemic chemotherapy is the preferred treatment strategy. Directed ocular therapies such as plaque radiotherapy, EBRT, or photodynamic therapy may be used in patients with unilateral metastasis, significant visual compromise, and/or inadequate response to chemotherapy. ■

Authors note: The Institution Review Board approval was waived for this retrospective case report study. The study was performed in compliance with the tenets of Declaration of Helsinki.

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IRIS DETAILS IN ADVANCED PVR

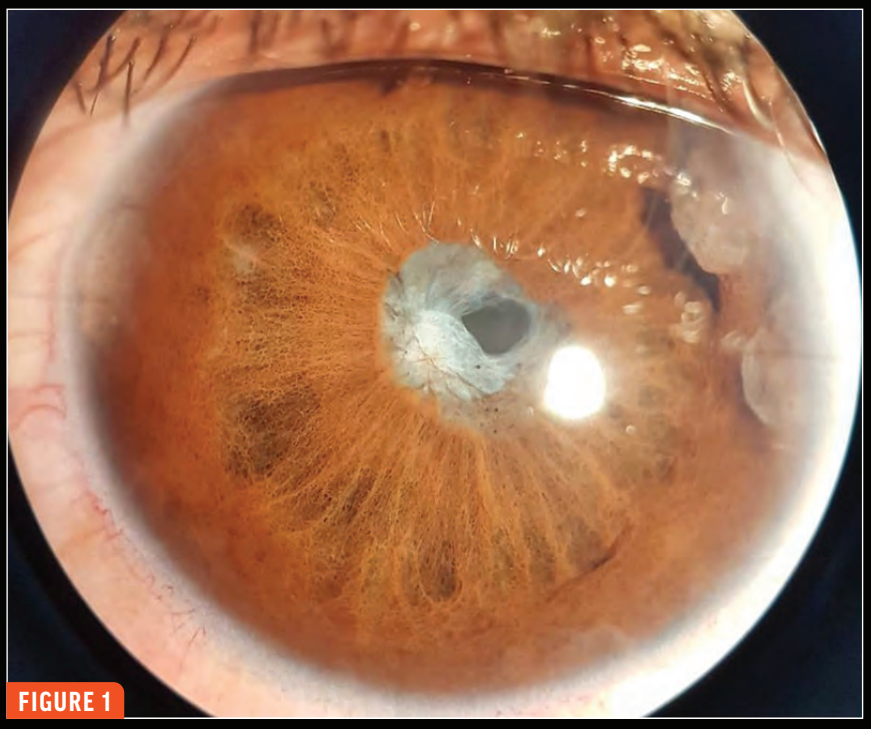


FIGURE 1

Examining the anterior segment can be informative when you suspect proliferative vitreoretinopathy.

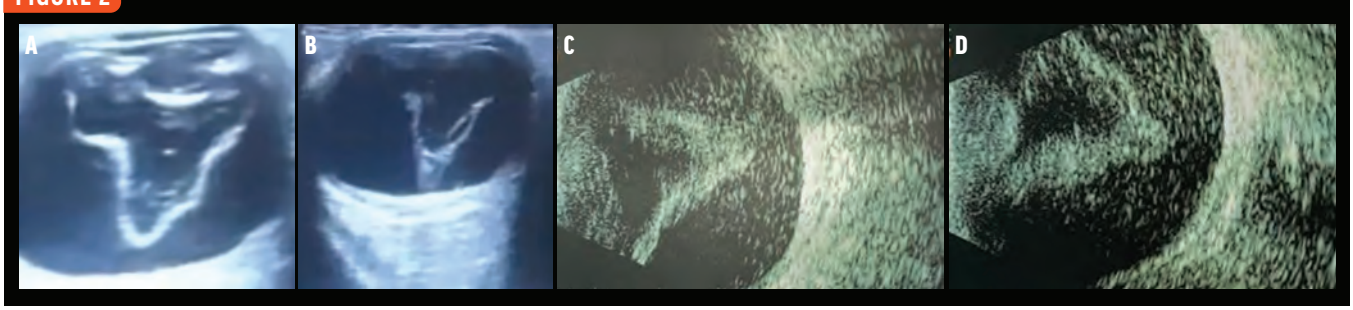
BY MAROUANE MASLIK, MD; YOUNES ABAAQIL, MD; NIDAL SHABAN, MD; SARAH BELGHMAIDI, MD, PHD; IBTISSAM HAJJI, MD, PHD; AND ABDELJALIL MOUTAOUAKIL, MD, PHD

Proliferative vitreoretinopathy (PVR) is a clinical syndrome associated with retinal traction and retinal detachment (RD), in which cells with proliferative potential multiply and contract on retinal surfaces and in the vitreous cavity.

PVR is the most common cause of surgical RD repair failure.[1] This condition presents with a spectrum of disease severity, ranging from subtle retinal wrinkling, to fixed folds and tears with rolled edges, to total rigid RD with retinal shortening and advanced periretinal proliferation.

Clinical evaluation of PVR is typically based on the fundus examination. However, certain clinical findings in the anterior segment can be highly indicative of the PVR stage, as demonstrated by the case presented here.

FIGURE 2



CASE PRESENTATION

A 52-year-old patient with high myopia and a familial history of RD presented to our clinic. He had undergone two prior surgeries for RD repair. VA was light perception OD. Anterior synechiae and peripheral iris retraction were noted in the anterior segment, signs that point to advanced PVR (Figure 1). Visualization of the retina was impossible, but B-scan ultrasonography confirmed a V-shaped RD (Figure 2).

DON'T NEGLECT THE ANTERIOR SEGMENT

The clinical evaluation of PVR should always start with an anterior segment examination to help determine the disease stage and inform the next steps in managing this serious complication of RD. If available, B-scan ultrasonography can help confirm findings noted on the anterior segment. ■

1. Idrees S, Sridhar J, Kuriyan AE. Proliferative vitreoretinopathy: a review. *Int Ophthalmol Clin*. 2019;59(1):221-240.

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ASHKAN M. ABBEY, MD

What led you to a career as a retina specialist?

My first exposure to ophthalmology was through my father, a comprehensive ophthalmologist. I vividly recall eating dinner and watching recordings of his cataract surgeries as a child. He assumed I would follow in his footsteps, but I was determined not to because I wanted to distinguish myself in my career.

In medical school, I quickly realized that microsurgery was my passion. I tried to convince myself that I wanted to be a hand surgeon, mostly to avoid the obvious path toward ophthalmology. After completing an uninspiring orthopedic surgery rotation, however, I was forced to admit that ophthalmology was the natural fit for my interests and abilities.

During my ophthalmology residency, I was most drawn to retina because I found it to be the most nuanced, challenging, and consequential thing I could do with my hands. Giving patients their vision back is one of the most rewarding things I can imagine. I love that I get to do interesting work that I'm passionate about and see it translate directly into a vastly improved quality of life for those I treat.

What is it like being the principal investigator for clinical trials?

Being a principal investigator for clinical trials enriches my career in many ways. It's exciting to help advance new, potentially sight-saving therapies that may eventually benefit patients. It also allows me to work with and learn from my counterparts in industry and academia and to manage a team in a different way than in my regular clinical practice. It brings a group of people together who are excited to advance the field of retina, and it seems to inspire all of us.

How did you choose Texas as your place of practice?

I came to Texas for the opportunities that I felt only Texas Retina Associates (TRA) could provide. TRA allowed me the latitude to craft the type of practice that I always hoped to have—with clinical and surgical aspects, but also a focus on research. With the blessing of my partners, many of whom have served as mentors to me, we have grown the research department in many exciting ways over the last few years.

Texas is a wonderful place to practice. I'm fortunate to practice in both urban and rural areas. Our flagship office in Dallas allows me to see unmatched diversity in both patients and pathology, and I often am challenged by complex secondary and tertiary referrals. I also travel to a satellite office in Rockwall, a growing city that is close to many rural areas east of Dallas. These patients are appreciative of quality care that doesn't require them to drive hours into the city.

Dr. Abbey with his wife, Melody, and children, Theo (6) and Elliott (3).

What do you hope to accomplish in the next year?

I hope to continue to maximize the potential of our research department at TRA while providing the highest quality care to my patients. We have initiated many new studies in the past few years, and many of our patients have benefited from participating in them. I also look forward to attending several retina meetings in 2023. It is gratifying to share data while also engaging, collaborating, and learning from my friends and colleagues in the retina community.

What changes on the horizon do you look forward to in the field?

I am excited about the potential for more durable therapies that can reduce the treatment burden for our patients. The pipeline has several exciting options in various phases of development that could address this challenge. I am specifically excited about gene therapy that creates an "ocular biofactory" in the eye to deliver anti-VEGF protein continuously for an extended period (possibly a lifetime). I also welcome the potential development of sustained-release polymers that may require an injection every 4 to 6 months.

Finally, I am looking forward to having options for the treatment of geographic atrophy (GA). Although I am happy to see that multiple therapies involving complement inhibition have been shown to reduce the progression of GA, I would love to see continued advancement of stem cell therapy to potentially restore vision for our GA patients. ■

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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)

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)]*.

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)]*

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 1,926 patients, which constituted the safety population in four Phase 3 studies *[see Clinical Studies (14.1, 14.2)]*.

Table 1: Common Adverse Reactions (≥ 1%)

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

The immunogenicity of VABYSMO was evaluated in plasma samples. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to VABYSMO in immunoassays. The detection of an immune response is highly dependent on the sensitivity and specificity of the assays used, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to VABYSMO with the incidence of antibodies to other products may be misleading.

There is a potential for an immune response in patients treated with VABYSMO. In the nAMD and DME studies, the pre-treatment incidence of anti-faricimab antibodies was approximately 1.8% and 0.8%, respectively. After initiation of dosing, anti-faricimab antibodies were detected in approximately 10.4% and 8.4% of patients with nAMD and DME respectively, treated with VABYSMO across studies and across treatment groups. As with all therapeutic proteins, there is a potential for immunogenicity with VABYSMO.

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 four clinical studies, approximately 60% (1,149/1,929) 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]
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*Primary endpoint of non-inferiority vs aflibercept was defined as the mean change from baseline in BCVA (measured by the ETDRS letter score) to 1 year (average of weeks 40, 44, and 48 in nAMD and weeks 48, 52, and 56 in DME) and was tested for non-inferiority using a margin of 4 letters.[1]
†After 4 or 6 monthly loading doses.[1] Please see below for more information.
‡Verana Health data from Q1–Q4 2022.[6]

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†Dosing Information:
DME dosing: 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). nAMD dosing: 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.[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) and Diabetic Macular Edema (DME).

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.

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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.

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 Brief Summary of full VABYSMO Prescribing Information on the following page.

References: 1. VABYSMO [package insert]. South San Francisco, CA: Genentech, Inc; 2023. **2.** Beovu® (brolucizumab-dbll) injection [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2022. **3.** Eylea® (aflibercept) [package insert]. Tarrytown, NY: Regeneron Pharmaceuticals, Inc; 2022. **4.** LUCENTIS® (ranibizumab) [package insert]. South San Francisco, CA: Genentech, Inc; 2018. **5.** SUSVIMO™ (ranibizumab injection) [package insert]. South San Francisco, CA: Genentech, Inc; 2022. **6.** Data on file. South San Francisco, CA: Genentech, Inc.

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

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