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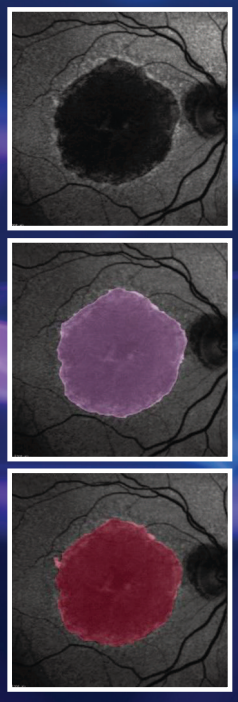


Digital Medicine in Retina

DEEP LEARNING for AMD screening and detection

The potential of automated imaging for identifying biomarkers. ***Page 18***

- How telemedicine and AI are changing DR screening. ***Page 22***

Also Inside

Online Videos

0.18 mg
YUTIQ®
(fluocinolone acetonide intravitreal implant) 0.18 mg

Discover continuous calm in uveitis[1]

YUTIQ is designed to deliver a sustained release of fluocinolone for up to 36 months for patients with chronic non-infectious uveitis affecting the posterior segment of the eye[1]

- Proven to reduce uveitis recurrence at 6 and 12 months[1]*
  At 6 months–18% for YUTIQ and 79% for sham for Study 1 and 22% for YUTIQ and 54% for sham for Study 2 (*P*<.01). At 12 months–28% for YUTIQ and 86% for sham for Study 1 and 33% for YUTIQ and 60% for sham for Study 2.
- Extended median time to first recurrence of uveitis[1,2]
  At 12 months–NE† for YUTIQ/92 days for sham in Study 1; NE for YUTIQ/187 days for sham in Study 2.
- Mean intraocular pressure (IOP) increase was comparable to sham[1,2]
  Study was not sized to detect statistically significant differences in mean IOP.

For more information, visit **YUTIQ.com**

*Study design: The efficacy of YUTIQ was assessed in 2 randomized, multicenter, sham-controlled, double-masked, Phase 3 studies in adult patients (N=282) with non-infectious uveitis affecting the posterior segment of the eye. The primary endpoint in both studies was the proportion of patients who experienced recurrence of uveitis in the study eye within 6 months of follow-up; recurrence was also assessed at 12 months. Recurrence was defined as either deterioration in visual acuity, vitreous haze attributable to non-infectious uveitis, or the need for rescue medications.

†NE=non-evaluable due to the low number of recurrences in the YUTIQ group.

INDICATIONS AND USAGE

YUTIQ® (fluocinolone acetonide intravitreal implant) 0.18 mg is indicated for the treatment of chronic non-infectious uveitis affecting the posterior segment of the eye.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

Ocular or Periocular Infections: YUTIQ is contraindicated in patients with active or suspected ocular or periocular infections including most viral disease of the cornea and conjunctiva including active epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections and fungal diseases.

Hypersensitivity: YUTIQ is contraindicated in patients with known hypersensitivity to any components of this product.

WARNINGS AND PRECAUTIONS

Intravitreal Injection-related Effects: Intravitreal injections, including those with YUTIQ, have been associated with endophthalmitis, eye inflammation, increased or decreased intraocular pressure, and choroidal or retinal detachments. Hypotony has been observed within 24 hours of injection and has resolved within 2 weeks. Patients should be monitored following the intravitreal injection.

Steroid-related Effects: Use of corticosteroids including YUTIQ may produce posterior subcapsular cataracts, increased intraocular pressure and glaucoma. Use of corticosteroids may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses. Corticosteroids are not recommended to be used in patients with a history of ocular herpes simplex because of the potential for reactivation of the viral infection.

Risk of Implant Migration: Patients in whom the posterior capsule of the lens is absent or has a tear are at risk of implant migration into the anterior chamber.

ADVERSE REACTIONS

In controlled studies, the most common adverse reactions reported were cataract development and increases in intraocular pressure.

Please see brief summary of full Prescribing Information on adjacent page.

References: 1. YUTIQ® (fluocinolone acetonide intravitreal implant) 0.18 mg full US Prescribing Information. EyePoint Pharmaceuticals, Inc. May 2021. **2.** Data on file.

EYEPOINT® PHARMACEUTICALS

480 Pleasant Street, Suite B300, Watertown, MA 02472
08/2021
US-YUT-2100061

YUTIQ® (fluocinolone acetonide intravitreal implant) 0.18 mg, for intravitreal injection
Initial U.S. Approval: 1963

BRIEF SUMMARY: Please see package insert for full prescribing information.

1. INDICATIONS AND USAGE. YUTIQ® (fluocinolone acetonide intravitreal implant) 0.18 mg is indicated for the treatment of chronic non-infectious uveitis affecting the posterior segment of the eye.

4. CONTRAINDICATIONS. 4.1. Ocular or Periocular Infections. YUTIQ is contraindicated in patients with active or suspected ocular or periocular infections including most viral disease of the cornea and conjunctiva including active epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections and fungal diseases. **4.2. Hypersensitivity.** YUTIQ is contraindicated in patients with known hypersensitivity to any components of this product.

5. WARNINGS AND PRECAUTIONS. 5.1. Intravitreal Injection-related Effects. Intravitreal injections, including those with YUTIQ, have been associated with endophthalmitis, eye inflammation, increased or decreased intraocular pressure, and choroidal or retinal detachments. Hypotony has been observed within 24 hours of injection and has resolved within 2 weeks. Patients should be monitored following the intravitreal injection *[see Patient Counseling Information (17) in the full prescribing information]*. **5.2. Steroid-related Effects.** Use of corticosteroids including YUTIQ may produce posterior subcapsular cataracts, increased intraocular pressure and glaucoma. Use of corticosteroids may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses. Corticosteroids are not recommended to be used in patients with a history of ocular herpes simplex because of the potential for reactivation of the viral infection. **5.3. Risk of Implant Migration.** Patients in whom the posterior capsule of the lens is absent or has a tear are at risk of implant migration into the anterior chamber.

6. ADVERSE REACTIONS. 6.1. Clinical Studies 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. Adverse reactions associated with ophthalmic steroids including YUTIQ include cataract formation and subsequent cataract surgery, elevated intraocular pressure, which may be associated with optic nerve damage, visual acuity and field defects, secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera. Studies 1 and 2 were multicenter, randomized, sham injection-controlled, masked trials in which patients with non-infectious uveitis affecting the posterior segment of the eye were treated once with either YUTIQ or sham injection, and then received standard care for the duration of the study. Study 3 was a multicenter, randomized, masked trial in which patients with non-infectious uveitis affecting the posterior segment of the eye were all treated once with YUTIQ, administered by one of two different applicators, and then received standard care for the duration of the study. Table 1 summarizes data available from studies 1, 2 and 3 through 12 months for study eyes treated with YUTIQ (n=226) or sham injection (n=94). The most common ocular (study eye) and non-ocular adverse reactions are shown in Table 1 and Table 2.

Table 1: Ocular Adverse Reactions Reported in ≥ 1% of Subject Eyes and Non-Ocular Adverse Reactions Reported in ≥ 2% of Patients

Ocular		
ADVERSE REACTIONS	**YUTIQ (N=226 Eyes) n (%)**	**Sham Injection (N=94 Eyes) n (%)**
Cataract[1]	63/113 (56%)	13/56 (23%)
Visual Acuity Reduced	33 (15%)	11 (12%)
Macular Edema	25 (11%)	33 (35%)
Uveitis	22 (10%)	33 (35%)
Conjunctival Hemorrhage	17 (8%)	5 (5%)
Eye Pain	17 (8%)	12 (13%)
Hypotony Of Eye	16 (7%)	1 (1%)
Anterior Chamber Inflammation	12 (5%)	6 (6%)
Dry Eye	10 (4%)	3 (3%)
Vitreous Opacities	9 (4%)	8 (9%)
Conjunctivitis	9 (4%)	5 (5%)
Posterior Capsule Opacification	8 (4%)	3 (3%)
Ocular Hyperemia	8 (4%)	7 (7%)
Vitreous Haze	7 (3%)	4 (4%)
Foreign Body Sensation In Eyes	7 (3%)	2 (2%)
Vitritis	6 (3%)	8 (9%)
Vitreous Floaters	6 (3%)	5 (5%)
Eye Pruritus	6 (3%)	5 (5%)
Conjunctival Hyperemia	5 (2%)	2 (2%)
Ocular Discomfort	5 (2%)	1 (1%)
Macular Fibrosis	5 (2%)	2 (2%)
Glaucoma	4 (2%)	1 (1%)
Photopsia	4 (2%)	2 (2%)

(continued)

Table 1: Ocular Adverse Reactions Reported in ≥ 1% of Subject Eyes and Non-Ocular Adverse Reactions Reported in ≥ 2% of Patients

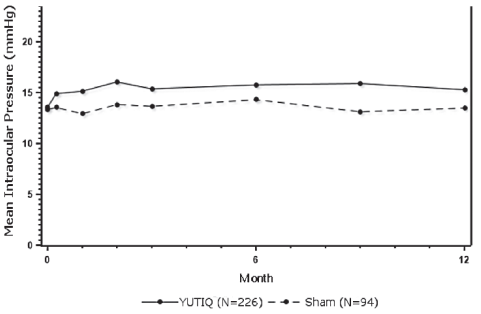
Ocular		
ADVERSE REACTIONS	**YUTIQ (N=226 Eyes) n (%)**	**Sham Injection (N=94 Eyes) n (%)**
Vitreous Hemorrhage	4 (2%)	0
Iridocyclitis	3 (1%)	7 (7%)
Eye Inflammation	3 (1%)	2 (2%)
Choroiditis	3 (1%)	1 (1%)
Eye Irritation	3 (1%)	1 (1%)
Visual Field Defect	3 (1%)	0
Lacrimation Increased	3 (1%)	0
Non-ocular		
ADVERSE REACTIONS	**YUTIQ (N=214 Patients) n (%)**	**Sham Injection (N=94 Patients) n (%)**
Nasopharyngitis	10 (5%)	5 (5%)
Hypertension	6 (3%)	1 (1%)
Arthralgia	5 (2%)	1 (1%)

1. Includes cataract, cataract subcapsular and lenticular opacities in study eyes that were phakic at baseline. 113 of the 226 YUTIQ study eyes were phakic at baseline; 56 of 94 sham-controlled study eyes were phakic at baseline.

Table 2: Summary of Elevated IOP Related Adverse Reactions

ADVERSE REACTIONS	YUTIQ (N=226 Eyes) n (%)	Sham (N=94 Eyes) n (%)
IOP elevation ≥ 10 mmHg from Baseline	50 (22%)	11 (12%)
IOP elevation > 30 mmHg	28 (12%)	3 (3%)
Any IOP-lowering medication	98 (43%)	39 (41%)
Any surgical intervention for elevated IOP	5 (2%)	2 (2%)

Figure 1: Mean IOP During the Studies



8. USE IN SPECIFIC POPULATIONS. 8.1 Pregnancy. Risk Summary. Adequate and well-controlled studies with YUTIQ have not been conducted in pregnant women to inform drug associated risk. Animal reproduction studies have not been conducted with YUTIQ. It is not known whether YUTIQ can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. YUTIQ should be given to a pregnant woman only if the potential benefit justifies the potential risk to the fetus. All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the United States general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. **8.2 Lactation.** Risk Summary. Systemically administered corticosteroids are present in human milk and can suppress growth, interfere with endogenous corticosteroid production. Clinical or nonclinical lactation studies have not been conducted with YUTIQ. It is not known whether intravitreal treatment with YUTIQ could result in sufficient systemic absorption to produce detectable quantities of fluocinolone acetonide in human milk, or affect breastfed infants or milk production. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for YUTIQ and any potential adverse effects on the breastfed child from YUTIQ. **8.4 Pediatric Use.** Safety and effectiveness of YUTIQ in pediatric patients have not been established. **8.5 Geriatric Use.** No overall differences in safety or effectiveness have been observed between elderly and younger patients.

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EDITORIAL

By Charles C. Wykoff, MD, PhD

'The FDA is on the line'

In the middle of a busy clinic on a Monday morning, my assistant stopped me and said, "The FDA is on the line for you." Over the next week, the Food and Drug Administration audited every patient I had enrolled in a clinical trial for a drug in regulatory review.

The auditors were impressive—professional, well-informed and meticulous, and they asked good questions. While auditing larger trial sites before final approval to verify the data within a new drug application is routine, the process can be anxiety-provoking.

Drug development in the United States is highly regulated. More than 90 percent of drugs that enter development fail.[1] The mean cost for those that make it to FDA approval is a stunning $1.34 billion, although the rate of ultimate FDA approval has increased among drugs entering Phase III trials from less than 50 percent to 62 percent between 2010 and 2017.[2]

One place where the FDA recently received constructive criticism is the use of advisory committees.[3] These are intended to be public forums that can offer insight to the FDA relating to decisions such as whether to approve a drug. They offer an opportunity for experts, patients, advocates and industry to offer views.

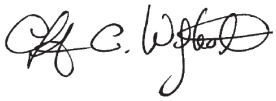
In 2010, more than half of new drug approvals had an associated advisory committee review. That dropped to 6 percent by 2021.[3] We're seeing this trend in retina as well. While pegaptanib, ranibizumab, aflibercept and ocriplasmin all received advisory committee reviews, more recent approvals, including brolucizumab, port-delivery system with ranibizumab and faricimab, did not.

There are many arguments on both sides, with some advocating for increased transparency regarding advisory committees,[3] especially after the controversy surrounding aducanumab for Alzheimer's disease.

Ultimately, all physicians play a critical role in this process. Brolucizumab is a perfect example. Intraocular inflammation and retinal vasculitis were only genuinely appreciated once the drug was commercialized.

I encourage you to engage in the regulatory process. It's easy to submit any problem encountered with a product through an FDA Form 3500. And remember the American Society of Retina Specialists' Research and Therapeutics (ReST) committee as well.

It's a privilege to serve on multiple teams dedicated to developing better therapeutics for our patients. I'm glad we are Team Retina together. And remember to always pick up the phone when the FDA is on the line.



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PROGRESSION IN GEOGRAPHIC ATROPHY IS RELENTLESS AND IRREVERSIBLE[1-4]

While GA progression may appear to move slowly, it can affect your patients faster than you think[1,4-6]

The consequences of Geographic Atrophy (GA) are too critical to be ignored[7-9]

IN A MEDIAN OF ONLY 2.5 YEARS,
GA lesions encroached on the fovea according to a prospective AREDS study (N=3640)[2]*

2 OUT OF 3 PATIENTS
lost the ability to drive in a median time of <2 years according to a retrospective study (n=523)[10]†

GA lesions can lead to visual impairment even before they reach the fovea[1,5,6]

See the effect of GA progression on your patients

*Data sourced from the Age-related Eye Disease Study (AREDS) Report #26—a long-term, multicenter, prospective study examining progression of GA area in a cohort of 3640 patients with signs of early and more advanced forms of AMD.

†A retrospective cohort analysis (N=1901) of a multicenter electronic medical record database examining disease burden and progression in patients in the United Kingdom with bilateral GA secondary to AMD.

BCVA=best-corrected visual acuity.

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Apellis

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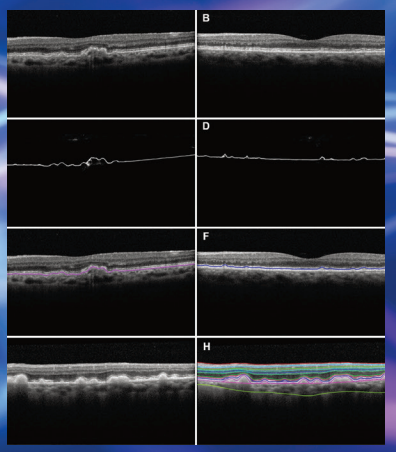
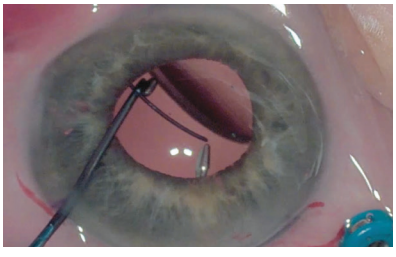
FEATURES

Focus on Digital Medicine in Retina



DEPARTMENTS



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Bevacizumab first, aflibercept second cost-effective for DME, Protocol AC finds

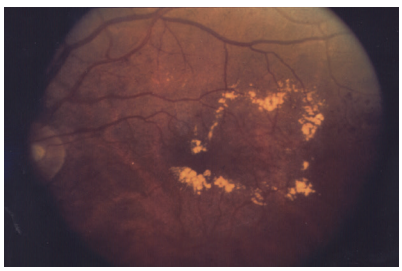
Starting treatment for diabetic macular degeneration with bevacizumab (Avastin) step therapy and switching to aflibercept (Eylea) seems to be just as effective for improving and maintaining vision over two years as starting and staying with aflibercept, and carries a substantial cost savings, according to the latest research from the DRCR Retina Network.[1]

Reporting results of the Protocol AC study, Chirag D. Jhaveri, MD, and colleagues evaluated 312 eyes in 270 adults who were randomized to aflibercept monotherapy (n=158) or bevacizumab first with a switch to aflibercept later (n=154). Dr. Jhaveri is with Retina Consultants of Austin and the Austin Research Center for Retina in Texas.

"Findings from this trial are particularly relevant given the increasing frequency of insurers mandating step therapy with bevacizumab before the use of other drugs that have been approved by the FDA," Dr. Jhaveri and colleagues wrote.

Obvious cost issues

Cost is the primary driver in the mandate for step therapy. The study noted that aflibercept is 26 times more expensive than bevacizumab: $1,830 vs. $70 per dose, according to Medicare data the study cited. DRCR Retina Network is developing a manuscript detailing the cost differences between the two treatment strategies, second author Adam R. Glassman, MS, executive director of the Jaeb Center for Health Research in Tampa, Fla., says in comments submitted via e-mail to *Retina Specialist*. The Jaeb Center organized the trial with the DRCR Retina Network,



For this, bevacizumab first then aflibercept may be as effective as aflibercept only, but the Protocol AC results aren't generalizable. (*NEI photo*)

Mr. Glassman further explains what this study adds to the literature.

"Prior to this study it was known that in eyes with center-involved diabetic macular edema and starting visual acuity of 20/50 or worse, treatment with aflibercept monotherapy resulted in superior outcomes compared with bevacizumab monotherapy," Mr. Glassman says. "It, however, was unknown how aflibercept monotherapy compared with bevacizumab first with a switch to aflibercept if the eye condition did not improve sufficiently.

"Based on the results of this study, we found no evidence that visual outcomes over a two-year period were different between aflibercept monotherapy and bevacizumab first with a switch to aflibercept when there was suboptimal response."

The primary outcome was mean change in visual acuity from baseline over two years (area under the curve): 15±8.5 letters for aflibercept monotherapy vs. 14±8.8 letters for bevacizumab-first (adjusted difference, 0.8 letters; 95% CI, –0.9 to 2.5; p=0.37).

Secondary outcomes

Findings for key secondary outcomes for the aflibercept monotherapy and bevacizumab-first groups, respectively, are:

- Mean change in visual acuity from baseline at two years: 14.7 ±14.5 vs. 15.9 ±12.4, with an adjusted between-group difference of –1.8 letters (95% CI, –4.9 to 1.2).

IN BRIEF

Apellis Pharmaceuticals reports that **pegcetacoplan** for treatment of geographic atrophy has shown lesion-growth reductions of 36 and 24 percent for monthly treatment and 29 and 25 percent for bimonthly dosing, according to the latest readouts from the Phase III DERBY and OAKS trials.

Twelve-month results of the Phase III GATHER2 trial of another investigative treatment for GA, **Zimura** (avacincaptad pegol), has shown a 14.3-percent reduction in lesion growth. Trial sponsor **Iveric Bio** says it plans to submit a New Drug Application with the Food and Drug Administration early next year.

Kodiak Sciences reports that the BEACON Phase III study of **KSI-301** (tarcocimab tedromer) met its primary endpoint—that is, noninferior change in visual acuity from baseline at 24 weeks compared to aflibercept in patients with macular edema due to retinal vein occlusion.

- 77 percent of eyes in each group had a >10-letter VA gain.
- Mean change in central subfield thickness from baseline to two years: –192 ±143 µm vs. –198 ±160 µm.

The aflibercept monotherapy eyes received fewer injections over two years on average: 14.6 ±4.1 vs. 16.1 ±4.1 injections. The bevacizumab-first eyes received 9.2 ±5.2 bevacizumab injections and 6.9 ±5.8 aflibercept treatments.

Study strengths

Regarding the strengths of the study, Mr. Glassman says, "This was a large National Institutes of Health-funded clinical trial conducted at 54 clinical sites across the United States. The study had strict criteria for retreatment and strict criteria for switching to aflibercept in the bevacizumab-first group, both of which were strongly adhered to during the study. The study also had good retention for a clinical trial in this population." Except for 14 patients who died, 88 percent of the patients completed the two-year trial.

"The biggest limitation in this study," Mr. Glassman adds, "is that we were only able to assess one set of switching criteria. Therefore, we do not know whether the results would have been different if stricter or milder criteria would have been used."

The study authors wrote that these findings are generalizable only to patients who receive therapy based on the same switching criteria, with the same anti-VEGF agents and using the same treatment algorithm in the Protocol AC trial.

"There are many components that go into deciding what treatment approach is best for an individual patient," Mr. Glassman says. "This study should allow for more informed decisions by clinicians and patients."

'Beyond reproach'

In an accompanying editorial,[2] David C. Musch, PhD, MPH, and Emily Y. Chew, MD, wrote, "The design, methods, and conduct of the current trial are beyond reproach."

They also noted that one of the issues with the bevacizumab-first strategy used in the trial is the frequent follow-up these patients required, which "exceeds what usually takes place in clinical practice." Dr. Musch and Dr. Chew cited previous DRCR Retina Network research that reported aflibercept wasn't cost-effective compared to ranibizumab,[3] but they added, "it is conceivable that some patients who receive bevacizumab first will have irreversible vision loss that might have been prevented with a prompt switch to aflibercept therapy."

Dr. Musch is with the University of Michigan and Dr. Chew with the National Eye Institute.

Dr. Jhaveri disclosed financial relationships with Genentech/Roche, Novartis and RegenxBio. Mr. Glassman disclosed relationships with Genentech/Roche and Regeneron Pharmaceuticals. The National Eye Institute and the National Institute of Diabetes and Digestive and Kidney Diseases provided study grants.

— Richard Mark Kirkner

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Epitheliopathy after a COVID-19 vaccine

Flashing spots and whitish blots: How OCTA can aid in diagnosis and surveillance.

By Saagar Pandit, MD, MPH, and Jason Hsu, MD

Saagar Pandit, MD, MPH

Jason Hsu, MD

A 39-year-old white female with no significant medical history presented with a complaint of increasing photopsias of both eyes for the previous two weeks. She received the first dose of her COVID-19 vaccine three weeks before the onset of ocular symptoms.

One week after she received the vaccination and two weeks before she came to the eye clinic, she developed viral-like symptoms of congestion, rhinorrhea and sore throat. She otherwise denied having a headache, fever, chills, joint aches, paresthesia or skin rashes. She was sexually active with only her husband.

Clinical work-up and imaging

Vision on presentation was 20/20 in both eyes. Intraocular pressure was 12 mmHg in both eyes and the anterior exam was unremarkable without cell or flare. The dilated fundus examination was significant for rare vitreous cell and multifocal hypopigmented plaques scattered throughout the macula and along the vascular arcades OU.

The optic nerves appeared normal with no evidence of disc edema, and the vasculature was normal without sheathing. No hemorrhages were noted in the periphery (*Figure 1*).

A targeted systemic work-up was unremarkable, including a quantiferon TB gold assay, syphilis immunoglobulin G antibody with reflex rapid plasma reagent and angiotensin converting enzyme, lysozyme, and an anteroposterior chest X-ray. Magnetic resonance imaging of the brain was deferred because her mini-mental status examination was normal and she had no neurologic deficits on examination.

Multimodal imaging of both eyes at presentation demonstrated globular hypoflourescent lesions on indocyanine green angiography with colocalizing optical coherence tomography angiography flow voids in the choriocapillaris (*Figure 2*).

OCT through the superior right macula highlighted retinal pigment epithelial atrophy, ellipsoid zone loss and outer nuclear layer thinning (*Figure 3*). OCT of the left macula through an active lesion demonstrated hyper-reflectivity of the ONL with underlying EZ attenuation (*Figure 3, green arrow*).

Fundus autofluorescence showed hypoautofluorescent lesions with edges of hyperautofluorescence, more prominent in the right eye than the left (*Figure 4*). Intravenous fluorescein angiography demonstrated classic early blocking with late hyperfluorescent lesions (*Figure 5, page 12*).

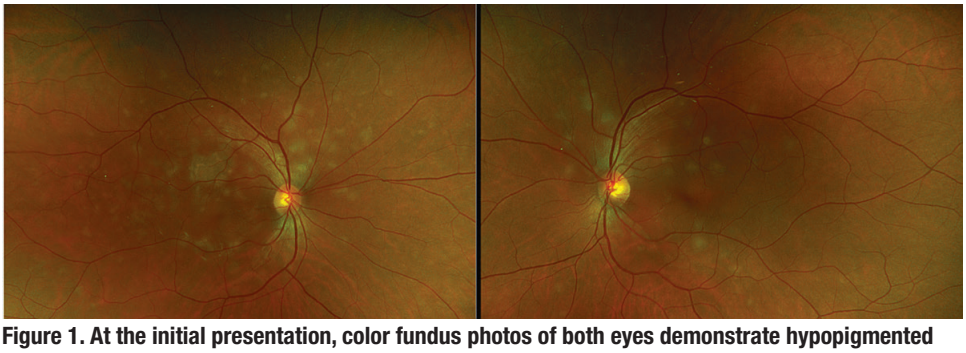

Figure 1. At the initial presentation, color fundus photos of both eyes demonstrate hypopigmented plaques within the macula and along the arcades.

Bios

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DISCLOSURES: Dr. Pandit and **Hsu** have no relevant financial relationships to disclose.

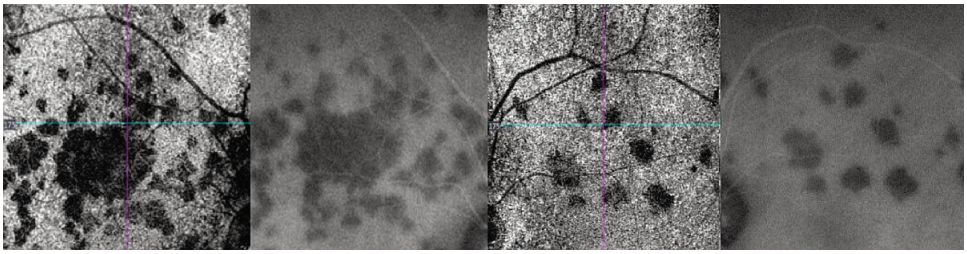

Figure 2. En-face choriocapillaris slabs on optical coherence tomography angiography demonstrate hypointense clustered lesions corresponding to areas of hypocyanescence on indocyanine green imaging. The correlation between the ICG and the OCTA slabs is excellent, which demonstrates choroidal changes in excess of what's seen on the fundus photo.

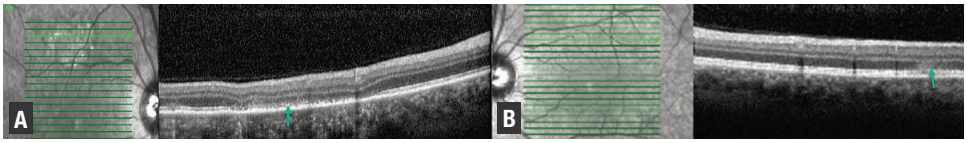

Figure 3. Spectral-domain optical coherence tomography of the right eye (A) shows areas of ellipsoid zone and retinal pigment epithelium (green arrow) disruption, while left eye scans (B) superior to the fovea demonstrate hyperreflectivity in the outer nuclear layer with underlying EZ attenuation (green arrow).

Additional work-up and treatment

We started the patient on 1 mg/kg oral prednisone (total of 50 mg) for the treatment of presumed acute posterior multifocal placoid pigment epitheliopathy (APMPPE). We tapered the steroids over three weeks.

On repeat examination two weeks later, the patient's vision remained at 20/20 and her floaters subsided. The plaque-like lesions were less prominent on fundus examination. OCTA demonstrated near complete resolution of flow voids within the choriocapillaris.

Five weeks after the initial presentation, the patient's fundus lesions resolved clinically with progressive RPE changes in the right eye only. OCT demonstrated persistent RPE thickening with overlying EZ loss in the right eye superior to the fovea. The remainder of the cube in the right and left eyes demonstrated EZ reconstitution and resolution of ONL hyper-reflectivity with trace ONL thinning. OCTA flow dramatically improved in the left eye, but with a few focal deficits within the macula that correlated to hypofluorescent spots on same-day ICG imaging (*Figure 6, page 12*).

Features of APMPPE

APMPPE is an inflammatory chorioretinopathy, with an estimated incidence of 0.15 cases per 100,000 people.[1] It typically presents between the second and fourth decades of life, affects men and women equally and can be associated with systemic conditions, most notably cerebral vasculitis.[2] Visual symptoms such as paracentral and central scotomas, photopsias and metamorphopsi, may occur. Approximately a

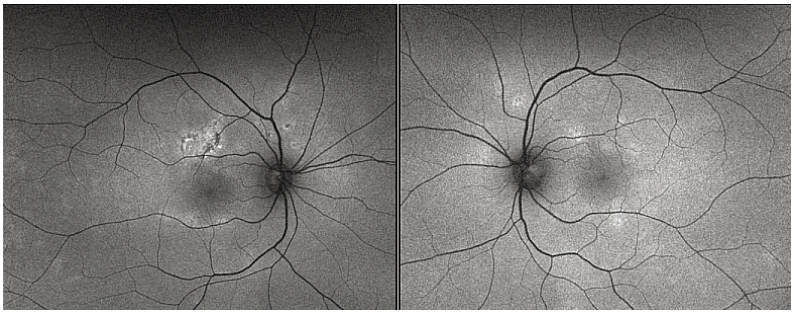

Figure 4. Fundus autofluorescence of the right and left eyes demonstrate corresponding areas of hypoautofluorescent superior to the fovea in the right eye and in the left eye bilateral multifocal hyperautofluorescent areas, which are fewer in quantity compared to the fundus photo.

third of patients will present with viral or flu-like illness before visual symptoms arise in APMPPE.[2] There have also been reports of development of APMPPE post-vaccine.[3]

The disease is usually self-limiting, with resolution typically occurring between four to six weeks, but it occasionally can take months to resolve. While most patients will have full visual recovery, a retrospective review of 183 patients with APMPPE demonstrated that approximately 25 percent will have a final visual acuity of 20/50 or worse, with foveal involvement conferring a worse visual prognosis.[3] Given its association with cerebral vasculitis and other neurologic conditions, a full neurologic evaluation and neuroimaging should be considered in patients suspected of having APMPPE.

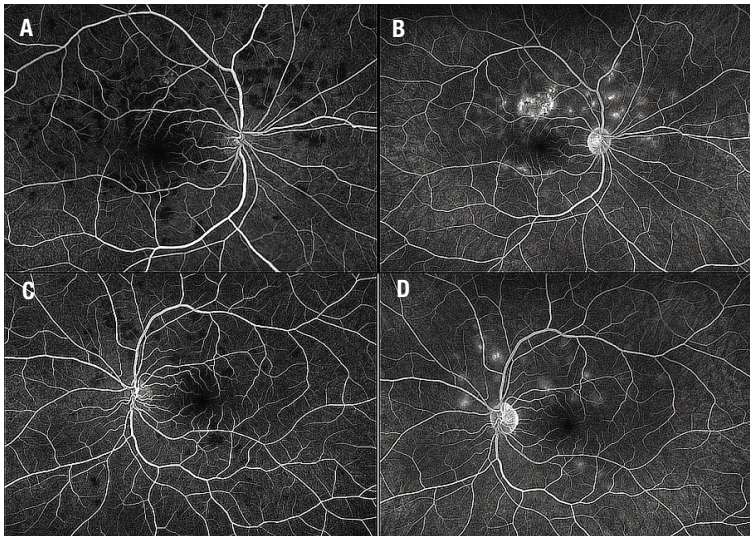

Figure 5. Intravenous fluorescein angiography shows early (A) blocking and late (B) staining in the right eye with similar findings in the left eye (C, D).

Pathogenesis of APMPPE

Currently, two theories regarding the pathogenesis of APMPPE prevail. The first, which J. Donald M. Gass, MD, proposed, suggested inflammation of the RPE and outer retina, characterized by the placoid lesions seen on examination during the acute phase of disease.[4] The second, by E. Michael Van Buskirk, MD, proposed that choroidal vasculitis was the cause of the placoid lesions.[5,6]

In active disease, IVFA will demonstrate hypofluorescent lesions, which are thought to represent masking of the choroidal fluorescence by the inflamed RPE and resultant blocking. In later phases of the study, these lesions then become hyperfluorescent. ICGA demonstrates early and late hypocyanescence due to poor perfusion to the choriocapillaris.

On FAF, lesions typically are hypoautofluorescent at the center with edges of hyperautofluorescence. OCT typically demonstrates

(Continued on page 41)

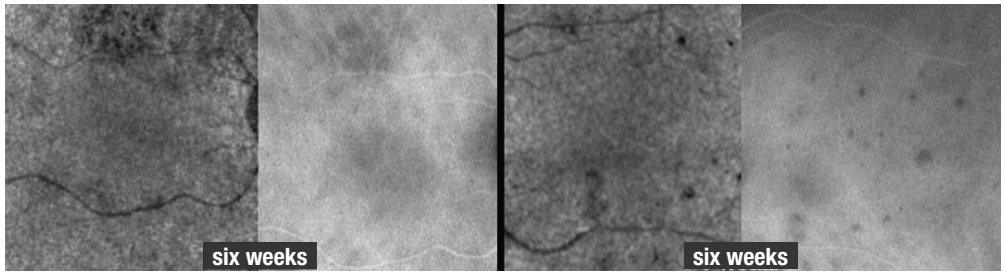

Figure 6. Optical coherence tomography angiography and indocyanine green angiography of the right and left eyes six weeks after the initial presentation show the lesions had significantly improved but haven't resolved (compare to Figure 2 for OCTA and ICGA images on initial presentation). A few more spots appear on ICG relative to the OCTA at six weeks, but the extent of improvement can be adequately visualized by both imaging modalities.

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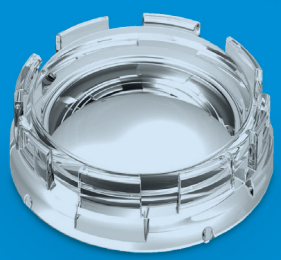

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Department Editor *By Akshay S. Thomas, MD, MS*

Managing UGH syndrome

Uveitis-glaucoma-hyphema syndrome, or Ellingson syndrome, requires surgery targeting the intraocular lens to resolve the cause of chafing.

By Andrew Nelson, MD, and Kareem Moussa, MD

Andrew Nelson, MD

Kareem Moussa, MD

Uveitis-glaucoma-hyphema syndrome, also known as Ellingson syndrome, was first described in 1977.[1] The syndrome is classically characterized by the triad of intraocular inflammation, recurrent hyphema and elevated intraocular pressure occurring in pseudophakic patients. Mechanical irritation of the iris, ciliary body or iridocorneal angle by foreign material, typically an intraocular lens implant, can result in pigment dispersion, hyphema, vitreous hemorrhage, increased intraocular pressure, intraocular inflammation and/or cystoid macular edema.

Diagnosis of UGH syndrome can be challenging due to this wide spectrum of findings. Definitive treatment is surgical, involving IOL repositioning, exchange or removal to resolve the cause of chafing.

UGH and anterior chamber IOLs

Thomas Ellingson, MD, first observed this syndrome in patients with a specific brand of anterior chamber IOLs, the Surgidev Mark VIII, and later observed it upon removal of the lenses after the footplates had warped.[1] He hypothesized that the footplates were mechanically irritating the iridocorneal angle structures, leading to recurrent hyphema and uveitis. Scanning electron microscopy of IOLs that were explanted due to UGH syndrome demonstrated irregular or sharpened IOL edges, along with deposition of inflammatory cells, erythrocytes and fibrous tissue at these edges, further supporting Dr. Ellingson's hypothesis.[2]

Other groups later further implicated anterior chamber IOLs in UGH syndrome.[3,4] These findings led to a movement toward improved quality control of IOL manufacturing as well as a preference for placing IOLs in the posterior chamber. Consequently, the incidence of UGH syndrome decreased in the subsequent years.[5]

UGH with posterior chamber IOLs

While anterior chamber IOLs are still a potential instigator of UGH syndrome, it was also shown to develop with IOLs placed in the posterior chamber. In 2009, a series of cases in which single-piece acrylic (SPA) IOLs were placed in the ciliary sulcus demonstrated an increased risk of UGH syndrome, as a majority of these patients developed pigment dispersion and iris transillumination defects, with smaller portions developing increased intraocular pressure and/or hyphema.[6]

SPA IOLs aren't manufactured for placement in the ciliary sulcus because the thick haptics, rough surface and lack of vaulting increase the risk of chafing of the posterior iris and ciliary body. So the recommendation is that, when intracapsular IOL placement isn't achievable, a three-piece IOL should be placed in the ciliary sulcus, with suture fixation if the capsular support isn't sufficient.

Rare cases of UGH syndrome with intracapsular SPA IOLs have also been reported, in which iris or ciliary body chafing was attributed to three causes:

- zonular laxity causing pseudophacodonesis;[7]
- anterior capsular fibrosis chafing anteriorly and displacing ciliary processes in plateau iris configuration;[7] or
- extensive capsular fibrosis (Soemmering ring) around the IOL haptics.[8]

Other causes of UGH syndrome may also be intraocular implants other than IOLs, including iris implants,[9] endocapsular tension rings[10] or glaucoma drainage implants,[11] though IOLs remain the most typical causative implant.

The retina specialist's role

Patients with UGH syndrome may be

Bios

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DISCLOSURES: Dr. Nelson and **Dr. Moussa** have no relationships to disclose.

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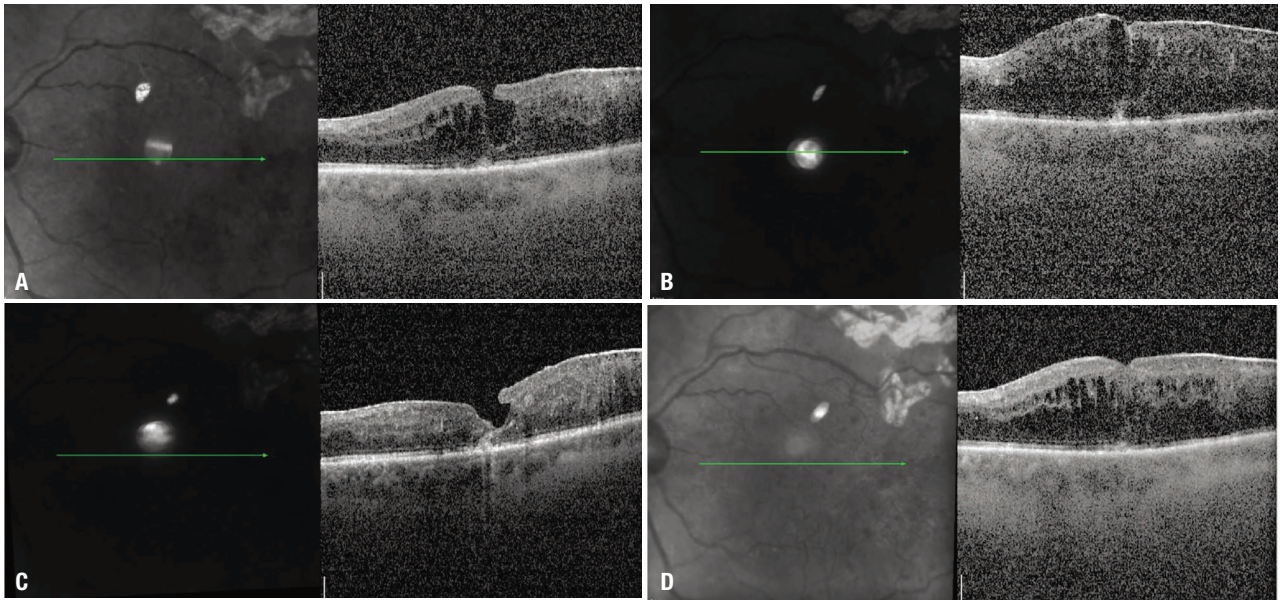

Figure 1. A) Optical coherence tomography scans demonstrate macular edema which (B) didn't improve after three intravitreal injections of aflibercept. C) The macular edema improved notably after an intravitreal injection of triamcinolone acetonide, although (D) it recurred four weeks later.

referred to a retina specialist for evaluation due to its potential for posterior-segment findings. A pseudophakic patient with a vitreous hemorrhage or macular edema of unclear etiology should raise suspicion for UGH syndrome. The workup should consist of a careful anterior segment examination, including evaluation of the IOL design, stability and haptic position in relation to the capsule.

Ultrasound biomicroscopy is useful in identifying any point of contact between IOL haptics and the posterior iris or ciliary processes.[12] We'll review two cases of UGH syndrome that presented with vitreoretinal involvement and discuss the key features on examination and imaging that helped us diagnose UGH syndrome as the cause of the posterior-segment pathology.

Case 1: Recurring UGH with DR

A 71-year-old man with a history of quiescent proliferative diabetic retinopathy in both eyes presented for evaluation of presumed diabetic macular edema in the left eye (*Figure 1A*). Visual acuity was 20/100. He received intravitreal aflibercept every four weeks for 12 weeks, but the macular edema continued to worsen (*Figure 1B*). He then underwent intravitreal triamcinolone acetonide (4 mg) injection, with significant improvement in macular edema two weeks later (*Figure 1C*).

Four weeks after the injection, the macular edema recurred (*Figure 1D*). A careful exam of the anterior segment showed a single-piece IOL in the sulcus with a transillumination defect in the iris in the shape of a haptic (*Figure 2A*). He was diagnosed with UGH syndrome and subsequently underwent pars plana vitrectomy, epiretinal membrane and internal limiting membrane peel, IOL removal and posterior sub-Tenon's triamcinolone acetonide injection. The macular edema resolved postoperatively (*Figure 2B*). His visual acuity was 20/50 with a contact lens and he chose to remain aphakic.

Case 2: Transient vision changes

A 73-year-old woman presented with transient vision changes in the left eye. She

described them as a sudden appearance of dark cobwebs, haziness and cloudiness that occurred three or four times over the past three months, lasting for hours each time. She reported a history of uncomplicated cataract surgery in both eyes four years earlier.

The examination revealed pseudophakia in both eyes, but was otherwise unremarkable. Based on the patient's symptoms, amaurosis fugax was a concern. The work-up for embolic disease was unremarkable. Carotid ultrasound revealed a 50 to 69 percent stenosis in the left internal carotid artery. Given the possibility for amaurosis fugax, the patient started on clopidogrel.

The patient continued to have recurrent symptoms. She presented three months later with elevated IOP, corneal edema, iritis and vitreous hemorrhage. An anterior segment exam showed temporal dislocation of a one-piece IOL out of the bag into the sulcus. Ultrasound biomicroscopy confirmed chafing of the intraocular lens in the sulcus and the posterior iris (*Figure 3*). The patient underwent pars plana vitrectomy and IOL exchange with a three-piece intraocular lens in the sulcus and subsequent resolution of symptoms.

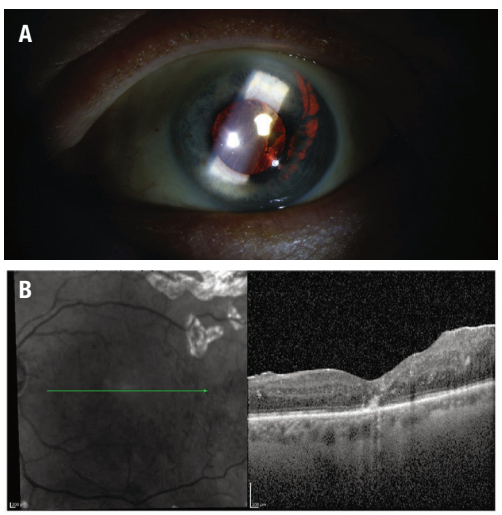

Figure 2. A) Slit-lamp photography shows a temporal iris transillumination defect in the shape of a lens haptic. B) The macular edema resolved postoperatively, as optical coherence tomography demonstrates.

Bottom line

UGH syndrome can cause vitreoretinal complications, such as CME and vitreous hemorrhage, and can masquerade as a primary retinal disease. Retina specialists should perform a careful exam of the lens in pseudophakic patients with CME or vitreous hemorrhage of unclear etiology to rule out UGH syndrome. Careful attention should be paid to the type of IOL placed (single- or three-piece) and the location of the lens relative to the lens capsule.

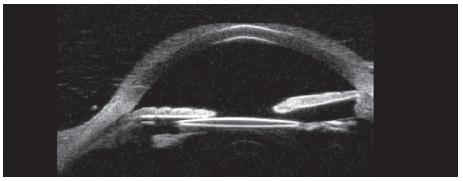

Figure 3. Ultrasound biomicroscopy shows dislocation of a portion of the intraocular lens out of the capsular bag with a point of contact between the lens optic and the posterior iris. *(Courtesy Karishma Chandra)*

A single-piece lens in the ciliary sulcus should raise a high suspicion for UGH. Ultrasound biomicroscopy can confirm a malpositioned IOL, especially if it's difficult to visualize the lens capsule on exam, which can happen with small pupils.

Surgery is indicated for treatment of UGH syndrome, either by repositioning a dislocated lens into the capsular bag or removing the malpositioned lens and replacing it with a three-piece lens in the sulcus—provided capsular support is sufficient. But if capsular support isn't sufficient to support a sulcus lens, consider a scleral-fixated or anterior-chamber IOL. RS

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GA: Recognizing the Burden

Peer Perspective with Dr Nancy Holekamp, Director of Retina Services at the Pepose Vision Institute

Sponsored by Apellis Pharmaceuticals

A 2021 survey of those living with geographic atrophy (GA) revealed that this disease has a profound effect on patients' lives, resulting in a large emotional burden and loss of independence. The global Geographic Atrophy Insights Survey (GAINS) (N=203), conducted by The Harris Poll and sponsored by Apellis Pharmaceuticals, found that for nearly 7 in 10 (68%) people living with GA, the impact of vision decline on their independence and quality of life is worse than they expected. There are several reasons for this, which we will explore in the following pages. To alleviate the added burden of misunderstanding or miscommunication, thinking about phrasing key clinical terms in a way that makes them easier for patients to grasp is an important consideration.[1,2]

Dispel GA Misconceptions

GA is not a well-understood disease. In fact, the GAINS survey found that respondents lacked basic information about GA, which could lead to significant consequences. For example, 76% of patients reported that they attributed their vision loss, prior to their diagnosis, to a natural part of aging. Half of patients (50%) were also under the assumption that wet AMD is the only form of AMD that can lead to vision loss. To that end, patients need a more accurate and comprehensive understanding of GA. Indeed, at diagnosis, patients express a strong desire for more information to better understand GA. In the current study, 86% of patients wish there were more educational materials for both patients and caregivers. Furthermore, patients want to know how progression can impact their lives. Specifically, 83% said they wish they knew at the time of diagnosis the irreversible impact GA would have on their vision.[1]

76% of people living with GA agree that prior to their diagnosis, **they attributed their vision loss to a natural part of aging***

86% **wish there were more educational materials** available for patients and caregivers

83% At the time of diagnosis, wish they understood **the irreversible impact GA would have on their vision**

**All statistical graphics in this article are from the GAINS study (N=203)*

Although we need to communicate the facts about GA, we should also be conscious of how we talk to our patients. One way we simplify communication and reduce misunderstandings at our clinic is to clearly explain what geographic atrophy is at the initial diagnosis. After that, I keep things simple with patients and use the term "GA," rather than "geographic atrophy" or "dry AMD." It may seem like a small thing, but whatever we can do to make the vocabulary easier for patients is worth considering. That said, even simple terms like "blindness" can be misunderstood. When patients hear this word, they think complete darkness, which can make coping with GA much more difficult. Granted, it is challenging to explain the nature of GA vision loss. It's not like wet AMD, where you can show patients a picture simulating the central distortion and blurred area caused by leakage from abnormal blood vessels. GA can produce scotomas, which are experienced as missing vision or lack of resolution. That's very difficult for patients to conceptualize and verbalize, which only adds to our difficulties in communicating about GA and how it affects vision. Also, no two people experience a GA scotoma the same way. Every scotoma is different.[2,3]

As ECPs, we have some misconceptions too. Best corrected visual acuity is widely accepted by the clinical community and regulatory authorities worldwide as a key measure of visual function. However, this is a measure of central acuity of the fovea, and is poorly correlated with GA lesion size. Best-corrected visual acuity does not assess all nuances of comprehensive visual function. GA can grow in a unique, foveal sparing pattern that tends to involve the fovea only late in the course of the disease. Snellen visual acuity measurements do not capture GA. Just because a patient can pick out letters on an eye chart doesn't mean they can read a book or feel comfortable driving. Other measurements are needed. This is also evidenced in The Harris Poll findings. Specifically, nearly 1 in 3 (31%) patients said their vision started to decline or worsen prior to diagnosis with GA. Similarly, it's important to consider all the ways that GA is experienced by patients—beyond visual acuity loss. The survey results elucidate this as well. Specifically, patients most commonly note that they need brighter light when reading or doing close-up work (85%) and that they also experience an inability to drive at night (ie, in the dark) (83%).[1,4]

83% of patients note that they experience **the inability to drive at night**

Progression of Vision Loss Is Urgent

In contrast to the medical community's perception of GA being a disease that progresses slowly, most patients in GAINS perceive the disease as advancing more quickly than they had originally expected. In fact, most patients surveyed by The Harris Poll were surprised by the severity and speed of the disease's impact on their vision. Specifically, 77% said that the impact on their vision happened faster than they expected and 68% said the impact of the vision decline on their quality of life and independence is worse than they expected.[1]

agree the **impact** of vision decline on **QOL** and **independence** is **worse than they expected**

As clinicians, we talk about GA being a slow-moving disease because we are comparing it to the faster progression of vision loss with untreated wet AMD, but patients may not be able to relate to this. We need to rethink how we describe disease progression. From the patient's perspective, vision loss may occur surprisingly fast because it's closely tied to their experience of the world and their quality of life. With that in mind, when discussing GA with patients, it's much clearer to explain what it will be like to experience the loss. Consider that the GAINS survey found 70% of patients rely on a caregiver to help with various tasks—most commonly driving at night (42%) or during the day (33%).[1] Any loss of independence is likely to substantially impact their quality of life.

70% of patients **rely on a caregiver to help with various tasks**

"In contrast to the medical community's perception of GA being a disease that progresses slowly, most patients in GAINS perceive the disease as advancing more quickly than they had originally expected."

~8 out of **10** (77%) agree their vision was impacted **faster than they expected**

"It may seem like a small thing, but whatever we can do to make the vocabulary easier for patients is worth considering."

Acknowledge Loss of Independence

Many of our GA patients' needs are met by spouses, sons, daughters and other caregivers. This might include driving them to medical appointments, shopping and preparing meals, reading mail, paying bills, and more. Adult children wonder when they should "take away" the car keys, write all of the checks, put out medications, and manage all the little things that we often take for granted but are indicators of our independence. Caregivers may perceive all of this responsibility as a burden, but in my experience, it's also often uncomfortable for the GA patients who don't want to rely on others, particularly their children.[1]

In patients who have GA, loss of independence may not be something that families grapple with decades after a diagnosis. It can happen much more quickly. On average, surveyed patients started relying on caregiver support as early as 2.6 years following diagnosis. In the US, caregiver dependency begins just 1.6 years on average after diagnosis. But asking for this help isn't easy. Although two-thirds (68%) of patients feel dependent on others due to their vision loss, more than half (53%) feel uncomfortable asking for help.[1]

1.6 YEARS In the US, **caregiver dependency begins just 1.6 years after diagnosis on average**

Of course, not everybody has a strong support network. Some patients have no one to turn to for the level of care they need with GA. We see this all the time in our clinic. As the patient's vision gets worse, they take a bus or a taxi to their appointment. In my clinic, we sometimes see patients who are struggling with personal grooming—through no fault of their own. It's important to look out for these subtle cues. When you talk to these patients, they might share that they're also having difficulty keeping their houses clean. In many cases, these patients may have to move into assisted living, which can be very difficult for those who cherish their independence or have lived in their family home for a long time.[1]

Recognize Emotional Toll

Most patients surveyed by The Harris Poll (68%) find it hard to enjoy life as much as they had prior to their GA diagnosis. For example, many report that the disease has a major or moderate negative impact on their ability to pursue activities such as driving (74%), reading (68%), traveling (62%), hobbies and social activities (43%), and the ability to work or volunteer (42%). Consequently, patients most commonly report feeling anxious (46%), powerless (39%), or frustrated (33%) as a result of their vision loss or impairment. Indeed, GA can have a deep emotional toll, so much so that about 1 in 3 (35%) patients reported that they had withdrawn from their social lives due to their condition.[1]

~1 in **3** (35%) **withdrew** from their **social lives** due to their condition

The atmosphere in the exam room often reflects this. When you're with a GA patient, the office visits tend to be very muted and the tone of the office visit is one of empathy and sympathy. Sometimes, patients are depressed and therefore quiet, and you have to rely on what the caregiver is noticing. It's a drain on everyone—medical staff included. As doctors, we know it's our job to help, yet our options are currently very limited. Meanwhile, it's a race against the clock as patients continue to progressively and irreversibly lose vision.[1,5]

68% of patients **find it hard to enjoy life as much as they had prior to their GA diagnosis**

"As clinicians, we talk about GA being a slow-moving disease because we are comparing it to the faster progression of vision loss with untreated wet AMD, but patients may not be able to relate to this."

Keeping a Positive Attitude

Mustering optimism can be a challenge in these circumstances, but I try to be forward thinking because I know that we must do everything we can to help these patients. This begins with awareness. We need to educate our patients about the realities of GA. GAINS found that 91% want more information and options about GA to feel empowered to take control of their disease.[1]

91% want more information and options about GA to feel empowered to take control of their disease

We can also do more to bring attention to GA within our profession. My hope is that one day we will be with GA where we are with wet AMD. In the meantime, it's important to recognize that there are really big differences in patient experiences with these 2 conditions and in how we need to approach care and communication. As with any disease, the earlier we detect it, the better. This will require further education of all primary eye care providers and increased utilization of non-invasive imaging techniques such as fundus autofluorescence and spectral domain OCT. We need to advocate for our patients by educating our peers about the importance of early detection and early action.[6,7]

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This article was developed in conjunction with and sponsored by Apellis Pharmaceuticals, based on an interview with Dr Nancy Holekamp. Dr Holekamp received a fee for her participation

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Survey Design

The global Geographic Atrophy Insights Survey (GAINS) was sponsored by Apellis and conducted by The Harris Poll between October 12 to December 10, 2021. To accommodate visually impaired respondents, the survey was conducted online and via the telephone among 203 participants aged 60 or over (mean age 70 years) residing in the US, UK, France, Germany, Italy, the Netherlands, Sweden, Canada, and Australia who self-reported that they have been diagnosed with age-related macular degeneration (AMD) and have dry AMD in at least 1 of their eyes. They must also have indicated that they have advanced atrophic age-related macular degeneration or advanced atrophic AMD, advanced/late/late-stage dry age-related macular degeneration or advanced dry AMD, or geographic atrophy (GA) in 1 or both of their eyes. Included patients must have been currently experiencing at least 3 GA symptoms and currently do/used to do/or have been suggested by an eye care professional but have not done at least one of the following: Take a high-dose formulation of antioxidant vitamins and minerals, stop smoking, maintain a healthy weight and exercise regularly, choose a healthy diet, manage other medical conditions, have check-ups of the retina regularly, or wear sunglasses with UV protection. Included patients must not have been diagnosed with glaucoma, Stargardt disease, or dementia, or be receiving regular injections into the affected eye every 4 to 6 weeks.

Raw data were not weighted at the individual country level and are therefore only representative of the individuals who completed the survey. For the global total, a post-weight was applied to adjust for the relative size of each country's adult population within the total adult population across all countries surveyed.

Respondents for this survey were selected from among those who have agreed to participate in our surveys. The sampling precision of Harris online polls is measured by using a Bayesian credible interval. For this study, the sample data is accurate to within ±7.8 percentage points using a 95% confidence level and ±6.5 percentage points using a 90% confidence level. This credible interval will be wider among subsets of the surveyed population of interest.

All sample surveys and polls, whether or not they use probability sampling, are subject to other multiple sources of error which are most often not possible to quantify or estimate, including, but not limited to coverage error, error associated with nonresponse, error associated with question wording and response options, and post-survey weighting and adjustments.

Sponsored by Apellis

Scleral-fixated IOLs: A modified approach

An optimization of methods to improve efficiency when managing a scleral-fixated intraocular lenses in the operating room.

By Venkatkrish M. Kasetty, MD, and Michael D. Ober, MD

For eyes without capsular support, a number of solutions are available including anterior chamber intraocular lenses, iris-fixated or sutured IOLs, and scleral-fixated intraocular lenses.[1] Once the realm of cataract surgeons, dislocated IOLs are often better suited to a posterior-segment approach, especially if they're displaced into the vitreous cavity.

Shin Yamane, MD, and colleagues popularized an anterior-segment method using needle docking of haptics for scleral fixation.[2] Jonathan Prenner, MD, further modified this technique for a posterior-segment surgeon. George Williams, MD, later substituted needles for 25-gauge cannulas, greatly simplifying the most tedious step.[3] Mark Walsh, MD, PhD, then published a description utilizing 27-g cannulas resulting in tighter haptic clearance. [4]

Following this evolution of techniques, we have modified a few minor steps to accommodate our own individual surgical preferences. The following highlight a few key components that can aid in the adoption of this complex yet elegant solution to the loss of capsular support.

Adjust the cannula position

Cannulas should be positioned 1.75 to 2 mm posterior to the limbus centered on the visual axis. A vertical orientation is preferred because the white-to-white distance is shorter than horizontal placement, resulting in reduced stretching forces on the haptics. However, rotation by up to one clock hour or so off the vertical axis may sometimes help to facilitate hand position around the nose (especially in a right eye) or to avoid areas with considerations such as a bleb (*Figure 1*).

Use a Kuglin hook

We prefer to always fixate the superior haptic first because this allows for an optimal view even through a small pupil. Drop the leading haptic through the pupil into the vitreous cavity and leave the trailing haptic in the corneal wound to hold it in place. Then with your left hand gently nudge the trailing haptic into the eye with a Kuglin hook through a paracentesis until the instrument suspends it over the pupillary axis (*Figure 2*). Next, use the forceps in your right hand to grasp the haptic tip.

Using the Kuglin hook has two key advantages over a more-often-used second forceps:

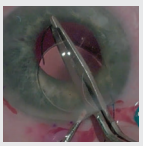
- it's autoclaved between cases and thus doesn't add to surgical case cost; and
- it won't crush or damage the haptic while holding it in place.

Using two forceps on the same haptic for a handshake maneuver requires differential force from each hand (firm for the tip, light to none for manipulation) and takes a

(Continued on p. 41)

View the Video

Dr. Kasetty and Dr. Ober demonstrate their techniques for scleral fixation of a dislocated intraocular lens. Available at: https://bit.ly/VideoPearl-031



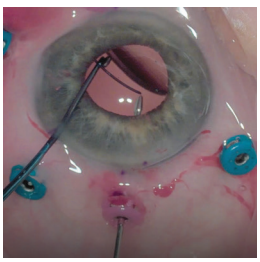


Figure 2. A Kuglin hook can be used to suspend the trailing haptic over the pupil where it can easily be accessed by the 27-gauge MAXgrip Forceps (Alcon).

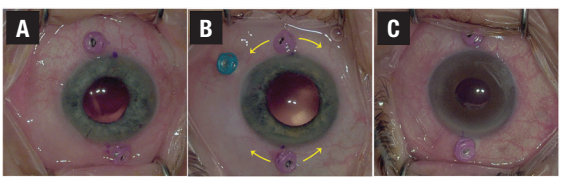
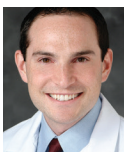


Figure 1. Cannulas are placed 1.75 to 2 mm posterior to the limbus, 180° apart and centered vertically on the visual axis. B) Cannulas can be placed clockwise or counterclockwise (arrows) a few degrees from vertical to avoid the nose or a bleb. A) and C) show examples of cannulas rotated from the vertical axis counterclockwise and clockwise, respectively.

Venkatkrish M. Kasetty, MD



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Bios

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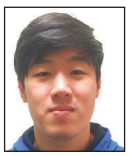
DISCLOSURES: The authors and **Dr. Hahn** have no relevant disclosures.

Focus on Digital Medicine in Retina

Deep learning for AMD screening and detection

The potential of automated imaging for finding and monitoring age-related macular degeneration biomarkers.


Zubin Mishra, BS


Ziyuan Wang


Sajib Saha, PhD


SriniVas Sadda, MD


Zhihong Jewel Hu, PhD, ECE

Bios

Mr. Mishra is a research intern at Doheny Eye Institute, Pasadena, California, and graduate student at the Case Western Reserve University School of Medicine, Cleveland.

Mr. Wang is a research intern at Doheny Eye Institute and an undergraduate student at the University of California Los Angeles School of Engineering.
(continued on page 19)

By Zubin Mishra, BS, Ziyuan Wang, Sajib Saha, PhD, SriniVas Sadda, MD, and Zhihong Jewel Hu, PhD, ECE

Take-home points

- Optical coherence tomography and fundus autofluorescence offer many opportunities to further understand age-related macular degeneration biomarkers, but they generate massive amounts of data. The artificial intelligence deep-learning technique is a potential solution to automatically analyze these data for clinical trials and research.
- Deep learning offers a potential solution to automatically screen for and detect advanced atrophic AMD or geographic atrophy while preserving much of the accuracy of manual delineation.
- Early identification of biomarkers associated with AMD could enable staging and monitoring of patients at appropriate intervals, while also enabling development of new preventative therapeutics and early intervention studies
- Automatic screening and detection of AMD features using deep learning has shown promise in facilitating further clinical trials and research and improving the efficiency of diagnosis and staging, reducing the burden of AMD on the health-care system.

An estimated 8 million people in the United States age 55 and older have some form of intermediate or advanced AMD[1, 2] and automated techniques could play a critical role in the timely screening and detection of these patients. Ideally, AMD would be caught in its early stages before it progresses to irreversible vision loss due to complications such as outer retinal atrophy or exudative neovascular membranes.

It's also critical to identify patients at high risk of progressing to advanced AMD, allowing for staging and establishing appropriate monitoring intervals. Early identification, accurate staging and risk stratification of early AMD stages could allow for prevention or possible early intervention, while also playing a role in facilitating the development of new treatments and preventative therapeutics.

Advanced AMD is defined by the hallmark features of central atrophy or macular neovascularization and commonly occurs with associated loss of vision. Patients with intermediate AMD have a 27 percent chance of progression to advanced AMD in five years, higher when the other eye is already afflicted with advanced AMD.[3]

Even with effective treatments for neovascular AMD, these patients still frequently lose vision due to the development of geographic atrophy, for no approved treatment yet exists, although some agents that may slow progression are under evaluation or regulatory assessment.[4] This article explores the potential for automated imaging for the detection and monitoring of AMD.

Challenges with current methods

Historically, color fundus photography has been the gold standard for detecting

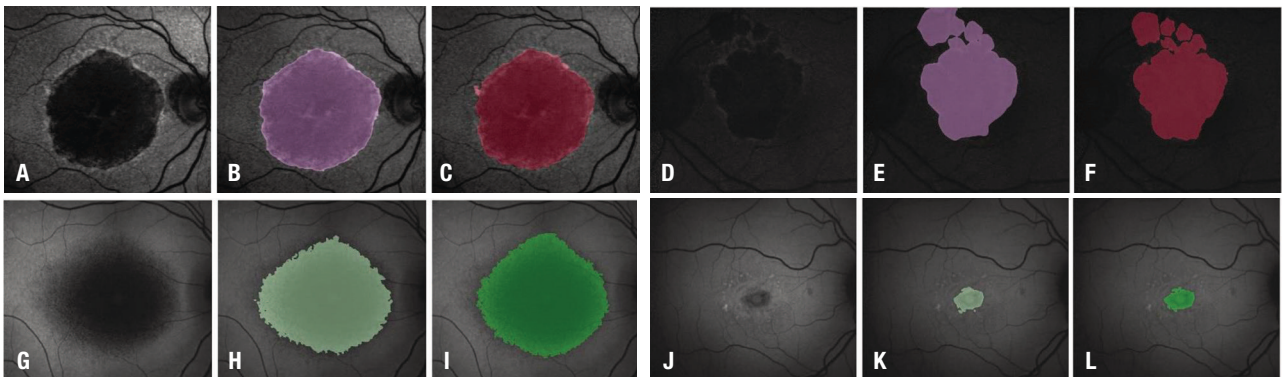


Figure 1: An illustration of segmentation system results. The upper row shows atrophic age-related macular degeneration segmentation: A and D fundus autofluorescence; B and E U-net segmentation; and C and F manual delineation. The lower row shows atrophic juvenile macular degeneration segmentation: G and J FAF images; H and K U-net segmentation; and I and L manual delineation. *(Source: Proc. SPIE 10950, Medical Imaging 2019: Computer-Aided Diagnosis, 109501Q [13 March 2019; open source]).*

and measuring GA. Fundus autofluorescence imaging is a noninvasive, *in vivo* two-dimensional imaging technique for metabolic mapping of naturally or pathologically occurring fluorophores of the ocular fundus.[5] It has proved to be a useful method for identifying atrophic lesions due to its ability to provide high contrast.

In atrophy, photoreceptors and retinal pigment epithelium cells are lost, leading to the depletion of the fluorophores (in lipofuscin) and, consequently, reduced autofluorescence or hypofluorescence. Well-demarcated FAF hypofluorescence is the hallmark of atrophy. Studies of color fundus photos have identified several risk markers for AMD progression: large drusen; increased total drusen area; hyperpigmentation; and depigmentation.[3,6,7]

Recently, optical coherence tomography, due to its ability to provide three-dimensional cross-sectional anatomic information of retinal abnormalities, has gained favor over color fundus photography.[8] Several novel OCT-based features have been identified as risk factors of AMD progression.[9] They include higher central drusen volume,[10] intraretinal hyperreflective foci,[11] heterogeneous internal reflectivity within drusenoid lesions (IRDL),[12] and reticular pseudodrusen (RPD) or subretinal drusenoid deposits (SDD).[13,14,15] Unfortunately, while OCT provides many opportunities to further understand AMD biomarkers, it requires expert training and generates massive amounts of image data (up to hundreds of B-scans per examination). This limits the practicality of manual OCT analysis.

Automated image segmentation and analysis are desirable for both FAF and OCT. This can be accomplished while preserving performance and accuracy through deep learning techniques.

Late-stage screening and detection

Previously, our group at the Doheny Image Analysis Laboratory (DIAL) developed a fully convolutional neural network-based algorithm for atrophic AMD (or GA) screening and segmentation on FAF images.[16] The U-net algorithm consists of the usual contracting network and expansive network,[17] but supplements it through the use of upsampling operators and concatenating the high-resolution features of the contracting network to the upsampled features of the expansive network, leading to a more precise final output.

This algorithm has also been applied to the segmentation of Stargardt disease or atrophic juvenile macular degeneration (JMD). Additionally, researchers used deep residual convolutional neural networks to screen and distinguish atrophic eyes from normal eyes.[18]

The screening system algorithm our

Bios

(continued from page 18)

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Dr. Hu leads the Doheny Eye Image Analysis Laboratory at the Doheny Eye Institute.

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The other authors have no relevant relationships to disclose.

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DIAL group developed demonstrated a high accuracy, with 0.98 for atrophic AMD and 0.95 for atrophic JMD against the manual gradings (*Figure 1, page 19*).[16] The segmentation system algorithm also demonstrated a high overlapping ratio: 0.89 ± 0.06 for atrophic AMD and 0.78 ± 0.17 for atrophic JMD compared with the manual delineations. These highly robust systems indicate the great potential to facilitate large-scale atrophic AMD and JMD clinic trials, clinical research and translation to clinic daily application.

Screening early AMD features

In 2019 our DIAL group reported on deep convolution neural networks trained to detect and classify several OCT B-scan features that had previously been found to be associated with AMD progression.[19] They include hyperreflective foci, hyporeflective foci within the drusen and subretinal drusenoid deposits.[9] The algorithm (*Figure 2*) employs transfer learning, with which state-of-the-art classification performance is achieved using relatively small datasets by using pretrained models to initiate network parameters, which are then fine-tuned by training on the desired image dataset.[20] This allows for fast network training while avoiding over-fitting and ensuring robust performance. The algorithm also uses a U-net (i.e., ReLayNet[21]) to presegment a region of interest to increase performance of the model.

This deep-learning system achieved an overall accuracy of 87 percent for detecting and classifying the early AMD biomarkers identified. In the clinic, such a system could rapidly screen B-scans that require further investigation, improving the accuracy and efficiency of the diagnosis. The reported deep-learning system is one way to ease the burden of AMD on the healthcare system, showing the potential to play a role in clinical decision support for patient management and screening.

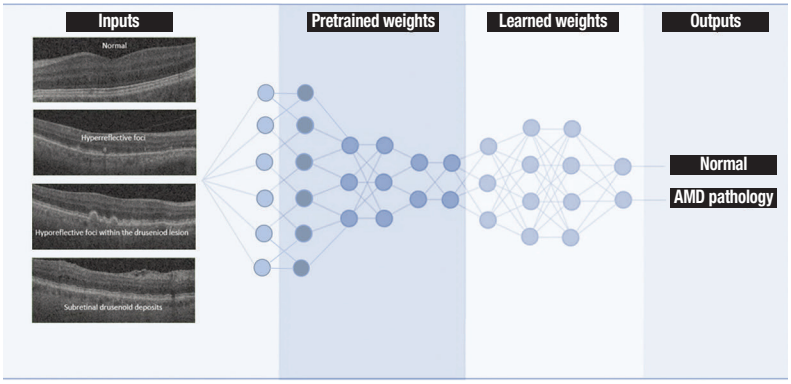

Figure 2: Deep learning for identifying the presence of early age-related macular degeneration biomarkers employs transfer learning, with which state-of-the-art classification performance is achieved with relatively small datasets by using pretrained models to initiate network parameters, which are then fine-tuned by training on the desired image dataset. Neuron connections shown here are for illustration only. *(Source: Sci Rep. 2019;9:10990 [open access]).*

Detection of early AMD features

DIAL developed a deep-learning system to automatically segment drusen and RPD in SD-OCT images.[22] The algorithm first uses a fully convolutional neural network based on the U-net to generate probability maps for the drusen and RPD present in each B-scan. Using these probability maps and the normalized gradient in the z-direction of the B-scan, a shortest-path algorithm automatically segmented both drusen and RPD. The neural network could also generate probability maps for the layers of the retina, making the what we described as the Deep Learning–Shortest Path algorithm generalizable to the segmentation of all retinal layers in addition to drusen and RPD.

The algorithm achieved a subpixel level mean difference for all retinal layers. For RPD in particular, mean and absolute mean differences between automated and manual segmentations were −0.75 ± 1.99 pixels (−2.92 ± 7.74 µm) and 1.53 ± 1.47 pixels (5.97 ± 5.74 µm), respectively. This study demonstrated that RPD, regular drusen and all retinal layers can be automatically and separately segmented on SD-OCT images (*Figure 3*). Quantifying and monitoring the progression of these features have significant potential for aiding in the further understanding of the

evolution of AMD.

Bottom line

While no effective treatment for atrophic AMD currently exists, early identification before permanent vision loss occurs could allow staging and monitoring at appropriate intervals, which could open the door to new preventative treatments and early intervention studies. However, identifying early AMD biomarkers manually is time-consuming and requires expert training, often making it impractical or unfeasible.

Deep learning offers a potential solution to automatically screen for and detect biomarkers of both early and late AMD while preserving much of the accuracy of manual segmentation. The studies we reviewed are encouraging for the application of deep-learning methods in the screening and detection of AMD biomarkers for further clinical research, early intervention clinical trials and daily clinical use.

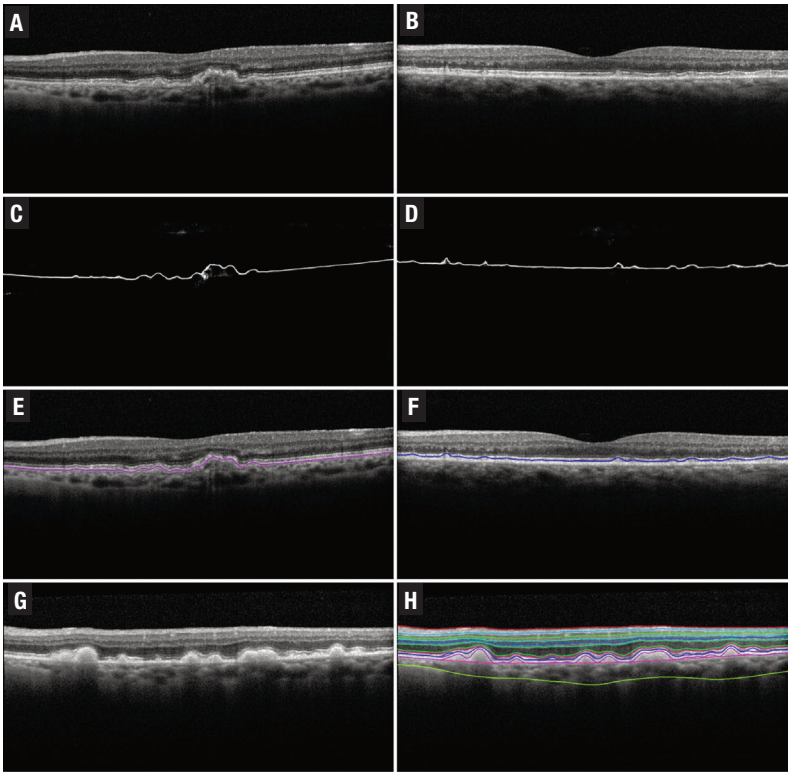

Figure 3: Segmentation of regular drusen, reticular psuedodrusen (RPD), and 11 retinal layers on spectral-domain optical coherence tomography B-scans. A and B) Original B-scans for the segmentations of regular drusen and RPD shown in E and F, respectively. The drusen segmentation shown in E arises from the deep learning probability map shown in C. The RPD segmentation shown in F arises from the deep-learning probability map shown in D and G) Original B-scan for the 11 retinal-layer segmentation shown in H. ***(Source: Sci Rep. 2020;10:9541 [open access])***

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Focus on Digital Medicine in Retina

How telemedicine and AI are changing DR screening

Teleophthalmology and artificial intelligence are bringing diabetic retinopathy screening into the primary-care setting.


Ali R. Salman, MD


Andrew J. Barkmeier, MD

By Ali R. Salman, MD, and Andrew J. Barkmeier, MD

Take-home points

- While telemedicine in ophthalmology—teleophthalmology—has been implemented successfully in the screening of patients with diabetic retinopathy, it's limited by the need for human interpretation of all images.
- Artificial intelligence can provide accurate, real-time grading of fundus photographs, allowing health-care systems to reduce the number of routine screening eye care referrals.
- Two Food and Drug Administration-approved AI-based algorithms have been shown to have high sensitivity and negative predictive value for detecting clinically relevant DR.
- The implementation of AI-based screening programs can improve patient access to care and decrease health-care costs.

Bio

Dr. Salman is a chief ophthalmology resident at Mayo Clinic in Rochester, Minnesota.

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DISCLOSURES: Dr. Salman and **Dr. Barkmeier** have no conflicting relationships to disclose.

Telemedicine has demonstrated significant potential to reduce barriers and improve adherence for diabetic retinopathy screening of asymptomatic patients in the primary-care setting.[1–3] However, one of the main limiting factors of telemedicine for DR screening is access to accurate and timely image interpretation.[4] This is where artificial intelligence can play a significant role.

AI-based image analysis has shown the potential to deliver accurate, real-time fundus photography grading, allowing health systems to reduce the number of routine screening eye care referrals.[1,2,5–7]

The scope of the problem has been well documented: More than 100 million people have diabetes[8] and an estimated 860,000 are functionally blind from DR. An additional 2.9 million suffer from moderate to severe visual impairment.[9] Although systemic management of diabetes mellitus has improved significantly over the past few decades, global prevalence continues to rise and with it the burden of DR. It remains the leading cause of new legal blindness among Americans ages 20 to 74 years.[1,2,9–11]

Here, we report on the advances made in using telemedicine for screening for DR and future directions.

Poor adherence to guidelines

Regular monitoring and early detection is the key to preventing DR-related visual impairment. American Academy of Ophthalmology guidelines recommend screening for DR at the time of diagnosis for patients with T2DM and at least annually starting five years after diagnosis of T1DM. Unfortunately, only about 60 percent of patients with DM receive eye exams at least yearly.[12] This discrepancy is multifactorial: the financial burden of follow-up

visits, inconvenience of traveling to a doctor's office, timing and duration of visits, and limitations in patient education.[1,3,13] An additional complicating factor is that many patients remain asymptomatic even when they have advanced, vision-threatening DR.[14]

In the United States, telemedicine systems have been implemented for screening and/or managing DR, as well as in emergency medicine teleophthalmology, retinopathy of prematurity screening, and management of age-related macular degeneration and glaucoma—with varying levels of success.[15]

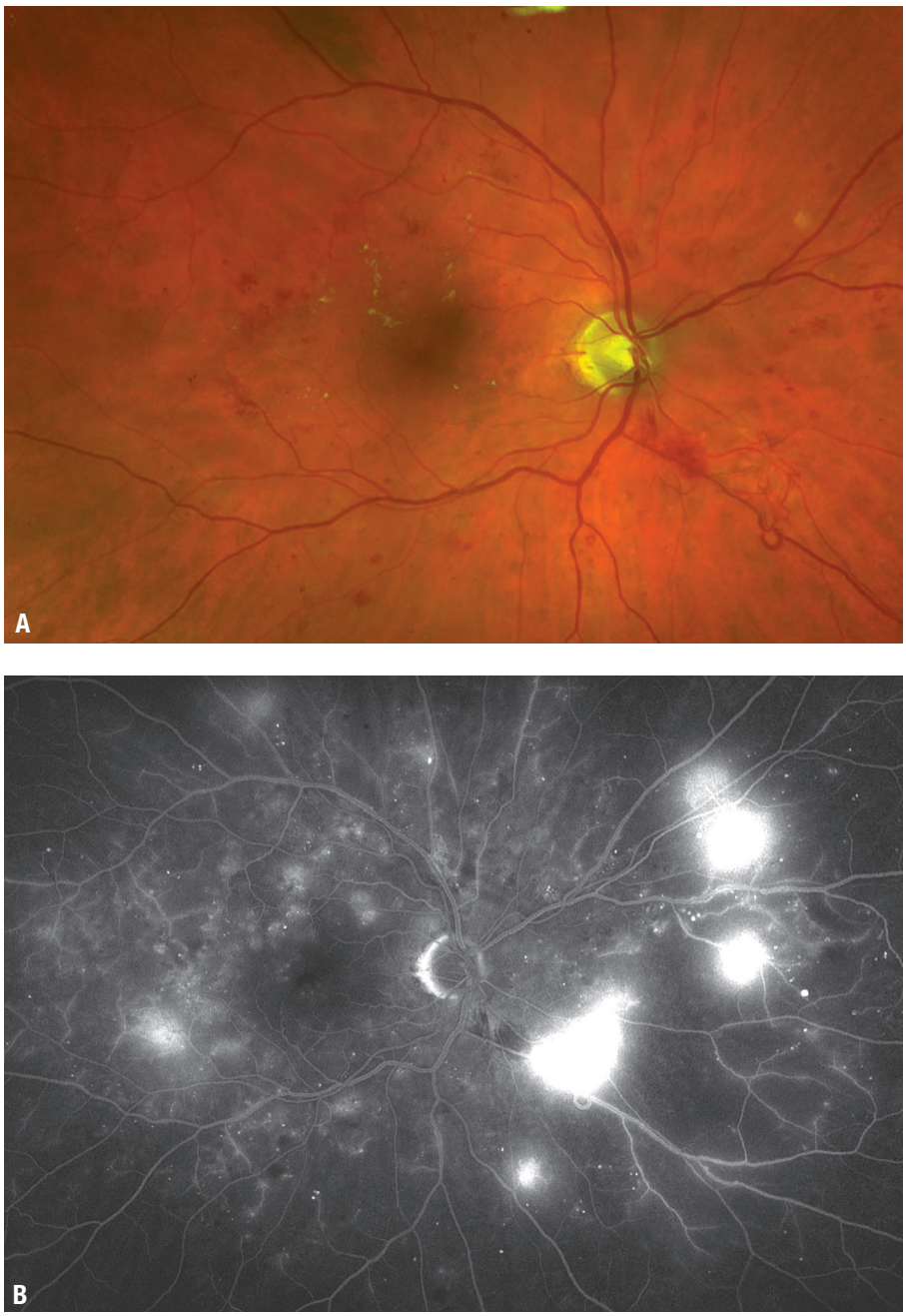
The Veterans Health Administration implemented a nonmydriatic teleretinal DR screening that has shown efficacy in reaching a larger population of patients while proving cost-effective for screening in populations of more than 3,500 patients under age 80 from diverse racial ethnic groups.[16]

Dilation and image gradeability

Teleophthalmology programs can use both mydriatic and nonmydriatic fundus photography. Dilation has the most significant impact on telemedicine image quality in older patients and those with known ocular media opacity. A recent study found the rate of gradable nonmydriatic images fell from 83 percent for patients ages <40 years to 50 percent for patients ages 61 to 70 ($p<0.001$) and 33 percent for those ages 71 to 80 ($p<0.001$).[17]

Although postdilation fundus images are typically of higher quality than nonmydriatic images, dilation adds time and cost for both patients and health-care systems, and may be inconvenient and

(Continued on page 27)



A) Ultrawide pseudocolor fundus photography of a 71-year-old man with newly diagnosed noninsulin dependent diabetes mellitus reveals intra- and extramacular dot and blot hemorrhages, macular exudates, intraretinal microvascular abnormalities and neovascularization elsewhere. B) Fluorescein angiography demonstrates several areas of late leakage as well as scattered areas of small-vessel leakage and vascular nonperfusion.

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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.

EYLEA ACHIEVED RAPID, SUSTAINED OUTCOMES IN DME

Demonstrated efficacy outcomes in VISTA and VIVID, phase 3 anti-VEGF trials in DME (N=862)[1]

Mean change in BCVA (ETDRS letters) at Year 1 from baseline[1-5,*]

	Initial Gains (Month 5)		Primary Endpoint (Year 1)		Prespecified Exploratory Endpoint (Year 3)	
	VISTA	VIVID	VISTA	VIVID	VISTA	VIVID
EYLEA Q4	+10.3 (n=154)	+9.3 (n=136)	+12.5 (n=154)	+10.5 (n=136)	+10.4 (n=154)	+10.3 (n=136)
EYLEA Q8†	+9.9 (n=151)	+9.3 (n=135)	+10.7 (n=151)	+10.7 (n=135)	+10.5 (n=151)	+11.7 (n=135)
Control	+1.8 (n=154)	+1.8 (n=132)	+0.2 (n=154)	+1.2 (n=132)	+1.4 (n=154)	+1.6 (n=132)

P<0.01 vs control at Year 1.

The analyses of these exploratory endpoints were not multiplicity protected and are descriptive only.

Year 2 data was consistent with results seen in Year 1.[5]

VISTA and VIVID study designs: Two randomized, multicenter, double-masked, controlled clinical studies in which patients with DME (N=862; age range: 23-87 years, with a mean of 63 years) were randomized and received: 1) EYLEA 2 mg Q8 following 5 initial monthly doses; 2) EYLEA 2 mg Q4; or 3) macular laser photocoagulation (control) at baseline and then as needed. From Week 100, laser control patients who had not received EYLEA rescue treatment received EYLEA as needed per re-treatment criteria. Protocol-specified visits occurred every 28 (±7) days.[1]

In both clinical studies, the primary efficacy endpoint was the mean change from baseline in BCVA at Week 52, as measured by ETDRS letter score.[1]

*Last observation carried forward; full analysis set.
†Following 5 initial monthly doses.

SEE WHAT EYLEA COULD DO FOR YOUR PATIENTS WITH DME AT HCP.EYLEA.US

anti-VEGF, anti–vascular endothelial growth factor; BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; Q4, every 4 weeks; Q8, every 8 weeks.

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).

References: 1. EYLEA® (aflibercept) Injection full U.S. Prescribing Information. Regeneron Pharmaceuticals, Inc. August 2019. **2.** Korobelnik JF, Do DV, Schmidt-Erfurth U, et al. Intravitreal aflibercept for diabetic macular edema. *Ophthalmology.* 2014;121(11):2247-2254. doi:10.1016/j.ophtha.2014.05.006 **3.** 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 **4.** Data on file. Regeneron Pharmaceuticals, Inc. **5.** Heier JS, Korobelnik JF, Brown DM, et al. Intravitreal aflibercept for diabetic macular edema: 148-week results from the VISTA and VIVID studies. *Ophthalmology.* 2016;123(11):2376-2385. doi:10.1016/j.ophtha.2016.07.032

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

04/2021
EYL.21.03.0211

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.

5.3 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 (5.3)*]

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 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).

6.2 Immunogenicity
As with all therapeutic proteins, there is a potential for an immune response in patients treated with EYLEA. The immunogenicity of EYLEA was evaluated in serum samples. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to EYLEA 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 EYLEA with the incidence of antibodies to other products may be misleading.
In the wet AMD, RVO, and DME studies, the pre-treatment incidence of immunoreactivity to EYLEA was approximately 1% to 3% across treatment groups. After dosing with EYLEA for 24-100 weeks, antibodies to EYLEA were detected in a similar percentage range of patients. There were no differences in efficacy or safety between patients with or without immunoreactivity.

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 humans 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 humans 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 in pediatric patients have not been established.

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.

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: 08/2019
Initial U.S. Approval: 2011

Based on the August 2019
EYLEA® (aflibercept) Injection full
Prescribing Information.

EYL.20.09.0052

uncomfortable for many patients.[18] Another potential concern regarding pharmacologic mydriasis in the primary-care setting is the risk of inducing acute angle closure due to pupillary block, although this has been exceedingly rare with tropicamide-only dilation.[19]

Screening programs in which ungradable nonmydriatic photography leads directly to a referral must balance the benefits of avoiding routine dilation with the costs of increased office visits and the risk of losing patients to follow-up.

Track record of AI algorithms

A recent, large-scale international prospective study demonstrated that an AI-based deep-learning program could offer 91.4-percent sensitivity for detecting vision-threatening DR with a specificity of 95.4 percent, which was at least as good as retina specialist grading.[20]

Another recent study compared the performance of seven different AI-based DR screening algorithms on real-world Veterans Affairs patient data and found widely varying sensitivities—51 to 86 percent.[21] Negative predictive values (NPV) ranged from 82.7 to 93.7 percent.

Two of the algorithms had slightly higher sensitivities than the teleretinal human grader control, although the algorithms had lower specificities. One algorithm had worse performance at all levels of DR severity compared with teleretinal control and missed a quarter of advanced retinopathy cases. These findings highlight the need for rigorous real-world algorithm validation before they're implemented in the clinic.

The VA study calculated value per encounter, defined as the cost saved avoiding unnecessary referrals to a provider, for all algorithms that performed no worse than teleretinal graders in detecting referable DR. This value was found to be $15 to $18 per screening visit for ophthalmologist human graders and $8 to $9 for optometrists.[21]

Existing AI-based systems

Two AI-based systems approved for DR screening are available commercially: the IDx-DR autonomous diagnostic platform (Digital Diagnostics); and the EyeArt AI screening system (Eyenuk).

IDx-DR analyzes two fundus photographs of each eye using the TRC 400NW 70 nonmydriatic fundus camera (Topcon) to identify patients with more than mild DR.[6] A retrospective study reported outcomes following incorporation of IDx-DR AI-based image interpretation into an established DR telemedicine screening program.[17] It evaluated 1,052 consecutive adult patients who received photoscreening for DR in a primary-care setting. IDx-DR analyzed nonmydriatic fundus photos captured for each patient.

When the program couldn't grade the nonmydriatic photos, the patients were dilated (1% tropicamide). The AI platform successfully analyzed the mydriatic fundus photos in 87.5 percent of patients who had ungradable nonmydriatic photos.[17] More than 90 percent ultimately had gradable fundus photos and 14.3 percent were graded as greater-than-mild DR.

Manual over-read was performed on all images. The AI-derived results compared to manual over-read had 100-percent sensitivity, 89.2-percent specificity and 100-percent NPV for identifying more than mild nonproliferative DR.[17]

A prospective trial last year showed the EyeArt system also had high sensitivity (95.5 percent) and specificity (85 percent) for detecting more-than-mild and vision-threatening DR (95.1-percent sensitivity, 89-percent specificity). Nearly 90 percent of eyes didn't require dilation for the AI algorithm to identify mild-to-moderate and vision-threatening DR.[22]

Potential to find referable disease

Findings from these studies demonstrate the potential of AI-based image interpretation systems to identify referral-eligible disease with a very high sensitivity and high

Screening programs in which ungradable nonmydriatic photography leadsdirectly to a referral mustbalance the benefits of avoiding routine dilation with the costs of increased office visits and the risk of losing patients to follow-up.

NPV. The low false-negative rate may allow telemedicine systems to either arrange a secondary review of only positive screening images or eliminate the secondary review only of images with positive screening results, or to even entirely eliminate the secondary review if the system can accommodate prompt access to dilated comprehensive eye exams for all patients with positive or ungradable results.

Introducing these systems for screening of patients with diabetes in the primary-care setting holds great potential for improving access to care. The unique characteristics and infrastructure of different systems will determine specific practices, such as how to manage positive or ungradable screenings either through secondary image review or with urgent referral of all patients with positive or ungradable screening results.

Patients with negative results may either continue getting telemedicine screening annually or some systems may recommend they get periodic comprehensive eye exams on a less-than-annual basis. Importantly, systems must be put in place to streamline referrals when indicated.

Patients with negative results may either continue telemedicine screening annually or some systems may recommend they get periodic comprehensive eye exams on a less-than-annual basis.

Every effort should be made to minimize the obstacles to getting patients into the clinic to avoid liability issues, including obtaining valid contact information on all and ensuring patients are fully informed on the potential risks of AI-based screening as well as the fact that they may still need an eye exam. Obstacles to wider implementation of AI-based screening programs include regulatory issues, variation in software and discrepancies in national screening programs.[20]

Bottom line

Incorporating AI-based image analysis into primary-care DR screening programs has the potential to improve patient access to recommended screening with a high sensitivity for detecting retinopathy warranting referral for a comprehensive eye examination. RS

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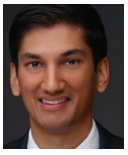
The clinical potential of WF-OCT and OCTA

A look at three clinically relevant applications for widefield optical coherence tomography and OCT angiography, along with future directions.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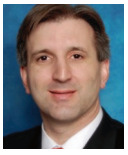
Amir H. Kashani, MD, PhD

By Anupam K. Garg, MD, PhD, John Peter Campbell, MD, PhD, and Amir H. Kashani, MD, PhD

Bios

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DISCLOSURES: Dr. Garg and **Dr. Campbell** have no relevant disclosures.

Dr. Kashani disclosed a relationship with Carl Zeiss Meditec.

Take-home points

- Widefield optical coherence tomography is noninvasive tool that provides near capillary level information about the retinal vasculature.
- WF-OCT is commercially available and provides useful information for diagnosis and management of diseases of the vitreoretinal interface.
- The application of WF-OCT and WF-OCT angiography to characterize central and peripheral retinal lesions is improving our understanding of retinal vascular diseases, such as diabetic retinopathy, retinal vein occlusion and retinopathy of prematurity.
- The adoption of widefield imaging into routine clinical practice has logistical and financial barriers but may offer significant advantages over conventional imaging techniques.

Optical coherence tomography, introduced in 1991,[1] has had a transformational impact on the diagnosis and management of macular pathology such as choroidal neovascularization and macular edema. In short order the application of OCT to diseases of the vitreoretinal interface also rapidly evolved.[2,3]

With these applications, the importance of peripheral retinal imaging also emerged when investigators began to use montages of spectral-domain OCT images[4] or larger scan patterns[5] to explore vitreoretinal interface findings outside the macula. These studies revealed that OCT of the retinal periphery was a significantly underutilized application that could provide important diagnostic information. However, the practical limitations in acquiring and montaging OCT images from outside the macula largely precluded the routine use of OCT for peripheral retinal pathology.

Over the past decade, the adoption of high-speed and ultrahigh-speed swept-source OCT technology has made it easier to image outside the macula—known as "widefield" imaging (WFI).[6] Consensus terminology for WFI has been developed both in the context of fundus imaging as well as OCT[7] and the pathophysiologic importance of imaging the periphery is widely acknowledged.[8] The increased scanning speeds (up to 100,000 A scans/s) of commercially available SS-OCT platforms enable acquisition of fields of view up to approximately 12-x-12 mm in a single-scan pattern in few seconds (*Table*).

The age of OCT angiography

More recently, OCT angiography has enabled high-resolution, noninvasive visualization of the retinal and choroidal

microvasculature with distinct advantages over fluorescein angiography,[9] including the absence of intravenous dye injection. OCTA provides capillary level resolution of the retinal vasculature and enables visualization of the peripapillary radial capillaries as well as the deep-retinal capillaries that conventional dye-based angiography doesn't visualize.

In addition, the speed and ease of use of commercially available WF-OCT and WF-OCTA systems allow for comfortable and rapid imaging of patients at each visit to closely monitor disease progression and therapy response.[10,11] In this article, we will review the currently available commercial WF-OCT and WF-OCTA systems as well as experimental concept instruments to illustrate clinical applications in adults and children. The accompanying table summarizes characteristics of several commercially available widefield OCT and OCTA systems.

While there are many clinical applications for WF-OCT and WF-OCTA, at least three have immediate clinical relevance and impact: diabetic retinopathy; retinal vein occlusion; and pediatric uses. Recent peer-reviewed clinical studies demonstrate and support these applications, but much room exists for improvement.

Diabetic retinopathy

Widefield fundus imaging has already demonstrated that the perfusion status of the retinal periphery is particularly important for patients with diabetic retinopathy because of an increased risk of DR progression when predominantly peripheral lesions are present.[12,13] Multiple studies have also shown the ability of WF-OCTA to identify regions of nonperfusion and neovascularization in patients with DR.[14,15]

In some studies, the ability of WF-OCTA to detect regions of impaired perfusion is debatably superior to that of FA.[15,16] Figure 1 demonstrates the capillary level resolution of WF-OCT images that highlight areas of impaired perfusion. Notably, these areas aren't clinically evident on dilated fundus examinations. Or in some cases FA and the benefit of imaging is significant in early identification of impaired perfusion.

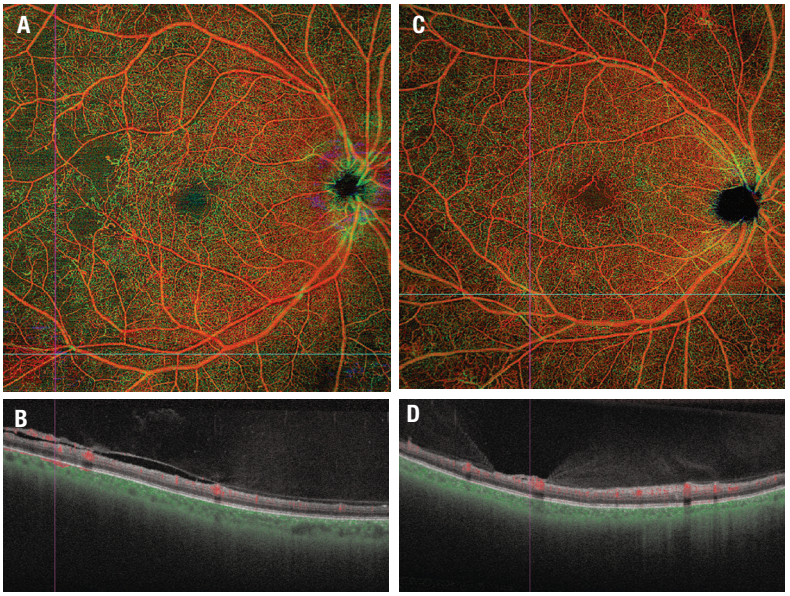

Figure 1. Widefield optical coherence tomography angiography of two patients with diabetic retinopathy illustrating regions of neovascularization with corresponding B-scans. A) En face 12-x-12mm field of view depth encoded pseudocolored OCTA of the right eye of a person with clinically apparent proliferative DR. B) Horizontal B-scan (corresponding to the white line in panel A), demonstrates retinal neovascularization in the vitreous. C) En face WF-OCTA of a patient with severe nonproliferative DR and (D) corresponding B-scan of the same patient with presumed severe NPDR demonstrate flat neovascularization above the internal limiting membrane that wasn't detected clinically. OCTA is particularly effective at identifying this flat neovascularization that can be very difficult to detect clinically. (Color coding for panels A and B: Red=superficial retinal layer; green=deep retinal layer; yellow=overlay of red/green. (*Images obtained on Zeiss PlexElite 9000, Carl Zeiss Meditec*)

Table. Commercially available widefield optical coherence tomography systems

Device	Technology	Scan speed	Reported field of view	OCT angiography available?
Optovue Avanti	Spectral domain	70,000 A-scans/s	40 degrees	Yes
Zeiss PLEX Elite 9000	Swept-source	100,000 A-scans/s	56 degrees	Yes
Canon Xephilio OCT-S1	Swept-source	100,000 A-scans/s	78x68 degrees	Yes
Heidelberg Spectralis OCT2	Spectral domain	85,000 A-scans/s	55 degrees	Yes
Optos Silverstone	Swept-source	100,000 A-scans/s	200 degrees	No

Figure 2 is a montage of several WFIs demonstrating even larger field-of-view capabilities likely to be commercially available in the near future.

A separate study used FA and WF-OCTA to detect regions of nonperfusion in nine patients with DR. Notably, the study found that all regions of nonperfusion detectable on FA were also detected on WF-OCTA, but that WF-OCTA could identify additional regions not detectable on FA.[15] A 2020 study of 20 eyes also demonstrated this finding,[17] observing that areas of nonperfusion could be more easily identified using WF-OCTA in eyes that had been treated with panretinal photocoagulation because of the appearance of PRP scars on FA.

A 2022 study in Japan used WF-OCTA to quantify the progression of neovascularization using swept-source widefield OCTA images.[18] The authors demonstrated the ability of widefield OCTA to not only identify, but also track the progression of neovascularization lesions. Figures 1C and D (*page 31*) illustrate a case where numerous areas of neovascularization are evident on WF-OCTA but weren't recognized on clinical examination.

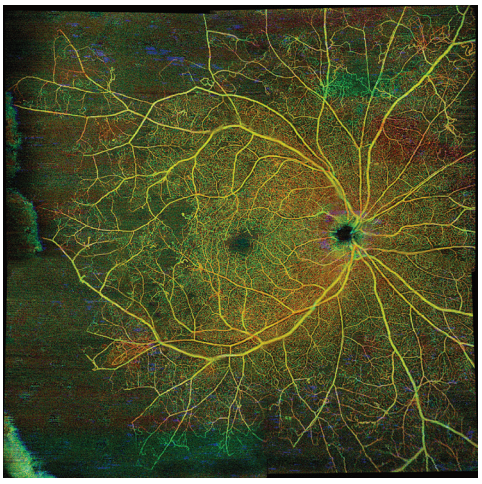

Figure 2. Wide-field montage of several images demonstrating visualization of peripheral retina. This figure provides an expanded field-of-view of the same patient imaged in Figure 1A and B and illustrates additional impaired temporal perfusion in the mid-periphery not seen in Figure 1. This montage feature is not yet Food and Drug Administration-approved. (*Obtained on Zeiss PlexElite 9000, Carl Zeiss Meditec*)

Retinal vein occlusion

Recent work has demonstrated the utility of WF-OCTA in assessment of nonperfusion in patients with RVO. A study from France last year comparing ultra-WF FA and WF-OCTA in patients with RVO calculated that WF-OCTA had a 100 percent sensitivity and 65 percent specificity for detection of nonperfusion, indicating that it may serve as an effective screening tool for patients with RVO.[19]

Another study retrospectively evaluated 39 eyes with ischemic RVO to detect neovascularization elsewhere as well as areas of nonperfusion.[20] WF-OCTA detected 100 percent of areas of nonperfusion and retinal neovascularization that FA had detected. In one case, neovascularization elsewhere found on OCTA wasn't detectable using FA. A separate study compared the area of nonperfusion between WF-OCTA and FA in 27 eyes with BRVO and found a strong and statistically significant correlation between the two modalities.[21]

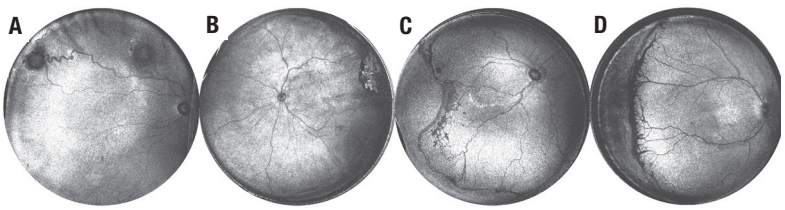

Figure 3. Examples of peripheral pathology visualized with ultra-widefield en face optical coherence tomography. All scans were acquired in 1.5 seconds using a prototype contact UWF handheld OCT system. A, B) Pediatric patients imaged with UWF OCT in the operating room. Patient A had Von Hippel Lindau syndrome and multiple hemangioblastomas, including one near the ora serrata. Patient B was diagnosed with retinoblastoma, which could be more effectively captured using UWF OCT than commercially available systems with lower fields of view. C, D) Retinopathy of prematurity seen on images obtained at the bedside in the neonatal intensive care unit. (*Courtesy Yifan Jian, PhD*)

Pediatric patients

In pediatric retina, OCT imaging is typically limited to cooperative children

who can position themselves into imaging systems designed for adults or patients in the operating room under anesthesia.[22,23] Under anesthesia, camera options are limited, particularly for OCT, which often isn't available. Furthermore, commercially available options for imaging under anesthesia are typically slower than those used in routine clinical practice.

Many pediatric retinal diseases have complicated vitreoretinal interface abnormalities and peripheral vascular abnormalities likely to benefit from OCT imaging. However, they're difficult to visualize using available portable OCT systems that have a limited field of view.[24] This limitation has delayed our understanding of both normal pediatric macular development and pathologic changes with disease.

Finally, diseases such as retinopathy of prematurity require repeated clinical examination at the bedside, which often occur without the benefits of imaging, especially OCT.[25] Some of these challenges can be overcome with improved optical designs and faster lasers that can facilitate more efficiency, higher resolution and greater field-of-view compared with currently available OCT systems.[26] We present a series of pediatric patients (*Figure 3*) imaged using a prototype 400 kHZ swept-source OCT with a field of view of up to 240 degrees to demonstrate the feasibility and potential clinical benefit of incorporating WF-OCT into the pediatric retinal practice in the future.[27]

Future applications and directions

As WF-OCT and OCTA devices continue to improve and are adopted into clinical practice, new research and clinical applications will undoubtedly emerge. Figure 4 provides a striking example of retinal hemangioblastomas imaged with a WF-OCTA montage, which isn't Food and Drug Administration-approved, compared with FA. In mouse models, WF-OCT has been combined with adaptive optics scanning laser ophthalmoscopy to localize individual cells and structures at a three-dimensional level, which may assist with precisely tracking cellular structure *in vivo* to better understand retinal pathologies.[28]

Importantly, as widefield imaging has become ubiquitous, an effort is being made to standardize nomenclature when discussing widefield imaging devices. The International Widefield Imaging Study Group, which was composed of several leading retinal specialists around the world, proposed a consistent nomenclature for

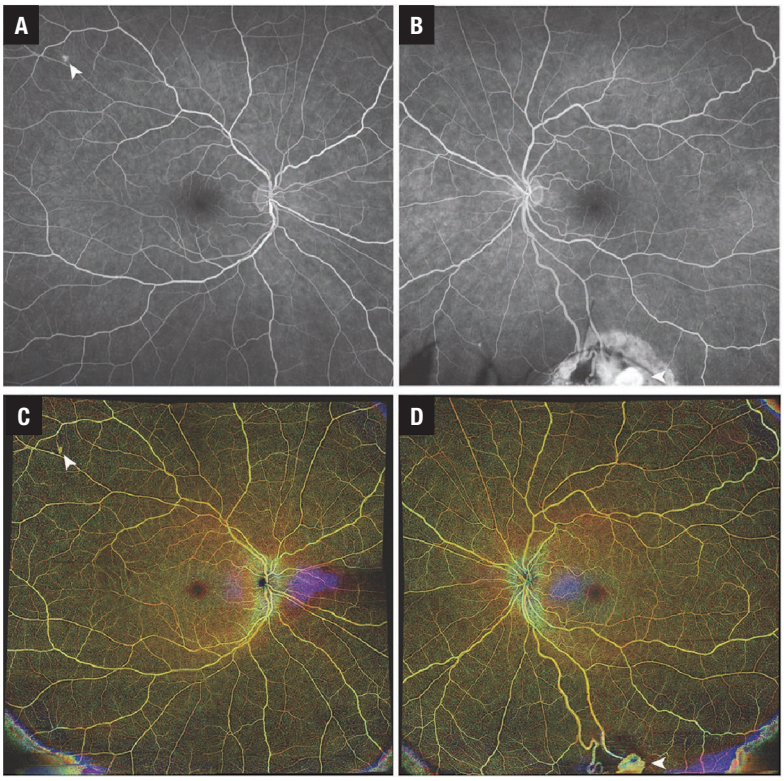

Figure 4. A 34-year-old woman with a history of pheochromocytoma, pancreatic tumors, central-nervous-system and retinal hemangioblastomas secondary to Von Hippel-Lindau syndrome underwent optical coherence tomography angiography imaging. She was diagnosed at age 24 based on ocular manifestations and confirmed with genetic testing (both parents tested negative). Visual acuity was 20/20 bilaterally. A) Fluorescein angiography of the right eye demonstrates small untreated capillary hemangioblastoma (arrowhead) temporally superior to the macula. B) FA of the left eye showed a large inferior hemangioblastoma (treated with cryotherapy nine years prior) with persistent flow. C, D) 12-x-12-mm OCTA montages reveal lesions consistent with hemangioblastomas identified in figures A and B. (*Images obtained on Zeiss PlexElite 9000, Carl Zeiss Meditec*)

widefield OCTA imaging, recommending that the term "widefield" be limited to images including all four quadrants as well as the posterior edge of the vortex vein ampulla.[7] These efforts to standardize imaging nomenclature will be critical as the body of literature utilizing widefield imaging continues to grow.

Bottom line

Since its introduction in 1991, OCT has become a transformational tool for clinical diagnosis and management of retinal diseases primarily involving the macula. Advances in OCT technology have enabled WF-OCT and, more recently, WF-OCTA that allow extramacular imaging of the posterior pole and even mid-to-far periphery. These technologies have enabled accurate and reliable, noninvasive, commercially available imaging platforms.

Improvements such as montaging features are expected in the near future and will continue to expand the applications and potential of WFI systems. Even now, a steady stream of studies has demonstrated WF-OCTA can reliably identify clinically relevant lesions in DR, RVO and other retinal vascular disorders with similar efficacy to dye-based angiography and with less inconvenience to staff and patients. Logistical and financial barriers to wide adoption of widefield imaging platforms still exist, but their benefit and potential are compelling enough that their adoption seems inevitable. RS

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

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Repair strategies for refractory macular holes

A review of techniques for operating on the small percentage of macular holes that remain problematic after primary surgery.

Homayoun Tabandeh, MD

Homayoun Tabandeh, MD

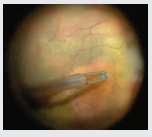
Take-home points

- Surgery for refractory macular holes is associated with a lower success rate than surgery for primary MHs.
- A smaller area of internal limited membrane removal at the time of MH surgery leaves accessible ILM for a future distal ILM flap in case the hole doesn't close.
- SWIFT—superior wide-base ILM flap transposition—is a distal ILM flap technique that can be used in refractory MHs with previously removed ILM.
- Observation is warranted in cases with poor visual potential.

Pars plana vitrectomy peeling of the internal limiting membrane with gas tamponade is the most common surgery for primary macular holes (*Figure 1*). It has been associated with an anatomic success rate around 90 percent, but the outcomes are significantly less favorable for refractory MHs.[1] The incidence of refractory MH has been reported to be 4.2 to 11.2 percent following PPV with or without ILM peel.[1]

To improve outcomes for MHs at higher risk of nonclosure, including refractory macular holes, various authors have described a number of different surgical approaches. These include in-office fluid-gas exchange or PPV/gas with prolonged face-down positioning, long-term tamponade with silicone oil, adjunct use of autologous blood or serum, manipulation of the MH rim and the surrounding retina, localized macula detachment, free or inverted ILM flaps, autologous lens capsule grafts, autologous retinal transplantation, amniotic membrane plug and macular buckle.[1-12]

View the Video



Dr. Tabandeh demonstrates superior wide-base internal limiting membrane flap transposition (SWIFT) in a video originally presented at the Retina Society's 54th annual scientific meeting last year in Chicago. Available at: https://bit.ly/RetSpecMag-2022-05

ILM peel

Depending on whether the ILM has been removed completely from around the MH in a previous surgery, further ILM peel or removal may be indicated. ILM removal reduces the tangential traction at the inner retina surface and increases retina tissue compliance. Advantages of ILM peel include a higher primary closure rate, reduced chance of late reopening (from 7.1 to 1.2 percent) and reduced rate of epiretinal membrane formation.[13,14]

Potential disadvantages of ILM peel are surgical trauma, including dissociated optic nerve fiber layer, localized NFL damage, deep inner retina dimples and potential risk

Bio

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DISCLOSURES: Dr. Tabandeh has no conflicts to disclose.

of chromophore toxicity. An extensive ILM peel may not be necessary for improved closure rate. Limiting the peel area to about 1 to 2 disc diameters reduces surgical trauma risk and leaves accessible residual ILM for a future distal ILM flap in cases of nonclosure.

Inverted ILM flap technique

Zofia Michalewska, MD, and colleagues first described the inverted ILM flap technique that involved peeling the ILM from the central macular region, leaving the base attached to the MH rim.[1] They trimmed the ILM flap and inverted it over the MH. They later described a temporal variation on this maneuver in which they peeled the ILM only over the temporal macula, reducing the potential risks of ILM peel.[2] They reported a high closure rate with both techniques.

Stanislao Rizzo, MD, and colleagues compared ILM peel to the inverted ILM flap technique for primary repair of idiopathic and myopic MHs.[15] They reported this technique was associated with a higher anatomic closure in large MHs (> 400 µm; 96 vs. 79 percent) and myopic MHs (88 vs. 39 percent).[15] Other studies reported improved anatomic outcomes with the flap technique but with variable visual acuity outcomes.

Although conventional and temporal inverted ILM flap techniques were originally described for primary MHs, they may be used in refractory MH cases in which a previous operation left ILM. In cases of persistent MH following a previous ILM flap, the procedure may be repeated if the flap is intact. Alternatively, the residual ILM may be removed from the central macula region and a distal flap technique, such as superior wide-base ILM flap transposition (SWIFT), may be used.

Other techniques include single-layer inverted flap (as opposed to multilayer flaps), pedicle flaps, retracting door flap and tucking the ILM into the MH, among others.[4,5,16] The latter may be associated with RPE trauma, interference with realignment of outer retina layers, intraretinal ILM remnants and suboptimal visual acuity.

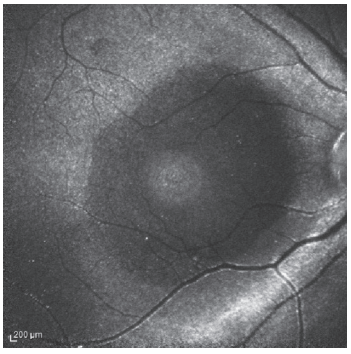

Figure 1. Indocyanine green fluorescence imaging in a patient following pars plana vitrectomy and internal limited membrane removal for a macular hole shows hyperfluorescence originating from the residual ILM. The dark circular area of relative hypofluorescence corresponds to the area of removed ILM. A smaller area of hyperfluorescence corresponds to the base of the MH.

SWIFT

In most refractory MHs, the ILM was removed in a previous surgery and rim-based ILM flaps aren't usable. In these situations, a distal ILM flap may be obtained to cover the MH, but these flaps can be unstable and prone to displacement.

SWIFT is a distal-ILM flap technique in which a wide-base flap is harvested from the superior residual ILM and subsequently inverted to drape over the MH in a single layer (*Figure 2, page 38*).[3] The wide base makes the flap stable, reducing the risk of tilting, rotation and displacement.

If there's not sufficient residual ILM superiorly, the ILM flap may be harvested from the temporal residual ILM. In a series of MHs with high-risk characteristics, including refractory MHs with previously removed ILM, our group reported a 94 percent closure rate.[3]

Optimal visualization of the ILM during the surgery is required for flap techniques. Brilliant blue G or indocyanine green aid in visualizing the ILM during surgery. ICG also allows for postoperative visualization and evaluation of the flap status with fluorescence imaging.[17] Manipulating the flap to maintain MH coverage may be challenging and typically involves a learning curve. Postoperative evaluation of the flap position helps surgeons refine their technique.

Other distal ILM flap techniques

Other distal flap techniques include the free ILM flap, ILM pedicle flap and autologous lens capsule flap.[4-6]

• ***Free-ILM flap technique.*** This approach involves harvesting the flap from a distal site and placing it over the MH. The flap often moves with the intraocular fluid currents and may get caught in instruments. Tucking the ILM flap into the MH, while it may help to stabilize the flap, can cause RPE trauma and intraretinal or subretinal ILM entrapment once the MH closes.

• ***Inverted or noninverted pedicle ILM flaps.*** This technique has been used for the primary management of MHs. While some aren't suitable for cases with previously removed ILM, others have been found useful for refractory MHs in which the ILM was removed from the central macula in a previous surgery. The technique involves peeling a narrow strip of distal ILM circumferentially and transposing it over the MH.[5] The flap stays attached to the residual ILM through a narrow pedicle, reducing the risk of flap loss compared with the free-flap technique. However, distal pedicle flaps are prone to rotation and displacement.

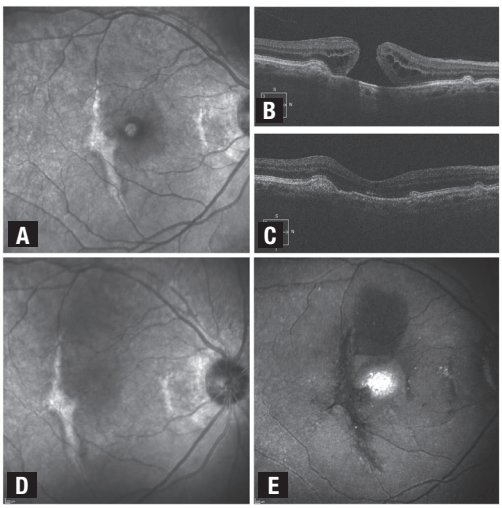

Figure 2. This patient with a full-thickness macular hole and distant history of traumatic maculopathy juxtafoveal subretinal fibrosis had pars plana vitrectomy, internal limiting membrane removal and superior wide-base ILM flap transposition (SWIFT) with gas tamponade. A) Baseline photograph shows full-thickness MH and adjacent subretinal fibrosis. B) Optical coherence tomography demonstrates the full-thickness MH with temporal and nasal subretinal fibrosis. C) and D) Postoperative OCT and photograph show the closed MH and adjacent subretinal fibrosis. E) Indocyanine green fluorescence imaging shows the ILM flap covering the MH. (*Used with permission: Ophthalmol Retina. 2021;5:317-323*)

• ***Autologous lens capsule flap technique.*** This technique involves obtaining a free flap from the posterior or anterior lens capsule in a pseudophakic eye or during concomitant cataract surgery. Lens capsule flap techniques have similar challenges as free ILM flaps—mainly flap instability. A number of adjuvants may be used for intraoperative flap stabilization including viscoelastics, perfluorocarbon liquid and autologous blood or plasma with variable effectiveness.

Retina tissue manipulation

Retinal manipulation techniques aim to improve retinal tissue compliance around the MH. These techniques include:[7,8]

- manually mobilizing the MH rim toward the center;
- gently massaging and stretching the MH rim and surrounding retina;
- relaxing microretinotomies; and
- inducing a localized retinal detachment through subretinal fluid infusion or MH hydrodissection.

Some of these techniques have become obsolete while others have gained popularity. They're relatively easy to perform and can be used with other methods, including flap and patch techniques. They're particularly useful when there's no residual ILM available for a flap or when the visualization is inadequate for ILM peel and flap formation. Surgical trauma to the RPE and neurosensory retina is a potential risk.

Autologous retinal graft

Dilraj Grewal, MD, and Tamir Mahmoud, MD, PhD, described harvesting an autologous retinal graft from the mid-periphery and transplanting it in an eye with a refractory myopic MH.[10] Postoperative OCT showed MH coverage with structural integration into the surrounding retina. Other studies showed a high coverage rate and integration, vascularization and graft reperfusion, with variable vision outcomes.[9,11,18]

In autologous neurosensory retinal transplant (ART), the graft may be placed within the MH or under or over the MH rim (*Figure 3*). PFCL can stabilize the graft during surgery and afterward as a tamponade, with removal in two to three weeks. Other tamponade agents include gas and silicone oil.

ART is useful in myopic MH associated retinal detachment (mMH/RD) and in large refractory MHs with a potential for vision improvement. In the former, sealing the MH allows for retinal reattachment and significant visual improvement in many cases.[14] Potential complications include graft displacement, retinal detachment and surgical trauma.

Human amniotic membrane graft

To avoid harvesting retina tissue, Dr. Rizzo described human amniotic membrane (hAM) graft for refractory MHs.[12] In a series that included eight eyes with refractory MH, the hAM plugged the MH in all eight eyes and VA improved.

The hAM graft patch is made 200 to 500 µm larger than the MH. Using a bimanual technique and PFCL for stabilization, the hAM is positioned over the MH with the chorion layer facing the RPE and the edges are tucked under the MH rim. Air, short- or long-acting gas or silicone oil have been used for postoperative tamponade. Refractory myopic MHs associated with retinal detachment and very large refractory MHs are suitable for hAM graft. Potential complications include graft displacement and surgical trauma to the RPE and retina. Choroidal neovascularization has been described following hAM graft.[19]

Observation

Although various technical modifications have resulted in improved anatomic success for refractory macular holes, visual improvement may not follow. Clinical indicators of a guarded visual prognosis include:

- RPE and chorioretinal atrophy affecting the central macular region;
- a thin flat rim to the MH; and
- loss of normal retinal architecture on optical coherence tomography.

When the potential benefits of surgery for refractory MHs don't justify the risks or patient inconvenience, observation becomes an appropriate management option.

Bottom line

A number of factors determine the best surgical approach for managing a refractory MH, including the potential for visual improvement, ILM status, MH size and previous surgeries. Some of the techniques may be combined for optimal results.

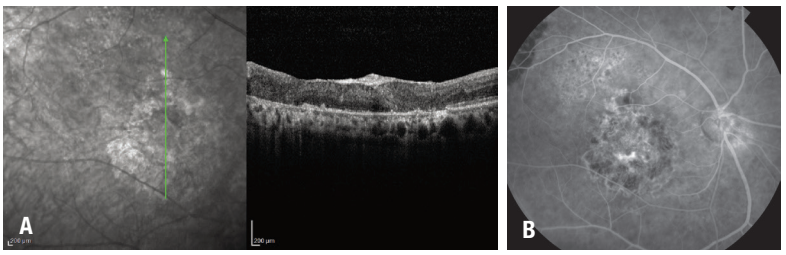

Figure 3. A) Optical coherence tomography and fundus fluorescein angiogram one year after autologous retinal transplant in a patient with giant macular hole shows coverage of the MH by the retinal graft with integration of the graft tissue with the surrounding retina. B) Fluorescein angiogram demonstrates that the graft blood vessels are perfused.

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When the potential benefits of surgery for refractory macular holes don't justify the risks or patient inconvenience, observation becomes an appropriate management option.

Department Editor *David R. P. Almeida, MD, PhD*

The upsides of social media

A reminder of how we can benefit patients and communities by promoting health literacy and justice.

By David R. P. Almeida, MD, PhD, MBA

In the last installment we welcomed 2022 by surveying the critical productivity applications for social media use by vitreoretinal specialists and physicians. Today, as we embark on the nostalgic "back to school" part of the year, I'll review two emerging and significant upsides of social media directly relevant to retina specialists, ophthalmologists and physicians.

Health literacy and misinformation

Eighty percent of cancer patients use social media to connect with peers.[1] For health organizations, more than 80 percent of state health departments have social media accounts.[2] Moreover, we know that our patients routinely seek out health information on social media. In fact, this is the central tenet why we, as physicians, deploy social media.

Our promotion of valid health content and our role as medical knowledge translator can serve to improve health literacy and counteract misinformation.[3] As we've discussed previously, with effective and professional (i.e., responsible) social media use, we can guide patients to the best available evidence for disease education and support an informed patient population.

Justice advocacy and equity

Despite the pitfalls social media poses to physicians, it remains a platform of communication that can ameliorate health equity and enhance justice advocacy. Numerous examples exist, from diversity in hospitals to gender equality and universal health care, where retina specialists and physicians can advocate for groups within the medical community and validate their appropriate concerns and questions.[4]

The versatile nature of social media justice advocacy will remain critical as a means to progress toward health and socioeconomic equity.[5] A bona fide use of social media is that it presents us as retinal specialists with an issue-agnostic platform.

Irrespective of whether the issue is pediatric myopia or access to diabetic retinal care, we can be vocal proponents of the causes timely in our local communities and society at large. Remembering to protect patient information, avoid politics and be on the right side of legal requirements are congruent to the necessary high standards of physician social media use.

Quotable

Despite the pitfalls social media poses to physicians, it remains a platform of communication that can ameliorate health equity and enhance justice advocacy.

Bottom line

Social media can be used for various health purposes with numerous benefits. New usages of social media, including the promotion of health literacy and justice advocacy, were discussed here as a reminder of the fundamental benefits social media can provide to patients and communities. RS

Bio

Dr. Almeida is a vitreoretinal surgeon at Erie Retinal Surgery in Erie, Pa.

DISCLOSURE: Dr. Almeida reports no relevant financial relationships.

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Scleral-fixated IOLs: A modified approach

(Continued from page 17)

conscious effort. An error can pinch the haptic, causing permanent damage and requiring immediate explantation.

Straighten the haptic

Target the very tip when grasping the haptic with the 27-g MAXgrip forceps (Alcon). Frequently, a right or oblique angle between the shaft of the forceps and the haptic is initially created. This angle must be straightened to facilitate removal through the sclerotomy (*Figure 3*).

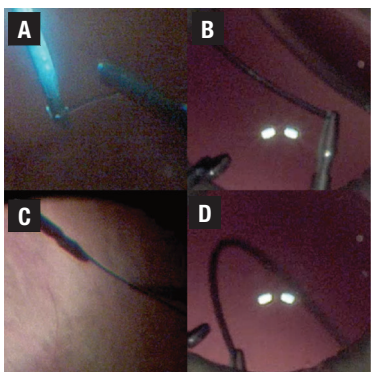

Figure 3. A) and B) show a perpendicular angle between the haptic and forceps that commonly occurs when first gripping the haptic. It should be straightened before attempting to externalize the haptic. C) and D) show appropriate linear orientation of the haptic-forceps complex.

Adjusting this angle requires a second instrument (a Kuglin hook in the AC or a light pipe in the vitreous cavity) and gentle adjustment of the grip on the forceps. If the grip is too tight, the haptic won't rotate. If the grip is too loose, the haptic will drop from the forceps. This also serves to verify an adequate hold on the haptic before the critical externalization step.

It's much better to drop a haptic and readjust it while all the instruments are in the eye rather than inadvertently releasing it during haptic externalization when the cannula is no longer in place and the forceps are exiting.

Bottom line

Scleral fixation of IOLs is frequently best approached using vitreoretinal surgical techniques. We describe augmentation of existing methods, which facilitate externalization of the haptics through 27-g sclerotomies.

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Epitheliopathy after a COVID-19 vaccine

(Continued from page 12)

hyper-reflectivity of the retinal layers from the outer plexiform layer to the RPE, with attenuation or disruption of the ellipsoid zone in some cases.[2]

A series of five APMPPE cases evaluated with OCTA revealed choriocapillaris flow abnormalities underlying acute and healed APMPPE lesions.[7] Acute lesions demonstrated significant loss of choriocapillaris flow while healed lesions showed distinct small-vascular flow channels with intervening no-flow zones, which appeared different compared to surrounding unaffected zones of the choriocapillaris. In addition, a prospective case series demonstrated that OCTA, in comparison to IVFA and ICGA, was able to more clearly distinguish and monitor APMPPE and related placoid disorder lesions.[8]

Bottom line

As this case illustrates, multimodal imaging is essential in diagnosing APMPPE and monitoring disease activity. The findings in our patient corroborate what has been previously reported: that is, excellent colocalization of flow voids on OCTA with hypocyanescent changes on ICGA. Additionally, we longitudinally followed the lesions with OCTA, observing resolution of these flow voids. A repeat ICGA and OCTA six weeks after this patient's initial presentation demonstrated significant improvement of the flow voids, but not complete normalization.

Even several weeks after the symptoms and clinical signs resolved, deficits in choroidal perfusion remained—easily imaged with OCTA and ICGA. Here, OCTA may be a suitable and noninvasive way to image patients with APMPPE and track their disease course over time.

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Comparing techniques for RRD, MH

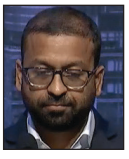
Prime cuts from ASRS also include a quick-response program for CRAO, and trials of agents for GA and mydriasis reversal.

By Ashkan M. Abbey, MD

The 40th annual scientific meeting of the American Society of Retina Specialists convened in New York City in July, bringing together retina specialists from around the world with a return to a full live format.

Among the cutting-edge clinical science presented at the meeting, here we review five abstracts that are worth a second look:

- A multicenter trial of adults with rhegmatogenous retinal detachment treated with a scleral buckle or combined pars plana vitrectomy-SB procedure.
- A hospital-based, prospective, randomized study of eyes with large macular holes treated with either the multilayered inverted limiting membrane flap technique or internal limiting membrane peel.
- Experience with a point-of-care program with optical coherence tomography for people with central retinal artery occlusion.
- A Phase II trial of an investigational antisense oligonucleotide for geographic atrophy.
- Results of a Phase III trial of an agent to reverse pharmacologically induced mydriasis.



Repair techniques for rhegmatogenous retinal detachment

This multicenter, prospective, nonrandomized comparative trial enrolled 83 adult patients with a primary macula-off rhegmatogenous retinal detachment who had scleral buckle or a combined pars plana vitrectomy-SB procedure. The goal was to evaluate the risk of low-integrity retinal attachment (LIRA), characterized by retinal displacement on fundus autofluorescence.[1]

In presenting the results, Aditya Bansal, MD, a vitreoretinal clinical fellow at St. Michael's Hospital in Toronto, said recent evidence suggests that LIRA is more likely to occur with PPV compared with a retinal pigment epithelium-pump procedure such as SB or pneumatic retinopexy—most likely due to the full-gas fill used during PPV that exerts a buoyant force on the retina and residual subretinal fluid, leading to stretching of the retina and worse function outcomes.

All patients had FAF and functional outcomes assessment. Two masked graders assessed the FAF images for retinal vessel printings and adjudicated any differences by consensus. Excluded were patients with poor-quality ungradable FAF images. Primary outcome was the risk of LIRA following SB vs. PPV-SB.

The study found that SB is associated with less retinal displacement/LIRA than PPV-SB, although functional outcomes were similar between the two groups.

Of the 83 eyes in the study, 41 percent (n=34) had SB and 59 percent (n=49) had PPV-SB. Two graders evaluated the FAF findings with a high rate of agreement in detecting LIRA (85.5 percent, Kappa=0.629; 95% CI=0.439–0.819).

Baseline characteristics differed with younger phakic patients in the SB group and patients with more extensive detachments in the PPV-SB group. In the SB group, 17.6 percent (n=6) had LIRA vs. 38.8 percent (n=19) in the PPV-SB group (p=0.039).

The study found a statistically significant association between LIRA and procedure type remained after a multivariable logistic regression adjusting for gender, lens status, extent of retinal detachment in quadrants and baseline logMAR visual acuity with odds of retinal displacement of 3.875 (95% CI=1.18–12.723, p=0.026) for PPV-SB vs. SB. There were no statistically significant differences in functional outcomes be-

Bio

Dr. Abbey is director of clinical research at Texas Retina Associates, Dallas, and a clinical assistant professor of ophthalmology at the University of Texas Southwestern Medical Center.

DISCLOSURES: Dr. Abbey is a consultant to Alcon, Allergan/AbbVie, Alimera Sciences, EyePoint Pharmaceuticals, Genentech/Roche, Novartis and Regeneron Pharmaceuticals.

tween the two groups.

Dr. Bansal said that further prospective studies with a larger sample size are required to assess the impact of retinal displacement on functional outcomes in patients undergoing SB or PPV-SB.

Dr. Bansal had no relevant financial relationships to disclose.

Comparison of repair techniques for large macular holes

Much controversy surrounds the use of two techniques for repairing large macular holes: the multilayered inverted internal limiting membrane (ML-IILM) flap technique with perfluorocarbon liquid; and the standard internal limiting membrane peeling technique.

Vishal Agrawal, MD, a professor at SMS Medical College in Jaipur, India, reported on a hospital-based, prospective, randomized, interventional consecutive study of 150 eyes, with an even number assigned to either the ILM peeling group or vitrectomy with the ML-IILM technique.[2] Patients were treatment-naive, age 50 years or older and had a full-traction macular hole with a base diameter of ≥600 µm. Excluded were patients with amblyopia, inflammatory eye disease, hypertensive and diabetic retinopathy, retinal detachment or retinal surgery, glaucoma, ≥–6D myopia or if they refused consent.

The study found that ML-IILM had significantly better rates of anatomical closure and visual outcome. Final follow-up was at one year. During follow-up at one, three, six and 12 months, the mean postoperative best-corrected visual acuity was significantly better in the ML-IILM group: 0.12 ±0.07 vs. 0.20 ±0.11; 0.14 ±0.10 vs. 0.22 ±0.13; 0.18 ±0.11 vs. 0.30 ±0.12; and 0.19 ±0.12 vs. 0.31 ±0.14, respectively (p=0.001 for all). Anatomical closure was achieved in all patients who had ML-IILM and 93.3 percent (n=70) in the ILM group.

Type 1 closure rates were also better in the ML-IILM group: 93.3 percent (n=70) vs. 78.7 percent (n=59). Type II closure occurred in 6.7 percent (n=5) of the patients who had ML-IILM vs. 15.6 percent (n=11) (p<0.05). Among the ILM patients, 6.67 percent (n=5) of cases failed to achieve any anatomical closure.

Dr. Agrawal said the ML-IILM technique under PFCL is a safe and easily reproducible and offers distinct advantages over ILM peeling in terms of flap-related complications.

Dr. Agrawal and colleagues had no relevant financial relationships to disclose.

Point-of-care OCT and management of central retinal artery occlusion

Central retinal artery occlusion can be visually debilitating and there's no universally accepted treatment. Fibrinolysis has been shown to improve visual outcomes, but timing is critical. Patients must have treatment within hours of symptom onset, but diagnosis delays reduce chances to improve their vision.

For this study, optical coherence tomography machines were installed at three stroke centers in the Mount Sinai health system in New York City.[3] The goal was to evaluate whether point-of-care diagnosis can improve vision and functional outcomes. Gareth Lema, MD, PhD, of New York Eye and Ear of Mount Sinai, reported that the point-of-care OCT in stroke centers can expedite time to treatment for CRAO, increase eligibility for patients to receive treatment and maximize visual improvement.

Dr. Lema noted that any patient who reports to the emergency department with painless monocular vision loss suspicious for a CRAO or stroke activates the stroke protocol. Simultaneously, the retina service gets an alert that a possible CRAO has arrived. The stroke team evaluates the patient, including visual acuity data, pupil exam and OCT of the macula. The clinical data and images are transmitted to mem-

The multilayered inverted internal limiting membrane technique under perfluorocarbon liquid was found safe and easy to reproduce for large macular holes.

bers of the retina service who assist in making the diagnosis.

If they confirm a CRAO and the patient can be treated within 12 hours of stroke onset, the patient goes directly for treatment with intra-arterial recombinant tissue plasminogen activator (tPA). If another diagnosis is considered at any time, a full ophthalmology consult is performed before any treatment is considered. Patients who aren't eligible for treatment still get evaluated with a full stroke work-up. Upon admission, patients are followed by the ophthalmology service to document visual outcomes and safety.

Dr. Lema reported on the experience with the protocol after one year. The study included 35 patients, 19 of whom had CRAOs. Seven of eight patients who met the treatment criteria for intra-arterial tPA (17 mg) received the treatment. All other patients underwent the stroke work-up.

In the preliminary results of five patients who received tPA, the average time to treatment was 8.6 hours (range: 6.5 to 11.75 hours). Visual gains were measured within 24 hours of treatment and all patients showed improvement in visual acuity. Interestingly, two patients lost vision again within two days of treatment, presumably from secondary emboli or thrombosis. In one, antiplatelet therapy reversed the vision loss. No significant adverse events were reported in patients who received tPA.

Dr. Lema had no relevant financial relationships to disclose.

In preliminary results of patients who received tPA for retinal artery occlusion, the average time to treatment was 8.6 hours with no significant adverse events reported.

Baseline characteristics for Phase II trial of antisense therapy for GA

IONIS-FB-LRx (Ionis Pharmaceuticals) is a novel investigational antisense oligonucleotide targeting liver factor B in the complement cascade as a treatment for geographic atrophy. Glenn Jaffe, MD, of Duke University, reported on the baseline characteristic for the ongoing Phase II GOLDEN trial,[4] the goal of which was to determine whether treatment with IONIS-FB-LRx reduced GA growth in eyes with age-related macular degeneration.

Dr. Jaffe noted the Phase I data supported further development of IONIS-FB-LRx. Based on analysis of the first 100 subjects in the Phase II trial, the median participant age is 76; approximately 58 percent are female. Two-thirds of the lesions are subfoveal in nature, 65 percent are multifocal, 95 percent are bilateral and the mean baseline GA area is 7.6 mm^2.

The mean annualized GA area change is approximately 2 mm^2 during the screening period. The growth rate was fastest for nonfoveal-centered multifocal lesions and slowest for unifocal nonfoveal-centered lesions. The baseline BCVA was more than 2 lines better for multifocal lesions than unifocal lesions and worse for foveal-centered lesions on average.

Dr. Jaffe said the baseline characteristics and annualized growth rates were similar to previously reported studies of investigative agents for GA, including the CHROMA/SPECTRI trials of lampalizumab, the FILLY trial of pegcetacoplan and the GATHER 1 trial of avacincaptad pegol.

Dr. Jaffe disclosed financial relationships with Novartis, Regeneron Pharmaceuticals and Roche.

Phase III results of phentolamine to reverse mydriasis

Phentolamine ophthalmic solution (POS) 0.75% is designed to reverse pharmacologically induced mydriasis. David Boyer, MD, of Retina-Vitreous Associates Medical Group in Los Angeles, reported that the MIRA-2 and MIRA-3 Phase III trials have shown that POS reduced mydriasis within 60 to 90 minutes in most patients.[5]

MIRA-2 and MIRA-3 were multicenter, randomized, placebo-controlled,

(Continued on page 46)

Department Editor ***Richard Mark Kirkner***

Senolytic therapy: 'Entirely new paradigm'

A look at UBX1325, a small-molecule B-cell inhibitor that targets the proteins senescent cells feed on for survival.

With Raj K. Maturi, MD

Raj K. Maturi, MD

UBX1325, a small-molecule B-cell inhibitor under investigation for treatment of neovascular age-related macular degeneration and diabetic macular edema, is the vanguard of medical therapies that target senescent cells. Senescence is defined as "the state of being old; the process of becoming old."

UBX1325 aims to inhibit Bcl-xL, one of the Bcl-2 family of apoptosis-regulating proteins that senescent cells need for survival. Raj K. Maturi, MD, of Midwest Eye Institute in Indianapolis and a clinical associate professor at the University of Indiana School of Medicine, and a UBX1325 investigator, describes senolytic therapy as "an entirely new paradigm of treatment." He adds, "Unlike other things that we do, where we try to do our best to preserve cells, the UBX paradigm is entirely the opposite."

The idea is to disrupt the proteins that senescent cells feed on for survival. Dr. Maturi reported 24-week Phase I results in people with chronic AMD and DME at the American Society of Retina Specialists' 40th annual scientific meeting.[1] Later, trial sponsor Unity Biotechnology reported 12- and 18-week outcomes from a Phase II trial in DME, which showed that treated patients gained +6.1 letters of vision after 18 weeks while maintaining central subfield thickness.[2]

Here, Dr. Maturi answers questions about UBX 1325. Dr. Maturi also serves on Unity Biotechnology's scientific advisory board.

Q What's the principle behind senolytic therapy?

A Inflammation or any other damage to a tissue or cell causes the most-affected cells to go into senescence. Typically, they stop dividing, a process that applies mostly to vascular tissue.

These damaged cells then excrete senescent factors, such as cytokines, inflammatory mediators and fibroblast attractors, all of which cause inflammation. UBX1325 aims to prevent production of these chemokines and other factors. Where steroids and other drugs inhibit them, the thinking is to eliminate this layer of senescent cells.

Q How would you describe the mechanism of action of UBX3125?

A UBX3125 looks for cells that are in senescence and eliminates them. This allows some space for normal endothelial cells to grow. That's the beauty of senescent treatment. The eye is ideal for it because, obviously, it's sequestered to this one tissue where we can make sure the effect is very local.

Q How did the preclinical research inform the in-human studies?

A First, researchers had to answer the question: Is there an increase in senescent cells in patients with AMD and diabetes? The answer is, yes; much more so than in healthy older people.

The second question was: Can we make sure senescent treatment with UBX doesn't harm any normal tissue? Testing in an oxygen-induced retinopathy mouse model, for diabetic retinopathy and leukemia, found that UBX, like anti-VEGF, doesn't cause new blood vessel growth.

But there was one big difference. With anti-VEGF treatments, the area of ischemic tissue is fairly large. The UBX-treated mice model showed a smaller area of ischemic tissue because abnormal endothelial cells were completely killed, which actually allowed more normal tissue to grow over the time.

Q What are the key messages from the 24-week Phase I trial?

A This was a standard dose-escalation study of low to medium to high doses in patients who continued to have edema with AMD and DME. (Dosing was at 0.5,

UBX3125 looks for cells that are in senescence and eliminates them. This allows some space for normal endothelial cells to grow. The eye is ideal for senescent treatment.

1.5, 5 and 10 µg.) Data were analyzed for each group separately.

There were no safety issues, no issues of inflammation and there were no significant dropouts. Both groups showed a significant increase in vision within the first two weeks. The diabetic patients (n=8) showed an almost 10-letter gain in vision, much of which lasted through 24 weeks without any additional treatments. Just a couple patients in the diabetes arm needed rescue, but these patients had that observation carried forward so their visual gain after rescue was not recorded. There was some nice vision gain in these patients. (At Week 24, 62.5 percent of DME patients gained ≥5 letters and 50 percent gained ≥10 letters.)

Optical coherence tomography improved initially, but then it came back to baseline somewhat after a few weeks. (Overall, central subfield thickness remained stable through 24 weeks in most DME patients.)

Q What were the results in the AMD patients?

A The results weren't as robust as in DME. The AMD patients (n=10) had a 5-letter gain on average in first two to three weeks of treatment. They maintained this vision gain throughout with more patients requiring rescue treatments than the DME group.

The biggest key takeaway is that we found that UBX1325 is actually relatively safe in the eye. The second key takeaway is that it actually had a biologic effect. There was improvement in vision in diabetes patients as well as the AMD patients, and some of the effect can be relatively long-lasting, especially in the diabetes populations.

Q What are the next steps in development of UBX1325?

A Because of the Phase I data, two Phase II studies have been started: one in DME using the highest dose from the Phase I study, 10 µg; and another in AMD in which patients could be given two doses about eight weeks apart. In the Phase I study, AMD patients needed more rescue and the concept here is that UBX could potentially decrease anti-VEGF dosing. Given what we learn from these studies, UBX may have some role in other ischemic diseases. RS

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Comparing techniques for RRD, MH

(Continued from page 44)

double-masked clinical trials in healthy subjects (n=553; age ≥12 years). Stratified by iris color, subjects were randomized to mydriatic agent 3:1:1 (2.5% phenylephrine, 1% tropicamide or Paremyd, respectively) and treatment 1:1 in MIRA-2 and 2:1 in MIRA-3 of POS or placebo. The primary endpoint was percent of subjects returning to ≤ 0.2 mm from baseline photopic pupil diameter (PD) at 90 minutes. Secondary endpoints included time to return to baseline PD, visual acuity, time savings and change from maximum dilation.

Across both studies, 338 patients received POS (average age 33 years, 60 percent female) and 215 received placebo (average age 33 years, 62 percent female). Across all mydriatic agents at 90 minutes, 49 percent and 58 percent of study eyes in MIRA-2 and MIRA-3, respectively, that received two drops of POS returned to ≤0.2 mm of baseline compared to 7 percent of placebo-treated subjects in MIRA-2 and 6 percent in MIRA-3 ($p<0.0001$).

Similar efficacy was also seen starting at 60 minutes and lasting up to 24 hours ($p<0.0001$) with one or two drops of treatment and across light and dark irides. Mean pupil diameter was significantly lower with POS at all time points starting at 60 minutes ($p<0.0001$).

POS was also found to produce a time savings of three to four hours. Adverse events were observed in around 5 percent of patients. They included mild, transient conjunctival hyperemia (11.5 percent, n=39) in POS patients and mild installation site discomfort. No serious AEs were reported across both trials and no patients withdrew from the studies because of them. Additionally, POS didn't compromise distance visual acuity.

Dr. Boyer disclosed being a consultant to Ocuphire Pharmaceuticals, sponsor of the studies. RS

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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 during the first year was 2% (25 out of 1,262) in patients treated with VABYSMO compared with 2% (14 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=1262	AMD N=622	DME N=625
Conjunctival hemorrhage	7%	7%	8%	6%
Vitreous floaters	3%	3%	2%	2%
Retinal pigment epithelial tear[a]	3%		1%	
Intraocular pressure increased	3%	3%	2%	2%
Eye pain	3%	2%	3%	3%
Intraocular inflammation[b]	2%	1%	1%	1%
Eye irritation	1%	1%	< 1%	1%
Ocular discomfort	1%	1%	< 1%	< 1%
Vitreous hemorrhage	< 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, lacrimation increased, ocular hyperemia, blurred vision, eye irritation, sensation of foreign body, endophthalmitis, visual acuity reduced transiently, 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]
Manufactured by:
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A Member of the Roche Group
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South San Francisco, CA 94080-4990
U.S. License No.: 1048

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VABYSMO™
faricimab-svoa injection 6 mg

WHERE 2 WORLDS MEET

The First and Only Dual-Pathway Inhibitor in Retinal Disease[1-5]

VABYSMO Is the First IVT Injection Approved for Q4W-Q16W Dosing Intervals in nAMD and DME[1-4]*

Image not intended to be a patient portrayal.

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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 inflammation, in patients with active intraocular inflammation, and in patients with known hypersensitivity to faricimab or any of the excipients in VABYSMO.

Warnings and Precautions

- Endophthalmitis and retinal detachments may occur following intravitreal injections. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay, to permit prompt and appropriate management.
- Increases in intraocular pressure have been seen within 60 minutes of an intravitreal injection.
- There is a potential risk of arterial thromboembolic events (ATEs) associated with VEGF inhibition.

Adverse Reactions

The most common adverse reaction (≥5%) reported in patients receiving VABYSMO was conjunctival hemorrhage (7%).

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 VABYSMO full Prescribing Information on the following page.

*Dosing Information:

In nAMD, the recommended dose for VABYSMO is 6 mg (0.05 mL of 120 mg/mL solution) IVT Q4W for the first 4 doses, followed by OCT and visual acuity evaluations 8 and 12 weeks later to inform whether to extend to: 1) Q16W (weeks 28 and 44); 2) Q12W (weeks 24, 36, and 48); or 3) Q8W (weeks 20, 28, 36, and 44).

In DME, the recommended dose for VABYSMO is 6 mg (0.05 mL of 120 mg/mL solution) IVT Q4W for ≥4 doses until CST is ≤325 µm (by OCT), followed by treat-and-extend dosing with 4-week interval extensions or 4- to 8-week interval reductions based on CST and visual acuity evaluations through week 52. Alternatively, VABYSMO can be administered IVT Q4W for the first 6 doses, followed by Q8W dosing over the next 28 weeks.

Although VABYSMO may be dosed as frequently as Q4W, additional efficacy was not demonstrated in most patients when VABYSMO was dosed Q4W vs Q8W. Some patients may need Q4W dosing after the first 4 doses. Patients should be assessed regularly and the dosing regimen reevaluated after the first year.

CST=central subfield thickness; IVT=intravitreal; OCT=optical coherence tomography; Q4W=every 4 weeks; Q8W=every 8 weeks; Q12W=every 12 weeks; Q16W=every 16 weeks.

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