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RETINA SPECIALIST

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HOW IMAGING IS ADVANCING MANAGEMENT OF DRY AMD

Emerging modalities and deep learning are helping to expose an old foe in non-neovascular disease. *Page 18*

Also Inside

Online Video

WHAT COULD SHE SEE THIS YEAR?

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

Inspired by a real patient with DME.

375 MATH TESTS

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.

REGENERON

777 Old Saw Mill River Road, Tarrytown, NY 10591

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

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EDITORIAL

By Charles C. Wykoff, MD, PhD

Untapped insights

Few subspecialties in medicine tailor treatment to the needs of an individual as intently as retina. Phil Rosenfeld, MD, PhD, pioneered individualized care in neovascular age-related macular degeneration by characterizing as-needed retreatment (*pro re nata*), which evolved into the familiar treat-and-extend approaches we most commonly employ today.

Both of these approaches leverage what are often subtle findings related to the presence of and qualitative changes in fluid patterns on optical coherence tomography, data explicitly not accessible with ophthalmoscopic examination alone, to guide management decisions.

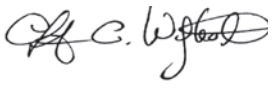
Recent work suggests that the retina imaging we perform so frequently holds many more biomarkers that promise to further refine our prognostic capabilities and management choices. Some of these biomarkers, such as reticular pseudodrusen, double-layer signs, intraretinal hyperreflective foci and hyporeflective foci within drusen, can be gleaned by simply applying a more nuanced qualitative review during our current workflow.

Other disease characteristics may best be appreciated using software algorithms. On page 23, Gagan Kalra, MD, and Justis Ehlers, MD, describe utilizing quantitative image analyses, including evaluation of OCT structural features and fluorescein angiographic vascular features, to better understand disease progression and response to treatment. For example, quantification of leakage patterns, microaneurysms, ischemic burden and vessel characteristics appear capable of substantively more accurately predicting the risk of diabetic retinopathy severity worsening.

Beyond guiding prognostication for local disease progression, retinal imaging has long been recognized as a plausible window into concurrent systemic disease states. It's quite possible that routine retinal imaging may help us to identify Alzheimer's and other neurodegenerative diseases, as well as diabetes mellitus and other vascular diseases, in preclinical stages. More practically for the clinic today, it's worth noting that reticular pseudodrusen, discussed by Jorge Orellana-Rios, MD, and colleagues on page 18, has been associated with an increased incidence of cardiovascular disease.

Furthermore, applying retinal biomarkers to the drug-development process may meaningfully accelerate timelines. For example, using imaging and genetic biomarkers to enrich a population of patients with intermediate dry AMD could improve the feasibility of a trial aimed at assessing a novel therapeutic's ability to impact the progression to advanced forms of AMD. On page 28, Johanna Seddon, MD, ScM, describes recent advances in our understanding of the interplay between genetics, diet and drusen size in AMD pathogenesis and progression.

Cumulatively, leveraging insights from imaging-based biomarkers appears to be bringing us closer to a key goal of individualized patient management: primary prevention of the pathologies that cause vision loss.



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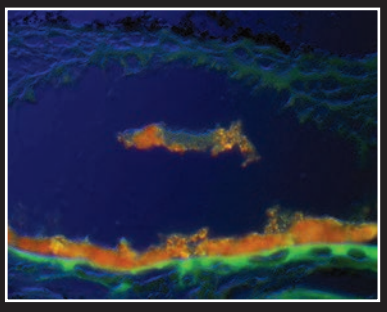
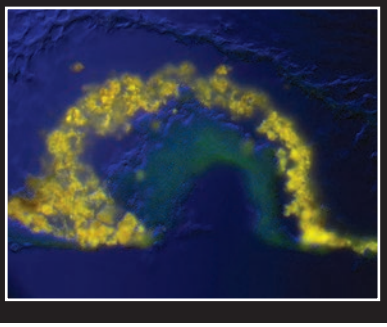
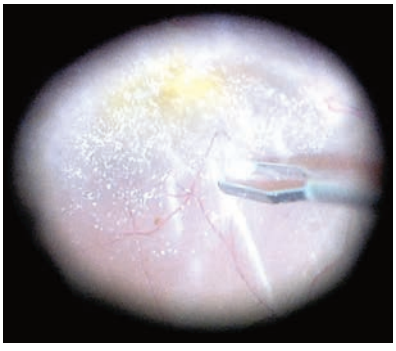
FEATURES





DEPARTMENTS



NEI-supported group is tackling ophthalmology's diversity problem

Ophthalmology has a long-documented diversity problem.

While minorities make up one-third of the U.S. population, they only comprise 6 percent of practicing ophthalmologists.[1] That underrepresentation carries over to medical schools, with minorities representing only 5.7 percent of ophthalmology faculty.[1] A recent analysis of 2019 American Association of Medical Colleges Faculty Roster data found that ophthalmology ranks in the bottom three of 17 specialties in terms of minority representation among department faculty.[2]

Last month, as Medscape reported, a coalition of Black physicians met with the American Medical Association to press the case for anti-racism initiatives in medicine.

The studies of the lack of diversity in ophthalmology defined minority groups traditionally underrepresented in medicine, known at URM. That includes Black, Hispanic, Native American, and Native Hawaiian or Pacific Islander. U.S. Census data shows these URM groups make up 33.4 percent of the population.

Rabb-Venable Program

Two ophthalmologists trying to do something about the lack of diversity in their ranks are Mildred M.G. Olivier, MD, assistant dean for diversity and inclusion and global health chair for Chicago Medical School and a professor at Rosalind Franklin University of Medicine and Science/John H. Stroger Jr. Hospital of Cook County, and Eydie Miller-Ellis, MD, professor and director of the glaucoma service at the Scheie Eye Institute, Perelman School of Medicine at the University of Pennsylvania, Philadelphia.

Mildred M.G. Olivier, MD, (left) and Eydie Miller-Ellis, MD, are co-directors of the Rabb-Venable Excellence in Ophthalmology Program.

They're co-directors of the Rabb-Venable Excellence in Ophthalmology Program (RVEOP), an organization whose mission is to entice minority medical students to pursue ophthalmology and to support those who want to work in underserved communities. RVEOP was established in 2000 by the National Medical Association, the oldest and largest organization of African-American physicians and healthcare professionals in the United States. RVEOP is named for two pioneering African-American ophthalmologists: Maurice F. Rabb Jr., MD, a retina specialist in Chicago who devoted his research to sickle cell disease; and Howard P. Venable, MD, the first African-American on faculty at Washington University, St. Louis. Dr. Rabb died in 2005; Dr. Venable died in 1998.

RVEOP's offerings include an annual awards scholarship as well as mentoring, career development and volunteer opportunities. The program also gets support from the National Eye Institute.

Improving diversity in retina

"I think that all of our subspecialties can use some diversification in them," Dr. Olivier says. She credits the American Academy of Ophthalmology's Minority Ophthalmology Mentoring program, or MOM, with bringing "a lot of those subspecialties … on board." Also, RVEOP fireside chats hosted by O'Rese Knight, MD, of the University of North Carolina, and Dolly Ann Padovani-Claudio,

IN BRIEF

Heidelberg Engineering and **RetinSight** announced plans to interface the latter's artificial intelligence-based fluid monitor application with the former's product line. The platform would use cloud exchange and application marketplace technologies.

Claire M. Gelfman, PhD, has been named chief scientific officer of **Foundation Fighting Blindness**. A former vice president with **Adverum Biotechnologies**, Dr. Gelfman will oversee FFB's nonclinical research portfolio.

Full 12-month results of the Phase IIb ALTISSIMO trial of **GB-102** of patients with age-related macular degeneration found the 1-mg dose to be safe and well-tolerated, trial sponsor **Graybug Vision** reports. Graybug last year terminated development of the 2-mg formulation of GB-102

MD, PhD, of Vanderbilt University exposed 30 ophthalmology training programs to RVEOP mentors and volunteers.

In retina, RVEOP has worked with the Retina, Macula and Vit-Buckle societies and American Society of Retina Specialists to engage minority trainees.

Last year the program matched 28 candidates with ophthalmology programs, four times the usual six or seven in a typical year, she says. "I think everybody was making a concerted effort to try to increase diversity," Dr. Olivier says.

Overcoming barriers

Dr. Miller-Ellis says the underrepresentation of minority ophthalmology residents is even more acute, with only 2 to 3 percent in her experience. She notes ophthalmology has some built-in disadvantages in attracting these candidates. "Many schools don't even require ophthalmology as a rotation, and before coming to medical school some students may not even have considered this as a career," she says. "So, we're starting off a little bit behind because ophthalmology has an early match; it's very competitive. So you have to provide exposure and opportunities so that they would be competitive when it's time to apply for the match."

Even before medical school, even before college, would-be doctors of economically disadvantaged backgrounds face a multitude of hurdles getting to their match moment.

"One of the barriers is not having institutional support or support from advisers in school to pursue this particular field," Dr. Miller-Ellis says. That gets to high school counselors discouraging minority students from pursuing a STEM (science, technology, engineering, math) curriculum, college advisers and peers directing them away from medicine, and, if they get into medical school, forces there directing them toward primary care and away from a specialty.

"We all need talented, dedicated, smart primary-care doctors, but so many of the subspecialties, particularly ophthalmology—it's like doing primary care for the eye," Dr. Miller-Ellis adds. "There is so much that goes on with eye disease that reflects systemic diseases, being advised that we're a super specialty and that you're somehow abandoning the people that need you by pursuing it, I think, is a real misconception."

The COVID-19 pandemic exposed many of those barriers on a more pedestrian level, Dr. Olivier notes. "When we had to go virtual, sometimes the broadband at their houses wasn't enough for them to do the medical training," she says. "You can look at the Latinx community; oftentimes they're very near family and they're still expected to be very involved with the family and yet they're going to medical school. I've had students who had to drive two hours because their husbands had a job somewhere and they were not willing to move."

Richard Mark Kirkner

REFERENCES

1. Xierali IM, Nivet MA, Wilson MR. Current and future status of diversity in ophthalmologist workforce. JAMA Ophthalmol. 2016;134:1016-1023.
2. Fairless EA, Nwanyanwu KH, Forster SH, Teng CC. Ophthalmology departments remain among the least diverse clinical department at United States Medical Schools. Ophthalmology. Published online January 10, 2021.

FOR THE RECORD

A reference in the article "Retina Rounds: A curious case of RAMA" (pages 16 to 19, March/April ***Retina Specialist***) was incorrect. The correct reference 10 is:

Klatz R, Goldman R, Punchuk B, Nelson K, Tarr R. The effects of gravity inversion on systemis blood pressure, intraocular pressure, and central retinal arterial pressure. J Am Osteopath Assoc. 1983;82:111-115.

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Improving Wet AMD Outcomes With a Fellow Eye Strategy

The importance of detecting early changes in the fellow eye through proactive remote monitoring

By Miguel A. Busquets, MD, FACS

In retina care today, advancing therapies and treat-and-extend regimens have enabled wet AMD patients to extend the time between their anti-VEGF injections, which has served to improve quality of life for those patients under treatment and freed up the retina clinic to see additional patients. While these improvements have positively impacted retina care in many ways, patients with wet AMD may now be seen less frequently than is ideal for following the fellow eye. Some are receiving injections every three or four months, and many are not receiving a bilateral OCT when they present for injections, for a variety of reasons. At the same time, patients may not notice changes that have occurred in their fellow eyes since their last visit. This is concerning because studies reveal that fellow eyes are at higher risk of conversion to wet AMD.[1,2,3]

These assessment gaps leave a great deal of room to miss conversion. Thankfully, though, advanced remote monitoring solutions make it possible for the patient and specialist to track the fellow eye between office visits, with a goal of catching any structural changes as soon as they occur.

RETINA CLINIC REALITIES

Data has shown us that once a patient begins treatment, the patient tends to be seen less frequently over time. In a paper presented at the American Academy of Ophthalmology Annual Meeting in October 2020, the percentage of patients seen after 8 weeks decreased from 56% (year 1) to 44% (year 2),[4] meaning in-office imaging frequency of the fellow eye also decreases over time.

I believe retina specialists have the best intentions in putting together comprehensive protocols for patients that include a bilateral exam and OCT with each encounter; however, a number of obstacles exist in retina care today.

One is flow restrictions in clinic. Patient care has become more targeted because of the increasing volume of patients being seen due to an aging population, and an overall shortage of retina specialists. In addition, due to the COVID-19 pandemic, patients may be hesitant to stay at the clinic for a long time. Additionally, unintended delays can be related to logistic hurdles such as bad weather and a lack of transportation, and other variables.

Looking to the future of wet AMD therapy, as longer-acting agents continue to come to market—enabling us to further extend patient treatment intervals—even larger gaps will arise when it comes to following the fellow eye.

These existing and evolving factors prolonging the time between visits make it even more imperative that we adopt available telemedicine technology to overcome these hurdles for patients and clinicians.

TOOLS TO TRACK THE FELLOW EYE

Functional vision is described as 20/40 or better, which is the required driving vision in many states; however, real-world data tells us that fellow eye conversion isn't being caught earlier than 20/79.[5] An analysis of the IRIS registry found that just 36% of fellow eyes had VA of 20/40 or better at treatment initiation.[5] At the same time, we know that early diagnosis with good VA is essential to preserving functional vision with anti-VEGF therapy.[6]

Retina specialists have a number of tools available to follow the fellow eye, but they suffer from several limitations. The Amsler grid, which was developed in the 1940s, is rudimentary and not very effective in detecting early wet AMD (20/40); one study showed it was only effective in detecting 9% of such patients.[7] In addition, we depend on the patient to use it without assistance. While present-day in-office technologies such as simple visual acuity tests, visual acuity charts, OCT imaging, fundus photography, and fluorescein angiography have improved detection of functional or structural changes, they are all subject to the previously mentioned constraints regarding time intervals between patient visits.

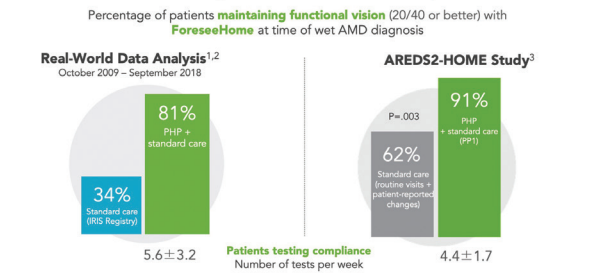
Thankfully, the ForeseeHome AMD Monitoring Program provided by the Notal Vision Diagnostic Clinic, a remote ophthalmic monitoring center directed by practicing ophthalmologists and supported by certified ophthalmic professionals, is able to overcome those gaps of time between patient visits. About three years ago, I was introduced to this program, and it has become an invaluable extension of my clinic's services for patients. It is a proven way, via patented Preferential Hyperacuity Perimetry® (PHP) technology developed by Notal Vision, to

ForeseeHome helps physicians detect wet AMD earlier

ForeseeHome helps physicians detect wet AMD earlier, based on the results of a pivotal clinical trial and real-world results.[1,2] The HOME study concluded that people at high risk for nAMD benefited from the home monitoring strategy for earlier detection of nAMD development, which increases the likelihood of better visual acuity results after intravitreal anti-VEGF therapy.

More recently, Ho, et al., found that real-world performance of a strategy including the ForeseeHome device monitoring program was comparable to its performance in the HOME study. Coupled with standard of care, its usage demonstrated a substantial benefit to patients by helping preserve an additional three lines of vision at the onset of nAMD, as compared to standard-of-care alone in real-world IRIS data, leading to excellent VA prognosis with current therapy.

ForeseeHome real-world performance resembles pivotal trial results



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. Ho, A.C.; Heier, J.S.; Holekamp, N.M.; Garfinkel, R.A.; Ladd, B.; Awh, C.C.; Singh, R.P.; Sanborn, G.E.; Jacobs, J.H.; Elman, M.J.; et al. Real-World Performance of a Self-Operated Home Monitoring System for Early Detection of Neovascular Age-Related Macular Degeneration. J. Clin. Med. 2021;10:1355
3. Chew EY, Clemons TE, Bressler SB, et al; AREDS2-HOME Study Research Group. Randomized trial of a home monitoring system for early detection of choroidal neovascularization home monitoring of the Eye (HOME) study. Ophthalmology. 2014;121(2):535-544.

detect minute vision changes and help catch wet AMD much earlier. In an unmasked, controlled, randomized clinical trial (HOME) of 1,520 subjects with a mean age of 72.5 years at high risk of CNV developing, 91% of patients who progressed to wet AMD maintained functional vision (20/40) upon presentation using ForeseeHome, regardless of test compliance, vs. just 62% of patients using standard detection methods alone.[8] Real-world performance of the program resembled the pivotal study results in which 81% of patients had 20/40 or better VA at wet AMD diagnosis[9] compared to only 34% in the IRIS Registry® data.[5]

BENEFITS OF A REMOTE MONITORING PROGRAM

The ForeseeHome remote monitoring program is an excellent way to monitor patients remotely for many reasons. The system's ability to detect minute changes in visual distortions means that the system is highly sensitive to detect early changes consistent with a conversion. The HOME study revealed that lesions were approximately three-fold smaller at CNV diagnosis with ForeseeHome vs. standard care alone.[8] Furthermore, the system's sensitivity and specificity in discriminating between patients with CNV and intermediate AMD has been verified by researchers.[10] Once an alert notification is received from the Notal Vision Diagnostic Clinic, the patient is immediately scheduled to come into our clinic where the change is validated, and, if verified, treatment is initiated. The advantage of this technology is to allow treatment of the patient at the earliest possible time, rather than one, two, or three months after the change has occurred. This is because the patient loses vision every day that a choroidal neovascular membrane is present due to hemorrhage and leakage. Since exudation causes visual loss via cellular damage through these mechanisms, identifying these processes at their inception with the aid of ForeseeHome enables clinicians to minimize retinal damage and, thus, preserve vision. As a result of early detection, patients can experience the full benefit of today's treatment options.

Another benefit of this program is that a team of clinicians at the Notal Vision Diagnostic Clinic monitors the system remotely to ensure that the signals coming through are reliable and that all parties are notified when alerts are issued. In addition, the treating physician obtains regular patient reports from the remote clinic to help them to stay informed about utilization rates, test results, and other relevant information.

Importantly, using ForeseeHome takes little time out of the patient's day and the clinic's workflow. For the patient, the device is easy to set up and use. The tests take a couple of minutes per eye per day for my patients, and I have them use it daily, with the majority using it 5 times a week. For the physician, the Notal Vision Diagnostic Clinic makes the patient "onboarding" process seamless and prevents it from disrupting my clinic flow. Once the patient agrees to use the system my staff sends an electronic referral to the Notal Vision Diagnostic Clinic which works with the patient directly for setup and assistance over the phone.

Home monitoring is needed to detect fellow eye conversion early

To improve outcomes for patients, home monitoring is needed to detect fellow eye conversion. The ForeseeHome AMD Monitoring Program has been proven to help physicians detect the conversion to wet AMD earlier. The ophthalmologist-led Notal Vision Diagnostic Clinic, provider of the remote monitoring service, helps physicians extend their care between office visits by providing:

- A digital, at-home concierge service from trained engagement specialists and certified ophthalmic professionals
- Benefits verification, disease education, comprehensive device set up assistance and training, and continuous engagement – all done remotely over the phone and via email
- Timely reporting and communications for physicians with information about patients' testing and alerts.

Ongoing patient satisfaction surveys show a 93% approval rating, and 80% of patients test compliantly (as per Medicare guidelines).

AN IMPORTANT EXTENSION OF THE RETINA CLINIC

In my clinic, ForeseeHome has become an important part of the monitoring approach for all eligible patients. When we see a patient receiving intravitreal injections, part of the protocol is that these patients will receive, as part of their workup, a folder with a referral to the Notal Vision Diagnostic Clinic for ForeseeHome. The Diagnostic Clinic provides all educational materials about intermediate AMD and the overall program. One of my technicians, who has been trained by the Notal Vision Diagnostic Clinic, takes a few minutes to educate the patient on the technology and its importance for a comprehensive monitoring strategy. When I come in to do the patient's injection, I simply reinforce the importance of this device and the reasons why it's valuable.

The patient compliance rate with this program is extremely high. I'd say that over 90% of the anti-VEGF patients with whom we have this discussion are not only open to proceeding with the home monitoring, but they're grateful because they know how important monitoring is for their visual outcomes. They've already had one eye under treatment and understand the need to protect the other eye.

The ForeseeHome remote monitoring system administered by the Notal Vision Diagnostic Clinic truly achieves the purpose of telemedicine and remote monitoring technologies, which is to provide an additional branch to our clinical services. It also enables clinicians to treat the eye that has converted while they rest assured that the fellow eye is being properly monitored between office visits as they receive regular reports from the ForeseeHome system. This all comes to fruition when a positive conversion occurs, and the patient is more likely to have vision of 20/25 or 20/30 rather than 20/80 or worse—a much better starting point for me to initiate treatment and preserve vision long-term in what is now a bilateral case under my care.

The ForeseeHome remote monitoring program creates a state-of-the-art model of care that is becoming more and more essential in retina clinics today. I have found it to be a tremendous benefit to my clinic, and my patients have been extremely grateful for it as well.

Miguel A. Busquets, MD, FACS, is a retina specialist at Retina Associates of Kentucky, based in Lexington, KY.

1. Ferris FL, Davis MD, Clemons TE, Lee LY, Chew EY, Lindblad AS, Milton RC, Bressler SB, Klein R; Age-Related Eye Disease Study (AREDS) Research Group. A simplified severity scale for age-related macular degeneration: AREDS Report No. 18. Arch Ophthalmol. 2005 Nov;123(11):1570-4.
2. Dow ER, Adeghate JO, Coombs PG, et al. Fellow-Eye Conversion and Treatment in Exudative Age-Related Macular Degeneration. Journal of VitreoRetinal Diseases. 2019;3(6):438-44.
3. Parikh R, Avery RL, Saroj N, et al. Incidence of New choroidal neovascularization in fellow eyes of patients with age-related macular degeneration treated with intravitreal aflibercept or ranibizumab. JAMA Ophthalmol. 2019 Jul 11;137(8):914-20.
4. MacCumber M, Yu, JS, Sagkriotis A, et al. Injection intervals in treatment-naïve neovascular AMD patients who received anti-VEGF agents: an analysis of the IRIS Registry. Paper Presented at: American Academy of Ophthalmology Annual Meeting 2019; October 12-15.
5. 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; Nov 1;51(11):633-9.
6. Ying GS, Maguire MG, Daniel E, et al; Comparison of Age-Related Macular Degeneration Treatments Trials (CATT) Research Group. Association of Baseline Characteristics and Early Vision Response with 2-Year Vision Outcomes in the Comparison of AMD Treatments Trials (CATT). Ophthalmology. 2015 Dec;122(12):2523-31.e1.
7. Loewenstein A, Malach R, Goldstein M, et al. Replacing the Amsler grid: a new method for monitoring patients with age-related macular degeneration. Ophthalmology. 2003;110(5):966-70.
8. Chew EY, Clemons TE, Bressler SB, et al; AREDS2-HOME Study Research Group. Randomized trial of a home monitoring system for early detection of choroidal neovascularization home monitoring of the Eye (HOME) study. Ophthalmology. 2014;121(2):535-44.
9. Ho AC, Heier JS, Holekamp NM, et al. Real-world performance of a self-operated home monitoring system for early detection of neovascular age-related macular degeneration. J Clin Med. 2021;10:1355
10. Loewenstein A, Ferencz JR, Lang Y, et al. Toward earlier detection of choroidal neovascularization secondary to age-related macular degeneration: multicenter evaluation of a preferential hyperacuity perimeter designed as a home device. Retina 2010; 30:1058–64.

"I was only seeing light flashes early on, but light FLASHES when you've not seen anything for so many years—it was wonderful"

—Keith H, retinal prosthesis recipient

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Department Editor *Jason Hsu, MD*

Retinal sequelae of novel oncology drugs

Getting to the cause of blurred vision in a man with Erdheim-Chester disease.

By John W. Hinkle, MD, and Jason Hsu, MD

John W. Hinkle, MD

Jason Hsu, MD

A 69-year-old man was referred to the retina clinic for evaluation of blurred vision in both eyes over the preceding several weeks. His medical history included Erdheim-Chester disease, hypertension, and gastroesophageal reflux disease, but his ocular history was unremarkable.

Work-up and imaging findings

At presentation, the patient's visual acuity was 20/40 OD and 20/70 OS, and intraocular pressures were within normal limits bilaterally. His anterior segment exam showed 1+ nuclear sclerosis in both eyes. No cell or flare was noted.

The fundus examination was remarkable for bilateral, multifocal areas of subretinal fluid (SRF) in the macula, including foveal involvement. There were no abnormalities in the periphery (*Figure 1*). Optical coherence tomography scans demonstrated subfoveal fluid in both eyes with multifocal, smaller collections of SRF. The interdigitation zone was thickened and irregular. With enhanced-depth imaging, the choroid appeared to be not substantially thickened bilaterally (*Figure 2*).

Given the ophthalmoscopic exam, we pursued further diagnostic imaging. Fundus autofluorescence revealed bilateral areas of hyperautofluorescence that correlated to the accumulation of SRF. We observed no foci of hyperautofluorescence in the periphery. Absent were gravity-dependent fluid shifts, or guttering (*Figure 3*).

Fluorescein angiography demonstrated a normal vascular pattern in both eyes. There was no evidence of dye leakage from the microvasculature or leakage into the collections of subretinal fluid (*Figure 4, page 12*).

Additional history and diagnosis

The patient's Erdheim-Chester disease (ECD) had been resistant to multiple therapies. However, before the onset of visual symptoms, he had started treatment with the BRAF enzyme inhibitor vemurafenib (marketed as Zelboraf), followed by the MEK inhibitor cobimetinib. (MEK stands for MAPK/ERK kinase, or mitogen-activated protein kinases [MAPKs], including extracellular signal-regulated kinases [ERKs].)

After he started the cobimetinib, the patient noticed changes in his vision. Given this history and the constellation of imag-

Bios

Dr. Hinkle is a first-year vitretoretinal fellow at Wills Eye Hospital/ Mid Atlantic Retina, Philadelphia.

Dr. Hsu is with Mid Atlantic Retina/Retina Service, Wills Eye Hospital.

DISCLOSURES: Drs. Hinkle and **Hsu** have no relevant financial relationships to disclose.

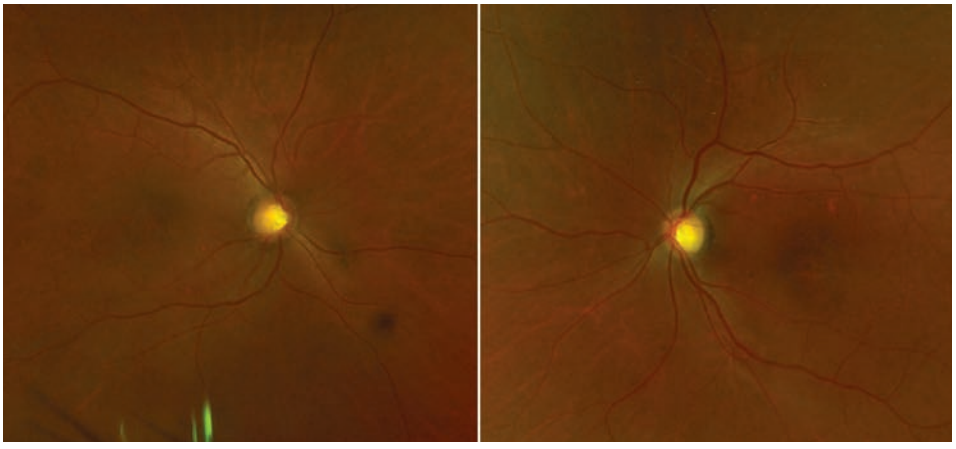

Figure 1. Fundus examination shows multifocal areas of subretinal fluid bilaterally.

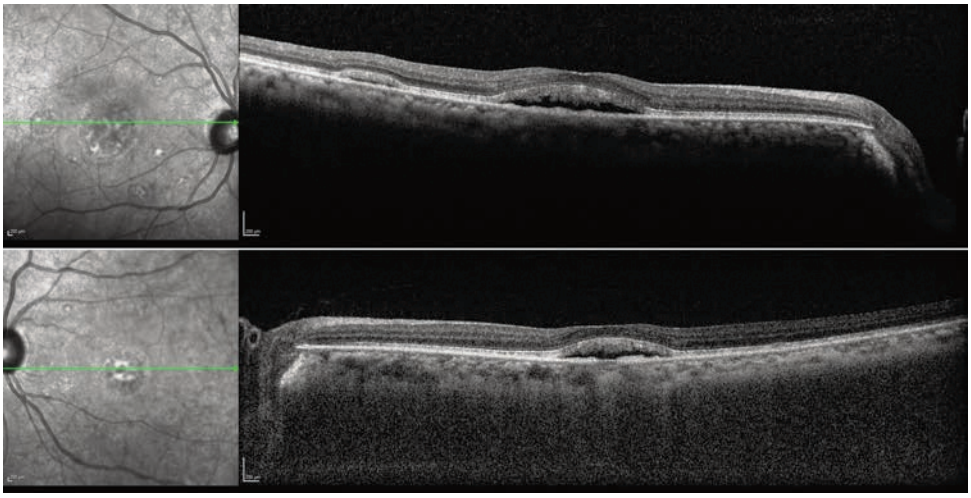

Figure 2. Optical coherence tomography scans demonstrate subfoveal and extrafoveal subretinal fluid.

ing findings, we diagnosed MEK inhibitor-associated retinopathy (MEKAR).

Follow-up

Although we counseled the patient that there was no definitive ocular indication to stop the MEK inhibitor, he was very bothered by the visual changes. After consulting with his oncologist, he decided to discontinue the cobimetinib. Four weeks after the initial visit, his visual acuity had improved to 20/40 OU.

A fundus examination showed a stable number of subretinal foci compared to the first visit. OCT scans showed interval improvement in the amount of SRF (*Figure 5, page 12*). OCT angiography didn't show any evidence of macular neovascularization (*Figure 6, page 13*). The SRF was nearly resolved at the four-month follow-up, and visual acuity had improved to 20/30 OD and 20/40 OS, although subfoveal changes persisted (*Figure 5*).

Novel treatments, novel side effects

After clinical trials reported that trametinib increased patient survival, this MEK inhibitor was the first medication of its class approved to treat metastatic melanoma in 2013.[1] The RAS-RAF-MEK-ERK signal-

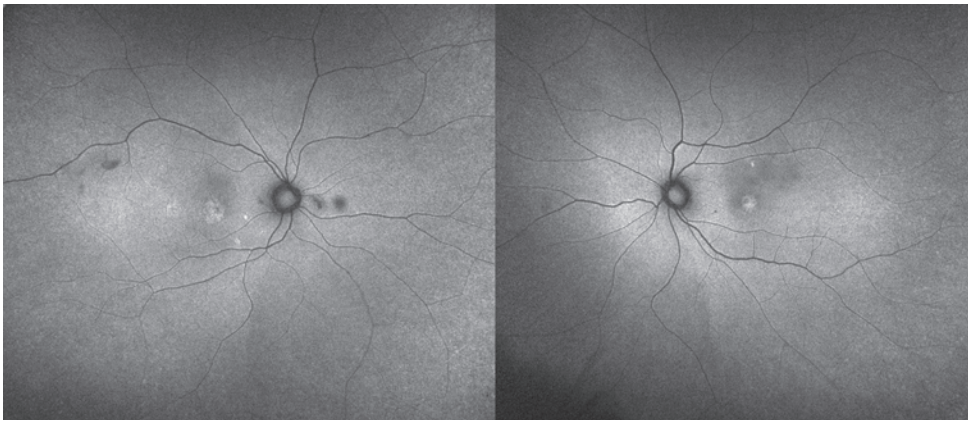

Figure 3. Fundus autofluorescence shows hyperautofluorescence corresponding to areas of subretinal fluid.

Although we counseled the patient that there was no reason to stop the MEK inhibitor, he was very bothered by the changes in his vision. After consulting with his oncologist, he decided to discontinue the cobimetinib.

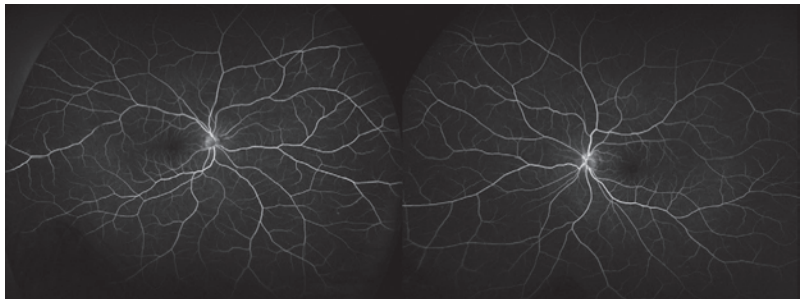

Figure 4. Fluorescein angiography doesn't show any abnormal dye leakage or pooling

ing pathway leads to cell cycle progression, and dysregulation of this cascade sequence is widely implicated in malignant cell proliferation. Within this sequence, MEKs phosphorylate and activate MAPK/ERK.[2] By blocking downstream effects, MEK inhibitors block tumor growth and induce cell death via apoptosis.[2]

In addition to melanoma, MEK inhibitors have been used in a growing range of oncologic conditions, including ovarian cancer, leukemia, lymphoma, thyroid cancer, colorectal cancer, non-small cell lung cancer, biliary cancer and pancreatic cancer.[3] Our patient was treated with cobimetinib, another MEK inhibitor approved by the Food and Drug Administration to treat advanced melanoma. ECD is a rare systemic histiocytic neoplasm that can involve almost any organ system, although it manifests most frequently in the bone.[4] Constitutive MAPK signaling has been shown to drive ECD, and growing evidence supports the efficacy of MEK inhibitors in this condition.[5]

A range of ocular adverse events are associated with MEK inhibitors, particularly blurred vision and characteristic subretinal fluid accumulation. This drug class-related effect has been termed MEK inhibitor associated retinopathy (MEKAR). It was first recognized as a "central serous chorioretinopathy-like" adverse event in oncology clinical trials, but has since been noted to be a distinct entity.[6] BRAF inhibitors are often used in combination with MEK inhibitors to increase efficacy. These molecules are associated with uveitis but not with retinal changes.[7] However, the combination of MEK inhibitors and BRAF inhibitors may lead to more ocular toxicities.[8,9]

Clinical characteristics of MEKAR

The understanding of MEKAR has evolved from case reports and case series.[10-12] SRF has been noted on examination in up to 90 percent of patients undergoing treatment with a MEK inhibitor. When it occurs, it's bilateral in more than 90 percent of cases.[13,14] Intensive monitoring of some clinical trial patients have shown rapid accumulation of SRF (within three hours of administration of the MEK inhibitor) followed by even more rapid resolution (by the fourth hour), although a large portion of patients continue to have SRF at their final follow-up

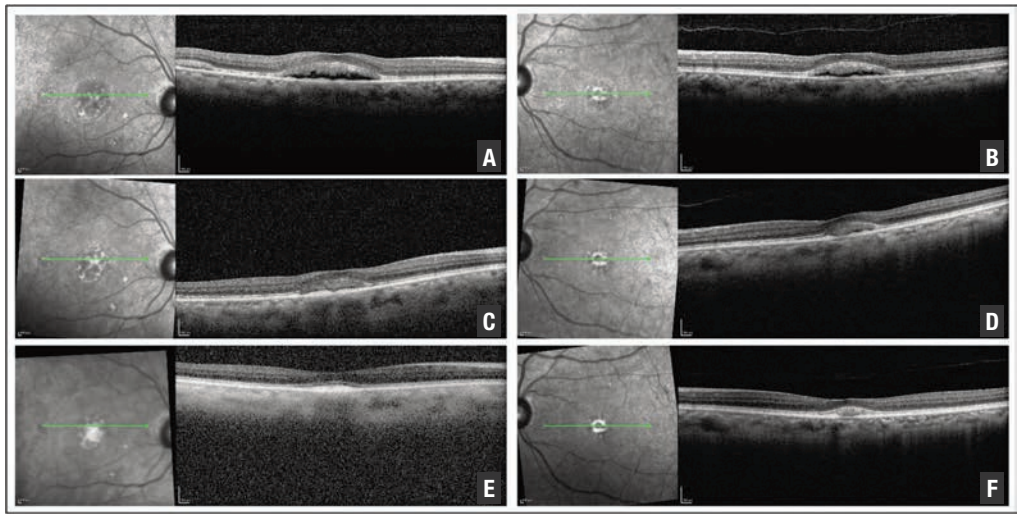

Figure 5. Optical coherence tomography scans at presentation (A, B), four weeks later (C, D) and four months later (E, F) demonstrate gradual resolution of subretinal fluid.

visit.[13] As this patient demonstrated, in spite of the SRF, fluorescein angiography doesn't demonstrate pooling or leakage in MEKAR.

Visual symptoms are much less common than the presence of SRF. In a larger series of patients, only 20 percent of those with SRF were symptomatic, typically reporting blurred vision.[13]

MEKAR has been termed CSR-like, but there are important differences between these two conditions. MEKAR is bilateral more than 90 percent of the time, while CSR is bilateral in less than half.[14] MEKAR is also frequently multifocal, involves the posterior pole at the fovea and along the arcades, and has no gravitational effect on the fluid as is seen in CSR.[14] Furthermore, the pigment epithelial detachments and increased choroidal thickness commonly observed in CSR don't necessarily occur in MEKAR.[14]

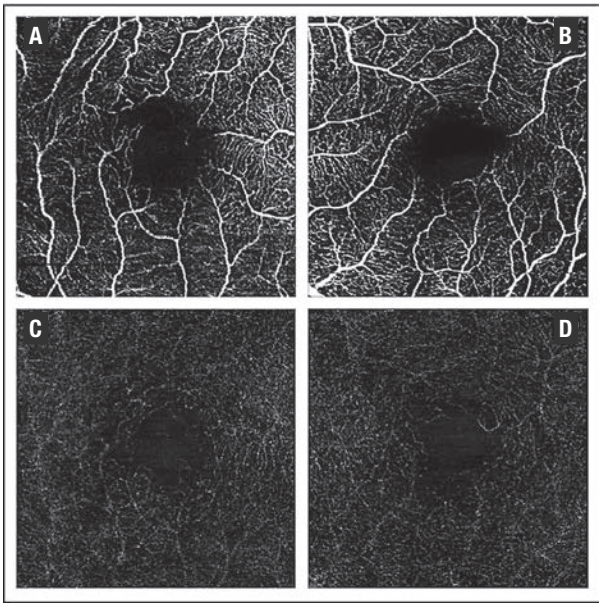

Figure 6. Optical coherence tomography angiography four weeks after presentation shows no evidence of macular neovascularization (OD right column, OS left column). A and B show the superficial vascular complex, C and D the avascular complex.

Treatment

The visual impacts of MEKAR are typically mild. As we note, many patients with SRF are asymptomatic, and those who have symptoms don't usually experience a decrease in vision of more than two lines.[14] Subjective visual changes frequently resolve within one month even if SRF persists, and final visual acuity remains within one line of the pretreatment baseline.[13] At the end of clinical trials, residual SRF after medication discontinuation was observed, but in less than 5 percent of cases.[13] Given these characteristics, cessation of the MEK inhibitor is generally not indicated in the setting of ocular adverse events alone.[13,14]

Bottom line

As these lifesaving medications are used in an expanding number of conditions, MEKAR is an important, increasingly common etiology for SRF. Although the fluid is usually bilateral, subfoveal and multifocal, the visual impact is usually mild and self-limited. Management should be coordinated with a patient's oncology team, and many patients can continue taking the medication safely.

REFERENCES

1. Flaherty KT, Robert C, Hersey P, et al; METRIC Study Group. Improved survival with MEK inhibition in BRAF-mutated melanoma. N Engl J Med. 2012;367:107-114.
2. Downward J. Targeting RAS signaling pathways in cancer therapy. Nat Rev Cancer. 2003;3:11–22.)
3. Duncan KE, Chang LY, Patronas M. MEK inhibitors: a new class of chemotherapeutic agents with ocular toxicity. Eye (Lond). 2015;29:1003-1012.
4. Goyal G, Heaney ML, Collin M, et al. Erdheim-Chester disease: consensus recommendations for evaluation, diagnosis, and treatment in the molecular era. Blood. 2020;135:1929-1945.
5. Diamond, EL, Durham, BH, Ulaner, GA, et al. Efficacy of MEK inhibition in patients with histiocytic neoplasms. Nature. 2019;567:521–524.
6. McCannel TA, Chmielowski B, Finn RS, et al. Bilateral subfoveal neurosensory retinal detachment associated with MEK inhibitor use for metastatic cancer. JAMA Ophthalmol. 2014;132:1005–1009.
7. Choe CH, McArthur GA, Caro I, et al. Ocular toxicity in BRAF mutant cutaneous melanoma patients treated with vemurafenib. Am J Ophthalmol. 2014;158:831-837.e2.
8. Stjepanovic N, Velazquez-Martin JP, Bedard PL. Ocular toxicities of MEK inhibitors and other targeted therapies. Ann Oncol. 2016;27:998-1005.
9. Menzies AM, Long GV. Dabrafenib and trametinib, alone and in combination for BRAF-mutant metastatic melanoma. Clin Cancer Res. 2014;20:2035-2043.
10. Velez-Montoya R, Olson J, Petrash M, et al. Acute onset central serous retinopathy with MEK inhibitor use for metastatic cancer. Invest Ophthalmol Vis Sci. 2011:Eeabstract 2153.
11.Urner-Bloch U, Urner M, Stieger P, et al. Transient MEK inhibitor-associated retinopathy in metastatic melanoma. Ann Oncol. 2014;25:1437-1441.
12. Schoenberger SD, Kim SJ. Bilateral multifocal central serous-like chorioretinopathy due to MEK inhibition for metastatic cutaneous melanoma. Case Rep Ophthalmol Med. 2013;2013:673796.
13. Weber ML, Liang MC, Flaherty KT, Heier JS. Subretinal fluid associated with MEK inhibitor use in the treatment of systemic cancer. JAMA Ophthalmol. 2016;134:855–862.
14. Francis JH, Habib LA, Abramson DH, et al. Clinical and morphologic characteristics of MEK inhibitor-associated retinopathy: differences from central serous chorioretinopathy. Ophthalmology. 2017;124:1788-1798.

As these lifesaving medications are used in an expanding number of conditions, MEKAR is an important, increasingly common etiology for subretinal fluid.

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

Taking treatment beyond adalimumab

An update on biologic alternatives for ocular inflammatory disease when the approved agent just won't cut it.

By Sandip Suresh, MD, and Eric Suhler, MD, MPH

Sandip Suresh, MD

Eric Suhler, MD, MPH

The treatment of noninfectious uveitis has long relied on the use of systemic immunosuppression, most commonly with first-line antimetabolite immunosuppressants such as methotrexate, azathioprine and mycophenolate mofetil, and with off-label biologics for refractory patients.

In 2016 the biologic tumor necrosis factor inhibitor (TNFi) adalimumab (Humira, AbbVie) became the first and only Food and Drug Administration-approved non-corticosteroid treatment for noninfectious uveitis in adults. That approval was based on the results of two large multicenter randomized clinical trials, VISUAL 1 and 2,[1] and extended to children after the SYCAMORE study.[2] Since the approval of adalimumab, the field of anti-inflammatory biologics has rapidly progressed, and multiple additional agents have been or are being investigated for the treatment of uveitis. We review them here.

Tumor necrosis factor inhibitors

TNF inhibitors are the most broadly utilized and effective class of biologics for the treatment of uveitis, and adalimumab remains the most widely used. Standard adalimumab dosing is a subcutaneous injection of 40 mg every two weeks after a loading dose of 80 mg followed by 40 mg one week later; loading doses are deferred in children.

Although highly effective, about 40 to 60 percent of patients on this regimen will develop treatment failure at one year, according to the VISUAL I and II studies.[1] Treatment failure can often be attributed to the development of anti-adalimumab neutralizing antibodies, although insufficient serum levels of adalimumab, or simply non-responsiveness to TNF blockade can also contribute. Testing for the presence of serum anti-adalimumab antibodies can help guide treatment decisions in cases of loss of response. If anti-adalimumab antibodies are absent, increasing the serum level of adalimumab by switching to weekly dosing has been shown to improve uveitis control in about 60 percent of patients.[3]

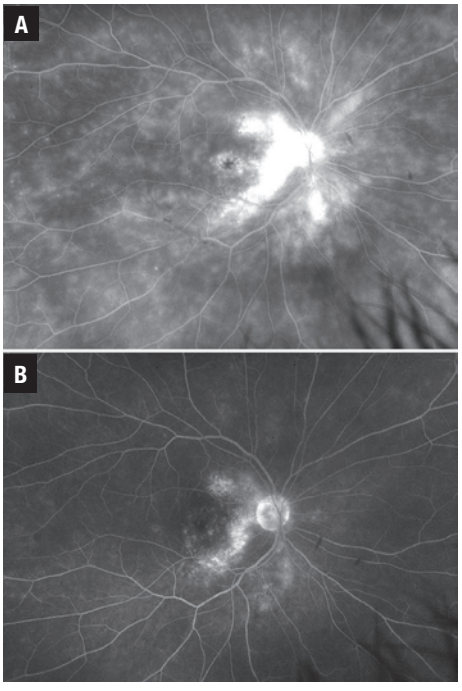

Figure 1. Vascular leakage in sarcoid retinal vasculitis on adalimumab 40 mg every two weeks (A) and after transitioning to tocilizumab 162 mg every two weeks (B).

Five alternative TNF inhibitors

Alternatively, the presence of anti-adalimumab antibodies might prompt a switch to an alternative TNFi rather than escalation to weekly therapy. Currently four FDA-approved alternative TNFis exist: infliximab (Remicade, Janssen); golimumab (Simponi, Janssen); certolizumab pegol (Cimzia, UCB); and etanercept (Enbrel, Amgen).

• ***Infliximab.*** Of the alternatives, this is the most-studied TNFi in uveitis. The efficacy of infliximab for the treatment of uveitis is likely similar to that of adalimumab.[4,5] Unlike adalimumab, which is a fully human monoclonal antibody, infliximab is a

Bios

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DISCLOSURES: Drs. Suresh, Suhler and Thomas have relevant financial relationships to disclose.

chimeric human/mouse antibody leading to a higher immunogenicity and greater risk of forming anti-drug antibodies. For this reason, many practitioners recommend concurrent use of an antimetabolite to reduce antibody formation.

The primary advantage of infliximab over adalimumab is the potential to achieve higher therapeutic levels. Infliximab is given as an intravenous infusion administered with three loading infusions over six weeks, followed by infusions at four-to-eight-week intervals at doses of 5 to 20 mg/kg.

• ***Golimumab.*** This humanized antibody can be administered as a subcutaneous injection every four weeks or as an intravenous infusion (Simponi Aria) every four to eight weeks. Although literature on its use in uveitis is still fairly limited, a few studies have shown a promising response for uveitis refractory to both adalimumab and infliximab.[6,7]

• ***Certolizumab pegol.*** This uniquely constructed agent uses a humanized anti-TNF Fab fragment joined with a polyethylene glycol molecule in place of the Fc fragment. The lack of an Fc fragment is thought to reduce the immunogenicity compared to other TNF inhibitors. Also, the lack of an Fc fragment prevents placental transfer of certolizumab, making it the safest TNFi to use in pregnancy.[8] Like golimumab, the available data on its efficacy in ocular inflammation is sparse, although it has shown promising results in treating patients refractory to multiple other TNFi.[9]

• ***Etanercept.*** A recombinant fusion protein composed of the TNF receptor and the Fc portion of immunoglobulin G1, etanercept is used extensively in rheumatoid arthritis. It's widely considered ineffective for uveitis and may even induce paradoxical flares of uveitis.[10]

Interleukin-6 inhibitors

Another class of drugs includes tocilizumab (Actemra, Genentech), a humanized interleukin-6 inhibitor that can be administered subcutaneously every one to two weeks or as an IV infusion every four weeks. It's currently approved for the treatment of RA, giant cell arteritis and some forms of juvenile idiopathic arthritis (JIA). Although highly effective in select cases of uveitis, IL-6 inhibition likely has a much narrower role in the treatment of ocular inflammatory disease than the TNFi.

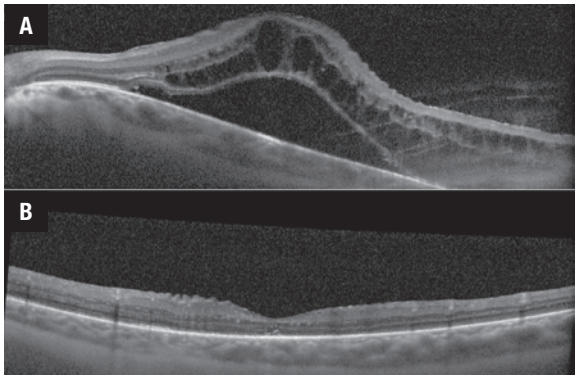


Figure 2. Optical coherence tomography scans demonstrate macular edema before (A) and after (B) intravenous tocilizumab therapy.

The APTITUDE trial evaluating tocilizumab in TNFi-refractory JIA uveitis failed to meet its primary endpoint of inflammatory control, although about 30 percent of patients showed improvement when switched from a TNFi to tocilizumab.[11] Tocilizumab does appear to be effective for the treatment of retinal vascular leakage, with 83 percent of patients showing improvement in angiographic inflammation (*Figure 1*).[12] Tocilizumab has also proven to be highly effective in the treatment of uveitic macular edema, with early studies showing a dramatic response to treatment (*Figure 2*).[13]

Sarilumab (Kevzara, Regeneron Pharmaceuticals) is an alternative to IL-6 inhibition. It has similarly shown efficacy in posterior segment disease, particularly uveitic macular edema.[14]

CD-20 inhibitors

Rituximab is a monoclonal antibody against the CD-20 antigen found on B-lymphocytes. Administered as an IV infusion every six to 12 months, rituximab leads to a depletion of the B-cell population. Compared with the other biologics, the long-lasting effect of rituximab increases its immunosuppressive risk. Although effective in the treatment of orbital inflammatory disease,

(Continued on page 17)

Pearls for epiretinal membrane peeling

Proper visualization and positioning are key to achieving a successful peel.

By Marlene Wang, MD, and Leo A. Kim, MD, PhD

Marlene Wang, MD

Leo A. Kim, MD, PhD

Vitreoretinal surgeons are often tasked with peeling visually significant epiretinal membranes off of the macula. Particularly adherent ERM can be difficult to remove entirely, posing a greater risk of iatrogenic trauma and/or postoperative recurrence. Here, we discuss some tips and tricks that can help ensure a complete and successful ERM peel.

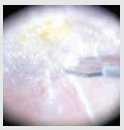
Initiating the peel

Identifying the proper spot to initiate the peel can be half the battle. Preoperative optical coherence tomography can help identify areas to avoid (e.g., areas of macular or nerve fiber layer schisis) and areas to target (e.g., raised areas of membrane that are situated away from the fovea). The ideal initiation spot should also allow for maximum dexterity and control of your chosen instruments with minimal reaching.

Initiation of the flap can be accomplished by aligning the internal limiting membrane forceps over the edge or ridge of the ERM and gently pinching, lifting and releasing. Alternatively, a membrane scraper or the Finesse loop (Alcon) can be used to gently initiate a flap, most effectively over a blood vessel at the edge of the macula. In our experience, the Finesse loop has a slightly longer reach than standard ILM forceps and can prove useful in high myopes.

View the Video

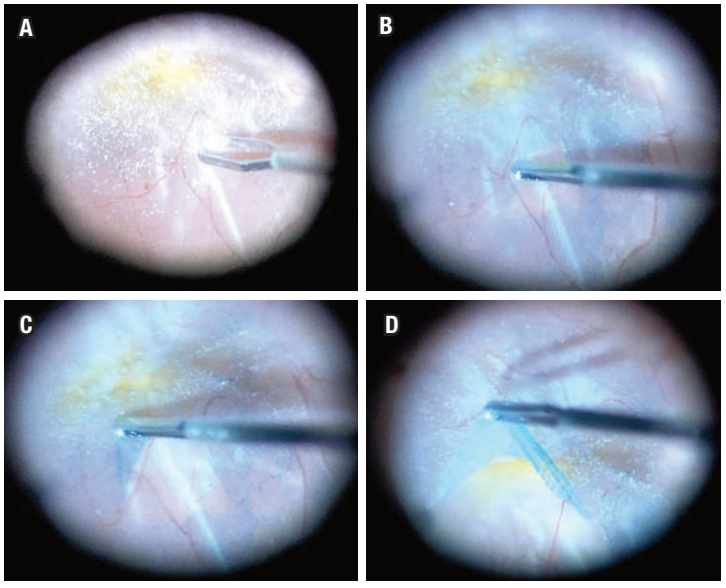
Watch as Drs. Wang and Kim peel a dense epiretinal membrane in the setting of a macula-involving retinal detachment. Available at: http://bit.ly/VideoPearl_023



Triamcinolone vs. BBG (or ICG)

When you encounter difficulty in initiating the flap, you can apply membrane stains to improve your visualization. Triamcinolone, while not exactly a stain, can be used to highlight the surface of the membrane and any elevated ridges as the microparticles settle and adhere to the surface of the membrane.

True stains such as indocyanine green or Brilliant Blue G (BBG, Tissue Blue, DORC) effectively stain the ILM underlying the ERM, making membrane flaps and edges at the interface of "negative stain-



Four steps for performing an easier epiretinal membrane peeling. A) Initiate the peel at the ERM edge with the internal limiting membrane forceps after triamcinolone administration. B) Following Brilliant Blue G staining, align the forceps parallel to and over the edge of membrane, avoiding a deep pinch. C) Pull the initiated flap tangentially along the retinal surface. D) Extend the flap edge circumferentially.

Bios

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DISCLOSURES:
Dr. Hahn disclosed serving as a consultant to DORC.

ing" obvious to the surgeon.

We prefer BBG and achieve a very effective stain by injecting under direct visualization with a soft-tip cannula aimed over the macula but away from the fovea. We hold the light pipe and the injection cannula in place for one minute to avoid inadvertent dye washout, as the dye settles over the macular area because of its high specific gravity. We then proceed with aspiration of the dye using the vitrector.

Keep forceps tangential to the surface

Once you've initiated and visualized a clear flap, you can use the ILM forceps to tangentially peel the membrane in a circumferential manner off the macula and fovea. The applied force should be steady and even. If the patient is a high myope, you may need longer instruments to keep the forceps tangential to the surface and to preserve maximum dexterity of the instruments.

Consider taking the ILM

When confronted with a particularly adherent ERM, we may opt to also peel the underlying ILM. Restaining after ERM peeling can ensure that residual ILM is appropriately visualized and removed. Often, ILM may already have been removed if the adhesive force between an adherent ERM and ILM exceeds that between the ILM and the underlying retina.

Bottom Line

Keep in mind throughout the procedure the goal of ERM peeling: Remove visually significant membrane as efficiently as possible without damaging the macula. Proper visualization and positioning are key to achieving a successful peel. RS

Beyond adalimumab

(Continued from page 15)

recurrent scleritis and severe JIA uveitis, the utility of rituximab in treating other forms of uveitis has been fairly limited.[15] As a result, rituximab is often relied on only in severe disease recalcitrant to other forms of treatment.

Other anti-inflammatory biologics

A number of biologics targeting alternative cytokines have been explored as potential therapeutics for uveitis. Some of these agents include inhibitors of IL-1 (anakinra, canakinumab), IL-2 (daclizumab), IL-17 (ixekizumab, secukinumab) and IL-23 (ustekinumab, guselkumab).

Currently, the utility of most of these agents for the treatment of uveitis is largely anecdotal and limited to case reports. Secukinumab is the only agent that has been evaluated in a clinical trial for the treatment of uveitis. However, results of this trial were mixed, with patients receiving intravenous secukinumab dosed at 30 mg/kg every four weeks showing a 73-percent response rate, although remission at 57 days was reported in only 27 percent of patients.[16] A clinical trial investigating ustekinumab for the treatment of Behçet's uveitis is under way.[17]

Bottom line

Adalimumab remains the mainstay of treatment for uveitis refractory to antimetabolite therapy. In cases of adalimumab failure, switching to a newer TNFi such as golimumab and certolizumab may provide inflammatory control. On the other hand, the IL-6 inhibitors tocilizumab and sarilumab provide an alternative treatment option and appear to be particularly effective when used in cases where uveitic macular edema and retinal vasculitis are predominant manifestations of disease. Rituximab has been shown to be effective in select cases of refractory scleritis, orbital inflammatory disease and JIA-associated uveitis. The optimal use of other targeted biologic anti-inflammatory agents in the treatment of uveitis is yet to be fully elucidated. RS

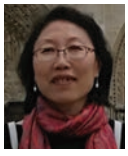
REFERENCES

1. Sheppard J, Joshi A, Betts KA, et al. Effect of adalimumab on visual functioning in patients with noninfectious intermediate uveitis, posterior uveitis, and panuveitis in the VISUAL-1 and VISUAL-2 trials. JAMA Ophthalmol. 2017;135:511-518.
2. Horton S, Jones AP, Guly CM, et al. Adalimumab in juvenile idiopathic arthritis-associated uveitis: 5-year follow-up of the Bristol participants of the SYCAMORE Trial. Am J Ophthalmol. 2019;207:170-174.
3. Lee J, Koreishi AF, Zumpf KB, Minkus CL, Goldstein DA. Success of weekly adalimumab in refractory ocular inflammatory disease. Ophthalmology. 2020;127:1431-1433.
4. Martel JN, Esterberg E, Nagpal A, Acharya NR. Infliximab and adalimumab for uveitis. Ocul Immunol Inflamm. 2012;20;18-26.5. Vallet H, Seve P, Biard L, et al. Infliximab versus adalimumab in the treatment of refractory inflammatory uveitis: A multicenter study from the French Uveitis Network. Arthritis Rheumatol. 2016;68:1522-1530.
6. Fabiani C, Sota J, Rigante D, et al. Rapid and sustained efficacy of golimumab in the treatment of multirefractory uveitis associated with Behçet's disease. Ocul Immunol Inflamm. 2019;27:58-63.
7. Miserocchi E, Modorati G, Pontikaki I, Meroni PL, Gerloni V. Long-term treatment with golimumab for severe uveitis. Ocul Immunol Inflamm. 2014;22:90-95.
8. Prieto-Peña D, Calderón-Goercke M, Adán A, et al. Efficacy and safety of certolizumab pegol in pregnant women with uveitis. Recommendations on the management with immunosuppressive and biologic therapies in uveitis during pregnancy. Clin Exp Rheumatol. 2021;39:105-114.
9. Llorenç V, Mesquida M, Sainz De La Maza M, et al. Certolizumab pegol, a new anti-TNF-α in the armamentarium against ocular inflammation. Ocul Immunol Inflamm. 2016;24:167-72
10. Ferreira LB, Smith AJ, Smith JR. Biologic drugs for the treatment of noninfectious uveitis. Asia-Pacific J Ophthalmol (Phila.). 2021;10:63-73
11. Ramanan A V., Dick AD, Guly C, et al. Tocilizumab in patients with anti-TNF refractory juvenile idiopathic arthritis-associated uveitis (APTITUDE): A multicentre, single-arm, Phase 2 trial. Lancet Rheumatol. 2020;2:e135-e141.
12. Sadiq MA, Hassan M, Afridi R, et al. Posterior segment inflammatory outcomes assessed using fluorescein angiography in the STOP-UVEITIS study. Int J Retin Vitr. Published online October 6, 2020.
13. Mesquida M, Molins B, Llorenç V, et al. Twenty-four month follow-up of tocilizumab therapy for refractory uveitis-related macular edema. Retina. 2018;38:1361-1370.
14. Heissigerová J, Callanan D, de Smet MD, et al. Efficacy and safety of sarilumab for the treatment of posterior segment noninfectious uveitis (SARIL-NIU): The Phase 2 SATURN study. Ophthalmology. 2019;126:428-437.
15. Miserocchi E, Pontikaki I, Modorati G, Gattinara M, Meroni PL, Gerloni V. Anti-CD 20 monoclonal antibody (rituximab) treatment for inflammatory ocular diseases. Autoimmun Rev. 2011;11:35-39.
16. Letko E, Yeh S, Stephen Foster C, Pleyer U, Brigell M, Grosskreutz CL. Efficacy and safety of intravenous secukinumab in noninfectious uveitis requiring steroid-sparing immunosuppressive therapy. Ophthalmology. 2015;122:939-948.
17. Pepple KL, Lin P. Targeting interleukin-23 in the treatment of noninfectious uveitis. Ophthalmology. 2018;125:1977-1983.

How imaging is advancing management of dry AMD

Emerging modalities and deep learning are helping to expose an old foe in non-neovascular age-related macular degeneration: reticular pseudodrusen.


Jorge Orellana-Rios, MD


Yuehong Tong, PhD


Nayanika Challa, BS


Roland Theodore Smith, MD, PhD

By Jorge Orellana-Rios MD, Yuehong Tong, PhD, Nayanika Challa, BS, and Roland Theodore Smith, MD, PhD

Take-home points

- Decrease of blue light fundus autofluorescence intensity signifies progression of age-related macular degeneration.
- The organelle signal source for near-infrared autofluorescence (NIR-AF) is a major open question for the field.
- Reticular pseudodrusen, a component of reticular macular disease in AMD, appear to be an ophthalmological biomarker for cardiovascular disease.
- Hyperspectral AF can detect the unique drusen fluorophores; a clinical hyperspectral AF camera could detect AMD at its earliest stage.

Dry age-related macular degeneration, or non-neovascular AMD, has proven a far more difficult disease to manage than neovascular AMD. Whereas nAMD can be stabilized with anti-VEGF therapy, no approved treatment exists for the dry form of the disease.

The retinal pigment epithelium cell plays a central role in AMD since one of the earliest detectable disease markers is an abnormal pattern of *in vivo* autofluorescence,[1] and fundus autofluorescence is a non-invasive imaging technology that allows us to assess the RPE monolayer. It's based on the topographic mapping of the distribution of RPE fluorophores such as lipofuscin (L) granules, many of which also contain melanin or melanolipofuscin (ML).

Therefore, FAF can give us not only an anatomic interpretation of what is happening in the retina, but it can also provide functional information of the health status of the RPE. In this article, we explore the potential of FAF in managing non-nAMD.

New understanding of AF principles

Lipofuscin is the undegradable fraction of the byproducts on the visual cycle. It's stored in the lysosomes inside the RPE cell, and it's naturally autofluorescent at the clinical excitation wavelengths between 480 and 510 nm. So, the FAF method utilizes light emitted from L-fluorophores at emission spectra ranging from 500 to 800 nm.

However, major components of macular FAF, a superb indicator of RPE metabolism, are still uncertain, as the well-studied bisretinoid A2E was confirmed as minimally abundant in the macula compared to the periphery.[2]

Currently, the confocal scanning laser ophthalmoscope (cSLO) attains a higher-quality RPE image than the conventional fundus camera. The FAF is the highest at 10 degrees from fovea, but diminishes at the fovea because of obstruction from the

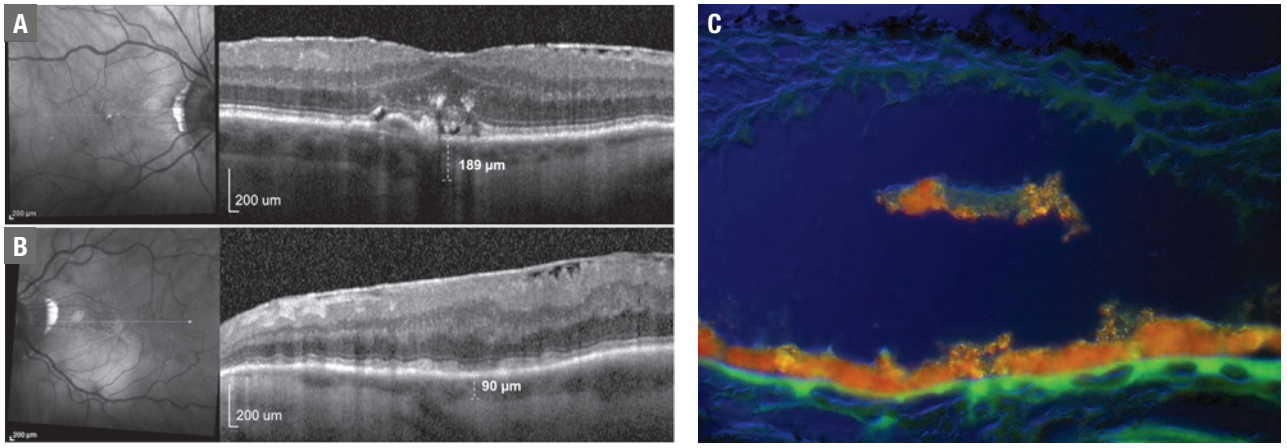


Figure 1. Bilateral near-infrared (NIR) and a spectral-domain optical coherence tomography scan of an 83-year-old man with age-related macular degeneration and unilateral left internal carotid artery occlusion shows in the right eye (A) a few bright reflections suggestive of retinal pigment epithelium loss. SD-OCT revealed confluent soft drusen with overlying RPE disruption and migration into the neural retina as hyperreflective foci (HRF). Subfoveal choroidal thickness was 189 µm. In the left eye (B) NIR shows a well-defined group of multiple homogeneous hyporeflectant lesions, typical of subretinal drusenoid deposits (SDD). The SD-OCT scan revealed multiple hyperreflective lesions between the RPE and ellipsoid zone, and a subfoveal choroidal thickness of 90 µm. Note that both features of reticular macular disease (RMD)—SDD and choroidal thinning—are present only in the left eye, where the ophthalmic artery perfusion of the choroid is compromised due to internal carotid occlusion. This is suggestive of choroidal hypoperfusion as a mechanism for the presence of RMD in AMD. An illustrative example (C) of migrating RPE (orange) using the hyperspectral AF technique. In figure A they appear on SD-OCT as HRF, which are strong predictors of future macular atrophy.

macular pigment, although FAF is relatively homogeneous over the remainder of the posterior pole and retinal periphery. Hence, FAF follows the distribution of rods. The outer segments of these photoreceptors are the primary precursors of lipofuscin-derived RPE fluorophores.[3]

Some studies have evaluated ultra-wide-field FAF imaging in patients with AMD, using a green excitatory beam of 532 nm and emission wavelengths between 540 and 800 nm. Interestingly, peripheral autofluorescence changes have been found more prevalent in eyes with AMD, supporting the idea that this disease is panretinal and not only in the macula.[4]

Subtypes of FAF imaging

Nevertheless, the most common subtypes of FAF utilized in a clinical setting include short-wavelength FAF (blue FAF), with an excitation laser at 488 nm, and near-infrared fundus autofluorescence (NIR-AF), which uses a 787-um excitation wavelength. Bluelight autofluorescence represents the more established method of FAF imaging and has been used in multiple classification schemes.

In contrast, the NIR-AF signal is considered to derive mostly from RPE melanin with smaller contributions from choroidal melanin when it's oxidized. However, questions remain about whether multiple fluorophores localize to each RPE organelle and which organelle provides FAF signal in the NIR range.[5]

Total ultrastructural reconstruction of adult human perifoveal RPE indicates that there are more than 1,400 organelles significant to imaging.[6] At least half are L or ML capable of generating FAF. Some of these organelles, specifically the melanosomes,

Bios

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preferentially localize to the apical processes of RPE cells. They not only shadow more posteriorly localized fluorophores, but they also may contribute their own FAF signal.[7]

A fascinating new finding from high-resolution microscopy is that ML dominates foveal RPE, and L dominates non-foveal RPE, thus relating regionally specific molecular heterogeneity to cones.[5,8]

Exposing an old foe: Reticular pseudodrusen

Reticular pseudodrusen (RPD), or subretinal drusenoid deposits (SDD), are lesions of AMD distinct from drusen, and, with choroidal insufficiency, make up the AMD phenotype of reticular macular disease (RMD).[9] RPD confer a greater risk than drusen of progression to the advanced stages of AMD, especially geographic atrophy, now termed complete RPE and outer retinal atrophy (cRORA).[10]

RPD are extracellular subretinal drusenoid deposits seen on spectral-domain optical coherence tomography above the hyperreflective band corresponding to the RPE monolayer.[11] They appear as associated hypoautofluorescent lesions on en face FAF along with hyporeflectant patterns on NIR imaging.

Owing to the poor visibility of RPD on clinical examination and on color fundus photography, the original Age-Related Eye Disease Study (AREDS) reports didn't describe the specific lesion called RPD. The advent of more recent imaging methods—namely FAF, NIR and OCT—makes it more likely to determine the presence of RPD with greater accuracy.

A recent study examined RPD in FAF images of 5,021 eyes of a subset of 2,516 AREDS2 participants.[12] It reported RPD in 24 percent of eyes and bilateral lesions in 62 percent of participants with RPD. Prevalence of RPD varied with baseline AREDS AMD severity level: from 6 percent in early AMD to 36 percent in GA.

After accounting for AMD level and fellow-eye status, participants had a twofold risk of progression to late AMD in eyes with RPD and a 2.5-fold risk of macular atrophy.

In eyes with very early AMD, AREDS also found that the presence of RPD raised the risk of late AMD almost tenfold, highlighting the role of RPD as an independent risk factor. This also affirmed the more recent reclassification of RPD as intermediate AMD, along with large soft drusen, as much more advanced AMD requiring early diagnosis. However, their detection in a clinical setting can remain a challenge.

Potential role of AI

Artificial intelligence may aid physicians on this task. Researchers applied deep learning (DL) to the automated detection of RPD from color fundus photographs, on which they're not consistently discernible by human graders, by training the DL from corresponding FAF images, on which graders can consistently identify RPD.[13]

This DL model, called label transfer, was applied to the AREDS2 dataset, studying FAF imaging and color photos on 4,724 eyes conducted at 66 selected clinic sites from a large population of more than 2,000 individuals with AMD. The positions of the RPD on the FAF images were transferred as labels to the color fundus images, and the DL was trained to identify the labeled lesions on color photos only.

By testing the DL on a different set of unlabeled photos, these researchers showed that it identified RPD presence on the corresponding FAF images with an accuracy equal or superior to that of a human grader. This model may even augment the detection of this high-risk AMD phenotype and could be applied to screening where only color photos are available.

Possible CVD-RPD connection

Additionally, growing evidence is linking cardiovascular disease (CVD) and RPD. Patients with coronary artery disease (CAD) have reticular macular disease more often

Researchers showed that a deep-learning model identified RPD presence on corresponding FAF images with accuracy equal or superior to that of a human grader.

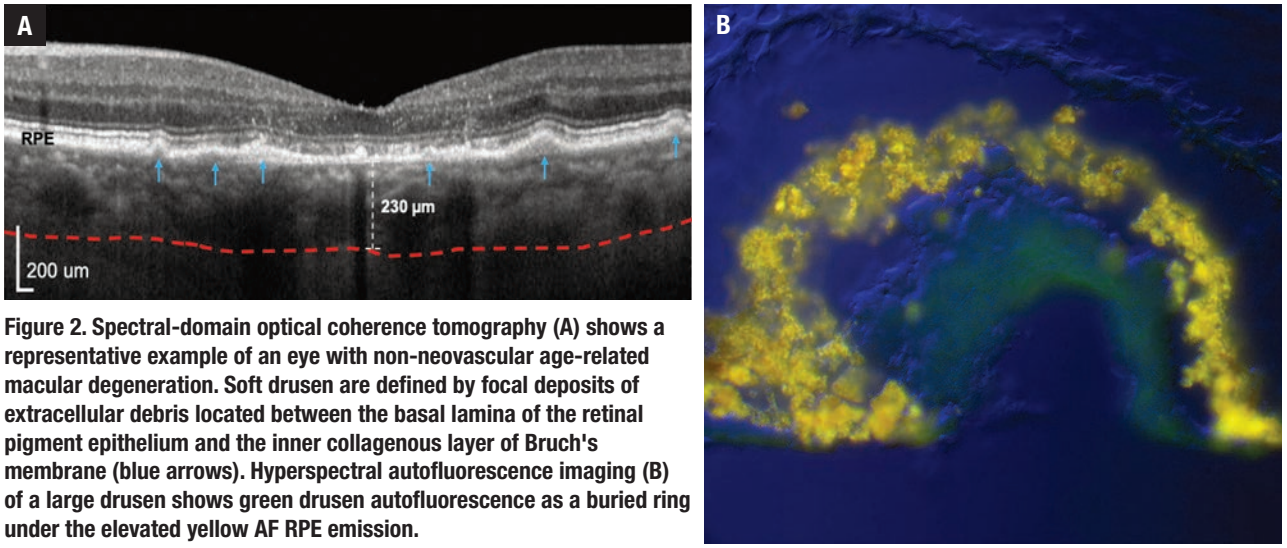

Figure 2. Spectral-domain optical coherence tomography (A) shows a representative example of an eye with non-neovascular age-related macular degeneration. Soft drusen are defined by focal deposits of extracellular debris located between the basal lamina of the retinal pigment epithelium and the inner collagenous layer of Bruch's membrane (blue arrows). Hyperspectral autofluorescence imaging (B) of a large drusen shows green drusen autofluorescence as a buried ring under the elevated yellow AF RPE emission.

than those who don't,[14] and definitely have thinner choroids.[15] RPD are associated with decreased longevity,[16] with CVD long suspected as the culprit. This theory of CVD causality received recent striking support from a histopathology of 1,777 study eyes.[17]

The authors classified donor eyes with both the four- and nine-step Minnesota Grading System and the AREDS AMD classification system for eye-bank eyes. They detected RPD in 13 percent of examined eyes. RPD, alone among the AMD lesions, were highly associated with cardiovascular death.

Other studies found that age-related maculopathy susceptibility (ARMS2) risk was highly associated with RPD,[12] whereas complement factor H risk was not.[18] There is also an association of ARMS2 with elevated C-reactive protein. That may be relevant in this context because C-reactive protein is associated with CAD (*Figure 1, Page 19*).

Next-gen AF assessment in AMD

FAF imaging may serve as a quantifiable endpoint in clinical trials related to non-nAMD. Most of the current classifications are based on qualitative description or patterns of FAF in AMD. Nevertheless, the strong AF signal has high potential for non-invasive, spatially and molecularly precise early detection, longitudinal follow-up and *in vivo* target discovery, as in the following methods:

• ***Quantitative fundus autofluorescence.*** qAF is a novel, innovative imaging modality to measure *in vivo* the L-related FAF from the RPE. This method, introduced in 2011, is performed by calibrating the FAF image to an internal reference of known fluorescence efficiency within a cSLO OCT, making it possible to reproducibly quantify and compare FAF intensity between patients and across time. It provides the spatial distribution of the fluorescence intensities, which can then be captured by a pattern or geometric region-of-interest on the macula.

As FAF has been established as a qualitative tool to visualize L components *in vivo*, qAF has demonstrated quantitatively a decline in fluorescence intensity with decreasing RPE health and increasing severity of non-nAMD. This suggests that loss, not increase, of L-fluorophores signifies AMD progression.[19]

• ***Fluorescence lifetime imaging ophthalmoscopy.*** FLIO is an emerging imaging modality for *in vivo* measurement of lifetimes of endogenous retinal fluorophores.

Growing evidence is linking cardiovascular disease and reticular pseudodrusen. Patients with coronary artery disease have reticular macular disease more so than those without CAD,and they definitely have thinner choroids.

The fluorescence lifetime is the average amount of time a fluorophore remains in the excited state following excitation. The FLIO device is also based on an OCT system. Autofluorescence lifetimes are excited at 473 nm and recorded in two spectral wavelengths channels. Typically, mean autofluorescence lifetimes in a 30-degree retinal field are investigated. For example, in non-nAMD, ring patterns of prolonged FLIO lifetimes 1.5 to 3 mm from the fovea can be appreciated. [20]

• ***Hyperspectral autofluorescence.*** Drusen are focal and recognizable clinically using color fundus photography and advanced OCT. Sub-RPE deposits contain basal linear (BLinD) and basal laminar deposits (BLamD). Very thick BLamD may be visible on OCT. BLinD is the precursor of soft drusen and isn't visible on OCT, hence the detection of BLinD would provide a way to diagnose AMD at the earliest stage (*Figure 2, page 21*).

Hyperspectral imaging combines conventional imaging and spectroscopy to obtain spectral and spatial information from specimens. This technology was recently applied in our studies to extract the spectra of the AF emissions of drusen and RPE after excitation by appropriate wavelengths—for example, 480 nm that's used in standard AF imaging—and thus identify these components in donor retina tissues.

The hyperspectral images were acquired at each emission wavelength between 420 and 720 nm with a hyperspectral camera at two excitation wavelengths (lambda$_{ex}$ 436 nm and lambda$_{ex}$ 480 nm). We analyzed the hyperspectral images to recover the strongest emission spectra and map their corresponding tissue localizations by using a non-negative tensor factorization (*Figure 3*).

We also studied the drusen spectral signature at lambda$_{ex}$ 450 nm excitation and demonstrated that it also has a peak at 510 nm and a similar shape to that at lambda$_{ex}$ 436 nm.[21]

This demonstrates the feasibility of a clinical hyperspectral AF camera with a safe 450 nm excitation. It could detect the spectra of drusen and sub-RPE deposits, diagnose AMD at an early stage *in vivo*, and facilitate the development and monitoring of new therapies based on specific molecular defects.

(Continued on page 27)

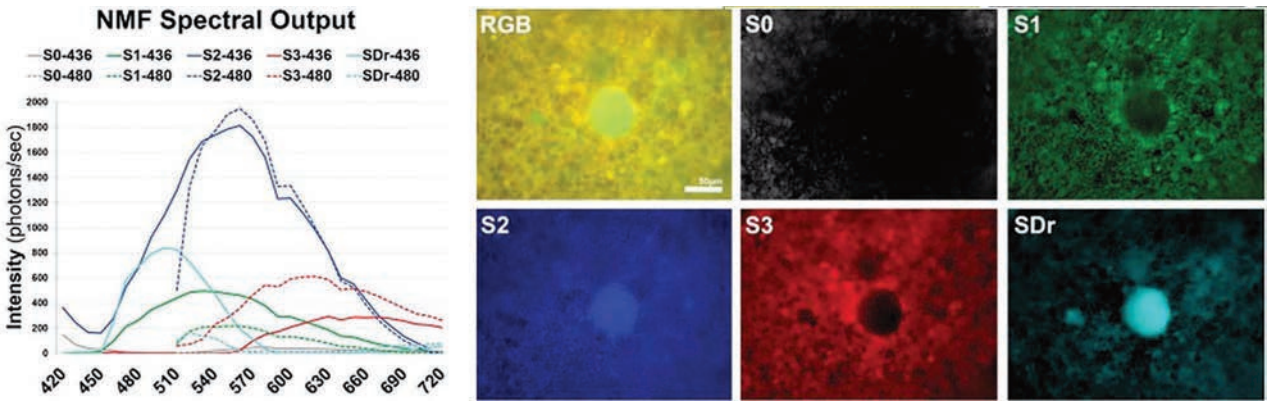

Figure 3. Recovered spectra (left) and tissue localizations (right) of the main fluorophores found in a flat-mounted retinal pigment epithelium/Bruch's membrane. The spectra from drusen and sub-RPE deposits in an age-related macular degeneration tissue at lambda$_{ex}$ 436 nm and lambda$_{ex}$ 480 nm are the two azure curves (SDr), and their corresponding tissue sources labeled SDr (note central druse). The peak of spectra from drusen is at 510 nm at lambda$_{ex}$ 436 nm excitation. This spectrum is sensitive and specific for drusen and sub-RPE deposits, and provides an excellent way to understand AMD biogenesis. The other three spectra (green, blue and red curves) come from the RPE lipofuscin (S1, S2) and melanolipofuscin (S3) organelles. S0 is from the Bruch's membrane. Scale bar: 50 µm.

Imaging biomarkers and precision medicine

Advances in computational power, and machine learning and diagnostic systems are creating new opportunities for understanding disease mechanisms.

By Gagan Kalra, MD, and Justis P. Ehlers, MD

Take-home points

- Quantitative imaging biomarkers using computational imaging techniques provide a unique opportunity for characterization of natural history, disease burden and treatment response of retinal diseases.
- Structural biomarkers using optical coherence tomography include layer-specific compartmental assessment and pathologic feature interrogation. These specific features may have implications for functional outcomes and therapeutic response.
- Vascular biomarkers that have been described using ultra-widefield fluorescein angiography and OCT angiography include quantitative leakage features, microaneurysm counts, ischemic burden and vascular characteristics. These vascular features have been linked to disease severity and may provide a tool for longitudinal assessment of treatment response.
- Emerging technology, including machine learning-based image assessment systems, will enable new expansion of imaging biomarkers that have the potential to enhance the practice of precision medicine and improve patient outcomes.

With technological advances, retinal imaging has grown tremendously over the past few decades, from providing histology-level detail of the retinal anatomy at the posterior pole with optical coherence tomography to capturing near panretinal disease burden with ultra-widefield imaging. Our diagnostic tools have opened up a whole new world of disease understanding, feature assessment and opportunities for personalized medicine.

A recent addition to our imaging armamentarium is OCT angiography, which had been increasingly adopted in part due to its depth-encoded, non-invasive, rapid-acquisition features. Specialists have traditionally interpreted visual information from these images to identify findings that may confirm diagnosis or assess treatment response.

Beyond diagnosis, qualitative imaging biomarkers have been identified in numerous modalities and retinal disorders that provide important contextual and predictive value for natural history or treatment response. More recently, the advancing field of computational image analysis and machine learning-enhanced image interrogation have opened doors to new biomarkers with quantitative features and potential objective feature parameters. In this review, we explore many of these imaging biomarkers for various modalities and retinal diseases.

Visualizing enhanced anatomy on OCT

The incredible anatomic details that spectral-domain OCT and swept-source OCT provide have revolutionized the field through their impact on diagnosis, disease surveillance and assessment of therapeutic response. Qualitative feature assessment of

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Bios

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specific retinal layers and zones has been linked to functional impact and outcomes, including location of retinal fluid and integrity of outer retinal bands. Historically, many of these assessments of retinal integrity were primarily qualitative and often binary. The inability to quantify these features limited the widespread impact of these assessments.

New segmentation platforms and higher-speed OCT systems have enabled quantitative parameter assessment of retinal layers within specific zones or across the entire macula.[1-3] En face OCT has provided unique opportunities for depth-specific assessments of features, such as outer retinal loss and network structure of outer retinal tubulation.[4]

Multi-layer segmentation platforms, including machine learning-enhanced systems, are now able to provide quantitative outputs for zones and inter-layer thickness/volumes that can be linked to function and other structural dynamics.[1-3] Quantitative fluid object characterization now provides next-generation detail of fluid burden and impact on overall disease outcomes and therapeutic response.

New segmentation platforms and higher-speed OCT systems have enabled quantitative parameter assessment of retinal layers within specific zones or across the entire macula.

Transformative OCT advances

Our understanding of diabetic eye disease has been transformed through the utilization of structural OCT. The rapid assessment of fluid burden and fluid localization and transitioned therapeutic management could be tailored to the OCT findings rather than the historical "clinically significant" definition of diabetic macular edema. In addition, specific layer alterations, such as disorganized retinal inner layers (DRIL), have been identified as important biomarkers of retinal function and severity of retinal disease.[5]

Quantitative feature extraction and multilayer assessment have also more recently provided insights into longitudinal retinal layer dynamics. Specifically, recent studies have confirmed improvements in quantitative ellipsoid zone integrity following anti-VEGF therapy for DME with distinct correlation to functional outcomes.[6]

Additionally, the ability to volumetrically quantify fluid across the macula and specific zones of interest (e.g., the central subfield) provides a unique opportunity for biomarkers, such as the retinal fluid index (RFI).[6,7]

The RFI represents the percentage of overall retinal volume from the internal limiting membrane to the retinal pigment epithelium that is composed of retinal fluid (measured as a percentage).[6] This biomarker has been demonstrated to be associated with functional outcomes and early instability in RFI during the treatment phase has been linked to long-term volatility to treatment response (*Figure 1*).[6,8]

Biomarkers in AMD, GA

Researchers have evaluated nonexudative age-related macular degeneration extensive-

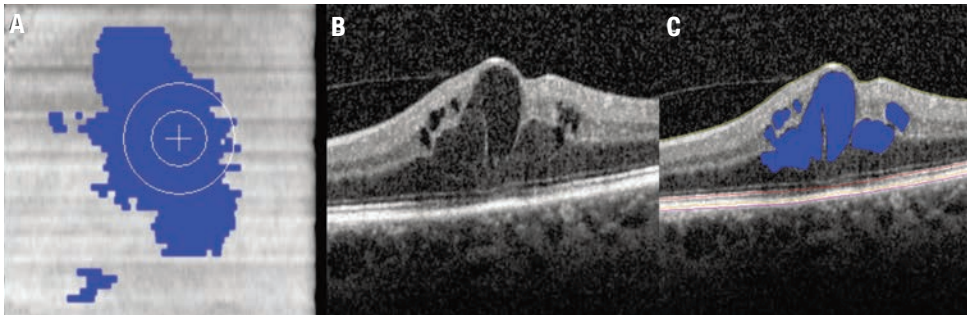

Figure 1. Automated fluid feature detection and optical coherence tomography biomarker detection in diabetic macular edema. A) Fundus OCT image demonstrates en face fluid distribution map. B) Foveal B-scan with significant foveal fluid. C) Foveal B-scan with intraretinal fluid automated segmentation (blue) and multi-layer segmentation lines.

ly for various imaging biomarkers. Qualitative features on SD-OCT that have been associated with progression to advanced AMD include intraretinal hyper-reflective foci (IHRF), complex drusenoid lesions (DL, i.e., heterogeneity of reflectivity), subretinal drusenoid deposits (SDD) and drusen burden (*Figure 2*).[9]

In fact, these qualitative features have demonstrated the following hazard ratios (HR) for developing late AMD:

- 5.21 for IHRF (95% confidence interval [CI], 3.29-8.26);
- 2.42 for hyporeflective foci (hRF) within DLs (95%CI, 1.74-3.38);
- 1.95 for SDD (95% CI, 1.34-2.82); and
- 1.46 for large drusen volume (95% CI, 1.03-2.07).[10]

Drusen volume quantification has been enabled through multiple research and commercial analysis platforms. RPE compartment analysis software has been used to evaluate automated drusen volumes in multiple zones of interest and has demonstrated a significant increased risk of the development of geographic atrophy or conversion to neovascular AMD in eyes with larger drusen volumes.[11]

Machine learning enhancements to segmentation and feature extraction are also providing new opportunities for disease characterization and evaluation of longitudinal therapeutic response, including in neovascular AMD. Multiple groups have demonstrated the feasibility of volumetric fluid characterization, compartmental OCT feature evaluation (such as ellipsoid zone integrity) and quantitative volumetric assessment of subretinal fibrosis/subretinal hyperreflective material (*Figure 3*).[12-14]

Vascular biomarkers on UWFA, OCTA

Traditionally, angiographic features have been described in a qualitative fashion or relative quantitative assessment, such as by comparing a feature of interest to the number of disc areas that it represents. Although these relative quantitative assessments provide important context, they limit the resolution of comparative evaluation between other key features of interest.

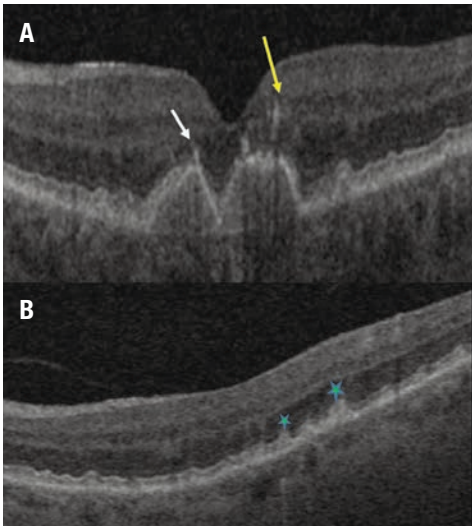

Figure 2: Examples of qualitative optical coherence tomography biomarkers in dry age-related macular degeneration. A) A horizontal spectral-domain OCT B-scan slice through the macula shows confluent hyperreflective foci over the drusenoid pigment epithelial detachment (arrows). B) Horizontal SD-OCT scans demonstrate subretinal drusenoid deposits (stars).

The labor-intensive nature of manual feature assessment had been a barrier to more widespread use. Recently, methods and systems have been developed to provide

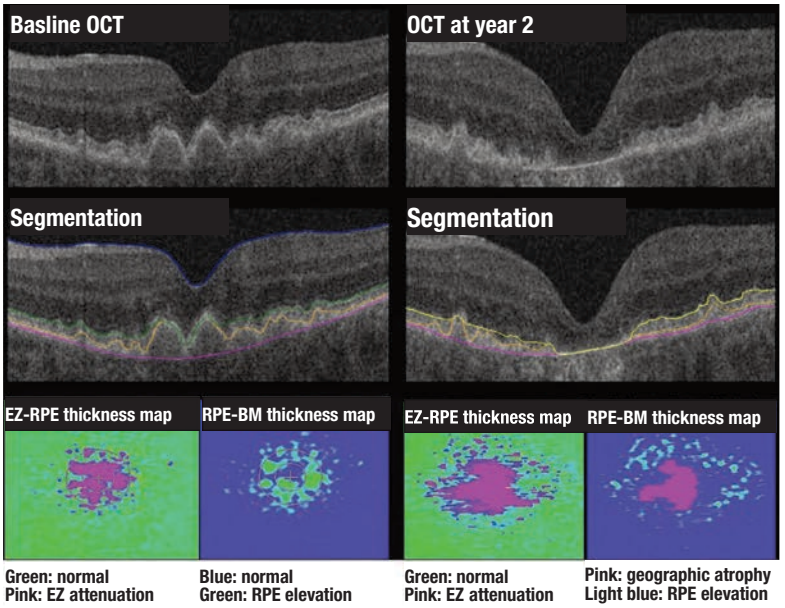

Figure 3: Examples of quantitative optical coherence tomography biomarkers in dry age-related macular degeneration. Two-year progression from intermediate AMD to advanced AMD with subfoveal geographic atrophy. Significant baseline ellipsoid zone attenuation is present that appears to be an important potential biomarker for progression to GA.

in-depth evaluation of leakage features, microaneurysm counts, ischemic burden and vascular characteristics (*Figure 4*).[15,16]

Machine learning systems have provided the ability to perform enhanced vascular segmentation, feature extraction, and more efficient methods for evaluating imaging characteristics.[17-19] The binary depth-encoded nature of OCTA has also provided a new frontier in quantitative feasibility of vascular analysis.

Vascular biomarkers in DR, DME

Automated angiographic quantitative assessment of UWFA features in DR has been shown to be strongly linked to DR severity.[20] The quantitative assessment of these disease burden features may be critical in optimizing predictive assessment for risk of progression or DR-related complications. Panretinal leakage index, panretinal ischemic index and total microaneurysm counts are all strongly correlated with DR severity.[20]

The panretinal leakage index, in particular, has been associated with predicting additional DR-related complications, such as vitreous hemorrhage and DME.[21,22] These quantitative parameters also provide a unique opportunity for evaluating a longitudinal treatment response. Using an automated UWFA system, intravitreal anti-VEGF therapy has demonstrated dramatic improvements in leakage index and total microaneurysm counts in DR.[21,23] In fact, one recent trial used the panretinal leakage index as the key biomarker for therapeutic decision-making and demonstrated similar efficacy results to DR severity-based treatment decision-making.[24] Leakage node distribution and morphology have also been linked to treatment interval tolerance in DME.[25]

Beyond traditional angiographic features, retinal vasculature analysis has emerged as a promising biomarker for diabetic eye disease generated from UWFA and OCTA. For instance, fractal dimension (FD) represents the complexity of the vascular geometry with higher values indicating dense, intricate, space-filling tree-like patterns. Robust magnification and distortion-related errors are major advantages of FD.[26,27] FD in DR has been found to be significantly lower in the far periphery in eyes with DR compared to normals. Additionally, FD for the entire retina showed negative correlation with global non-perfusion area.[28]

One study of swept-source OCTA found the foveal avascular zone to be significantly higher in diabetic eyes than controls.[29] In addition, eyes with DR had larger mean perifoveal intercapillary area (PIA) than controls.[29] Utilizing quantitative OCTA parameters, novel classification systems for DR have also been proposed using features such as blood vessel tortuosity, vascular caliber, vessel perimeter index, blood vessel density, FAZ area and FAZ contour irregularity.[30,31]

Bottom line

The exploration, validation and discovery of imaging biomarkers for retinal disease is an exciting and evolving area of research. Thanks to advances in computational power, machine learning systems and diagnostic systems are providing unique opportunities for enhanced understanding of the mechanisms and natural history of disease and the development of a personalized approach to treatment decision-making. Further exploration and validation of these biomarkers and others are needed to provide greater clarity of their optimal role in patient education, clinical trial enrollment optimization and precision medicine. RS

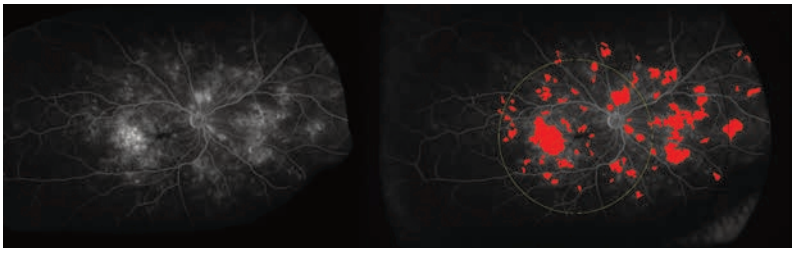

Figure 4: Examples of quantitative leakage measurements on fluorescein angiography in diabetic retinopathy: (left) the original ultra-widefield FA scan; and (right) UWFA scan showing automated segmentation of leakage activity.

REFERENCES

1. Chiu SJ, Li XT, Nicholas P, Toth CA, Izatt JA, Farsiu S. Automatic segmentation of seven retinal layers in SDOCT images congruent with expert manual segmentation. Opt Express. 2010;18:19413-19428.
2. Schmidt-Erfurth U, Sadeghipour A, Gerendas BS, Waldstein SM, Bogunovi H. Artificial intelligence in retina. Prog Retin Eye Res. 2018; 67:1-29.
3. Itoh Y, Vasanji A, Ehlers JP. Volumetric ellipsoid zone mapping for enhanced visualisation of outer retinal integrity with optical coherence tomography. Br J Ophthalmol. 2016; 100:295-299.
4. Dolz-Marco R, Litts KM, Tan AC, Freund KB, Curcio CA. The evolution of outer retinal tubulation, a neurodegeneration and gliosis prominent in macular diseases. Ophthalmology. 2017;124:1353-1367.
5. Sun JK, Lin MM, Lammer J, et al. Disorganization of the retinal inner layers as a predictor of visual acuity in eyes with center-involved diabetic macular edema. JAMA Ophthalmol. 2014;132:1309-1316.
6. Ehlers JP, Uchida A, Hu M, et al. Higher-order assessment of oct in diabetic macular edema from the vista study: Ellipsoid zone dynamics and the retinal fluid index. Ophthalmol Retina. 2019;3: 1056-1066.
7. Roberts PK, Vogl W-D, Gerendas BS, et al. Quantification of fluid resolution and visual acuity gain in patients with diabetic macular edema using deep learning: a post hoc analysis of a randomized clinical trial. JAMA Ophthalmol. 2020;138:945-953.
8. Ehlers JP, Uchida A, Sevgi DD, et al. Retinal fluid volatility associated with interval tolerance and visual outcomes in diabetic macular edema in the VISTA Phase III trial. Am J Ophthalmol. 2021;224: 217-227.
9. Toth CA, Tai V, Chiu SJ, et al. Linking OCT, angiographic, and photographic lesion components in neovascular age-related macular degeneration. Ophthalmol Retina. 2018;2:481-493.
10. Nassisi M, Lei J, Abdelfattah NS, et al. OCT risk factors for development of late age-related macular degeneration in the fellow eyes of patients enrolled in the HARBOR Study. Ophthalmology. 2019;126:1667-1674.
11. Abdelfattah NS, Zhang H, Boyer DS, et al. Drusen volume as a predictor of disease progression in patients with late age-related macular degeneration in the fellow eye. Invest Ophthalmol Vis Sci. 2016;57:1839-1846.
12. Ehlers JP, Zahid R, Kaiser PK, et al. Longitudinal assessment of ellipsoid zone integrity, subretinal hyperreflective material, and subretinal pigment epithelium disease in neovascular age-related macular degeneration. Ophthalmol Retina. Published online February 26, 2021.
13. Ehlers JP, Clark J, Uchida A, et al. Longitudinal higher-order OCT assessment of quantitative fluid dynamics and the total retinal fluid index in neovascular AMD. Trans Vis Sci Tech. 2021;10:29.
14. Waldstein SM, Philip A-M, Leitner R, et al. Correlation of 3-dimensionally quantified intraretinal and subretinal fluid with visual acuity in neovascular age-related macular degeneration. JAMA Ophthalmol. 2016;134:182-190.
15. Rabbani H, Allingham MJ, Mettu PS, Cousins SW, Farsiu S. Fully automatic segmentation of fluorescein leakage in subjects with diabetic macular edema. Invest Ophthalmol Vis Sci. 2015; 56:1482-1492.
16. Ehlers JP, Wang K, Vasanji A, Hu M, Srivastava SK. Automated quantitative characterisation of retinal vascular leakage and microaneurysms in ultra-widefield fluorescein angiography. Br J Ophthalmol. 2017;101:696-699.
17. Sevgi DD, Scott AW, Martin A, et al. Longitudinal assessment of quantitative ultra-widefield ischaemic and vascular parameters in sickle cell retinopathy. Br J Ophthalmol. Published online October 31, 2020.
18. O'Connell M, Sevgi DD, Srivastava SK, et al. Longitudinal precision of vasculature parameter assessment on ultra-widefield fluorescein angiography using a deep-learning model for vascular segmentation in eyes without vascular pathology. Invest Ophthalmol Vis Sci. 2020;61: 2010.
19. Sevgi DD, Hach J, Srivastava SK, et al. Automated quality optimized phase selection in ultra-widefield angiography using retinal vessel segmentation with deep neural networks. Inves Ophthalmol Vis Sci. 2020; 61: PB00125.
20. Ehlers JP, Jiang AC, Boss JD, et al. Quantitative ultra-widefield angiography and diabetic retinopathy severity: an assessment of panretinal leakage index, ischemic index and microaneurysm count. Ophthalmology. 2019; 126:1527-1532.
21. Babiuch AS, Wykoff CC, Srivastava SK, et al. Retinal leakage index dynamics on ultra-widefield fluorescein angiography in eyes treated with intravitreal aflibercept for proliferative diabetic retinopathy in the RECOVERY study. Retina. 2020; 40:2175-2183.
22. Jiang AC, Srivastava SK, Hu M, et al. Quantitative ultra-widefield angiographic features and associations with diabetic macular edema. Ophthalmol Retina. 2020;4:49-56.
23. Figueiredo N, Srivastava SK, Singh RP, et al. Longitudinal panretinal leakage and ischemic indices in retinal vascular disease after aflibercept therapy: The PERMEATE Study. Ophthalmol Retina. 2020;4:154-163.
24. Hannah JY, Ehlers JP, Sevgi DD, et al. Real-time photographic-and fluorescein angiographic-guided management of diabetic retinopathy: Randomized PRIME Trial outcomes. Am J Ophthalmol. 2021;226:126-136.
25. Prasanna P, Bobba V, Figueiredo N, et al. Radiomics-based assessment of ultra-widefield leakage patterns and vessel network architecture in the PERMEATE study: insights into treatment durability. Br J Ophthalmol. Published online August 19, 2020.
26. Mainster MA. The fractal properties of retinal vessels: embryological and clinical implications. Eye. 1990;4:235-241.
27. Li H, Mitchell P, Liew G, et al. Lens opacity and refractive influences on the measurement of retinal vascular fractal dimension. Acta Ophthalmologica. 2010;88:e234-e240.
28. Fan W, Nittala MG, Fleming A, et al. Relationship between retinal fractal dimension and nonperfusion in diabetic retinopathy on ultrawide-field fluorescein angiography. Am J Ophthalmol. 2020;209:99-106.
29. Salz DA, de Carlo TE, Adhi M, et al. Select features of diabetic retinopathy on swept-source optical coherence tomographic angiography compared with fluorescein angiography and normal eyes. JAMA Ophthalmol. 2016;134:644-650.
30. Alam M, Zhang Y, Lim JI, Chan RVP, Yang M, Yao X. Quantitative optical coherence tomography angiography features for objective classification and staging of diabetic retinopathy. Retina. 2020;40.
31. Alam M, Thapa D, Lim JI, Cao D, Yao X. Quantitative characteristics of sickle cell retinopathy in optical coherence tomography angiography. Biomed Opt Express 2017; 8: 1741-53.

How imaging is advancing management of dry AMD

(Continued from page 22)

Bottom line

Fundus autofluorescence is a valuable tool for imaging eyes with dry AMD and allows for identification of patients with not only a high risk of progression to late AMD, such as eyes with RPD, but also major morbidity and mortality due to cardiovascular diseases. Newer methods of FAF may serve as a quantifiable endpoint in ongoing clinical trials related to non-neovascular AMD. These advances may extend profound health and social benefits to our aging population. RS

REFERENCES

1. Schmitz-Valckenberg S, Holz FG, Bird AC, Spaide RF. Fundus autofluorescence imaging: Review and perspectives. Retina. 2008;28:385-409.
2. Ablonczy Z, Higbee D, Anderson DM, et al. Lack of correlation between the spatial distribution of A2E and lipofuscin fluorescence in the human retinal pigment epithelium. Invest Ophthalmol Vis Sci. 2013;54:5535-5542.
3. Ach T, Huisingh C, McGwin G Jr, et al. Quantitative autofluorescence and cell density maps of the human retinal pigment epithelium. Invest Ophthalmol Vis Sci. 2014;55:4832-4841.
4. Küçükiba K, Erol N, Bilgin M. Evaluation of peripheral retinal changes on ultra-widefield fundus autofluorescence images of patients with age-related macular degeneration. Turk J Ophthalmol. 2020;50:6-14.
5. Bermond K, Wobbe C, Tarau IS, et al. Autofluorescent granules of the human retinal pigment epithelium: phenotypes, intracellular distribution, and age-related topography. Invest Ophthalmol Vis Sci. 2020;61:35.
6. Pollreisz A, Messinger JD, Sloan KR, et al. Visualizing melanosomes, lipofuscin, and melanolipofuscin in human retinal pigment epithelium using serial block face scanning electron microscopy. Exp Eye Res. 2018;166:131-139.
7. Guan Z, Li Y, Jiao S, et al. A2E distribution in rpe granules in human eyes. Molecules. 2020;25:1413.
8. Anderson DMG, Messinger JD, Patterson NH, et al. Lipid landscape of the human retina and supporting tissues revealed by high-resolution imaging mass spectrometry. J Am Soc Mass Spectrom. 2020;31:2426-2436.
9. Smith RT, Sohrab MA, Busuioc M, Barile G. Reticular macular disease. Am J Ophthalmol. 2009;148:733-743.e2.
10. Sadda SR, Guymer R, Holz FG, et al. Consensus definition for atrophy associated with age-related macular degeneration on OCT: Classification of Atrophy Report 3. Ophthalmology. 2018;125:537-548.
11. Zweifel SA, Spaide RF, Curcio CA, Malek G, Imamura Y. Reticular pseudodrusen are subretinal drusenoid deposits. Ophthalmology. 2010;117:303-312.e1.
12. Domalpally A, Agrón E, Pak JW, et al. Prevalence, risk, and genetic association of reticular pseudodrusen in age-related macular degeneration: Age-Related Eye Disease Study 2 Report 21. Ophthalmology. 2019;126:1659-1666.
13. Keenan TDL, Chen Q, Peng Y, et al. Deep learning automated detection of reticular pseudodrusen from fundus autofluorescence images or color fundus photographs in AREDS2. Ophthalmology. 2020;127:1674-1687.
14. Cymerman RM, Skolnick AH, Cole WJ, Nabati C, Curcio CA, Smith RT. Coronary artery disease and reticular macular disease, a subphenotype of early age-related macular degeneration. Curr Eye Res. 2016;41:1482-1488.
15. Ahmad M, Kaszubski PA, Cobbs L, Reynolds H, Smith RT. Choroidal thickness in patients with coronary artery disease. PLoS One. 2017;12:e0175691.
16. Klein R, Meuer SM, Knudtson MD, Iyengar SK, Klein BE. The epidemiology of retinal reticular drusen. Am J Ophthalmol. 2008;145:317-326.
17. Mano F, Sprehe N, Olsen TW. Association of drusen phenotype in age-related macular degeneration from human eye-bank eyes to disease stage and cause of death. Ophthalmol Retina. 2020;S2468-6530(20)30462-0.
18. Smith RT, Merriam JE, Sohrab MA, Pumariega NM, Barile G, Blonska AM, et al. Complement factor H 402H variant and reticular macular disease. Arch Ophthalmol. 2011;129:1061-1066.
19. Orellana-Rios J, Yokoyama S, Agee JM, et al. Quantitative fundus autofluorescence in non-neovascular age-related macular degeneration. Ophthalm Surg Lasers Imaging Retina. 2018;49:S34-S42.
20. Sauer L, Vitale AS, Modersitzki NK, Bernstein PS. Fluorescence lifetime imaging ophthalmoscopy: autofluorescence imaging and beyond. Eye (Lond). 2021;35:93-109.
21. Tong Y, Ach T, Curcio CA, Smith RT. Hyperspectral autofluorescence characterization of drusen and sub-RPE deposits in age-related macular degeneration. Ann Eye Sci. 2021;6:4.

Where genetics, diet and drusen size intersect

A close look at research into how diet may reverse the effect of genetic susceptibility in drusen size progression in age-related macular degeneration.

Johanna Seddon, MD, ScM

By Johanna Seddon, MD, ScM

Take-home points

- Genetic susceptibility is independently related to drusen growth in age-related macular degeneration.
- A Mediterranean-style diet with healthful nutrient-rich foods may remediate the effect of genetic susceptibility on drusen growth.
- Our group's research identified risks and protective genetic variants associated with a two-step progression in drusen size.
- Our research has previously shown that lower systemic inflammatory biomarker C-reactive protein levels associated with higher consumption of lutein and zeaxanthin, vitamin C and fish, supports the beneficial role of an anti-inflammatory diet.

Bios

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Disclosures: Dr. Seddon disclosed financial relationships with Gemini Therapeutics, Apellis and Thea Pharmaceuticals, and funding support from the National Institutes of Health.

It's been well established that a number of factors play a role in progression from non-advanced to advanced age-related macular degeneration.[1] These factors include, but are not limited to, age, smoking history,[2] diet and nutrition,[3-5] environmental influences and a number of genetic variants.[6-11] However, little research has been done to investigate factors associated with drusen size progression, even though drusen in early and intermediate AMD increase the risk of developing more advanced disease.

Our group evaluated the relationship between drusen size progression, common and rare AMD genetic variants, and diet[12] to gain a better understanding of the biology of drusen growth that could lead to preventive measures and thwart the development of vision-disabling forms of AMD. We reported for the first time that a healthy diet—specifically, higher adherence to the Mediterranean diet—was linked with a lower risk of drusen growth.

To investigate this nexus of genetics, diet and drusen growth, we evaluated 1,838 patients (3,023 eyes) at risk for drusen progression based on fundus photographs graded at a reading center. These patients had an average follow-up time of 10.2 years in the Age-Related Eye Disease database.

Evaluating the role of diet

We calculated an alternate Mediterranean diet (aMeDi) score based on the food frequency questionnaire, an instrument that's been used to estimate the prevalence of the Mediterranean diet in the United States. Our group published the first report that demonstrated the aMeDi score was linked to progression to advanced AMD.[5] These findings were later confirmed in a European cohort.[13] The aMeDi score includes these nine components (*Figure 1*):

- vegetables (excluding potatoes);
- fruits;

- legumes;
- whole grains;
- nuts;
- fish;
- red and processed meats;
- alcohol consumption; and
- the ratio of monounsaturated to saturated fatty acid (MUFA:SFA).

Scores of 1 or 0 were assigned depending on intake of these components. A score of 9 represents perfect adherence; 0 represents complete non-adherence. For our purposes, we categorized aMeDi scores in two categories: low (0 to 3); and medium-high (4 to 9).

Genotype data

We found that the following genetic variants in the complement pathway were significantly associated with a two-step progression in drusen size, adjusting for other covariates:

- *CFH* Y402H;
- *CFH* rs1410996;
- *CFH* R1210C;
- *C2* E318D;
- *C3* R102G; and
- *C3* K155Q.

Variants in the following genes were also significantly associated with a two-step progression in drusen size:

- *ARMS2/HTRA1;*
- *VEGF-A;*
- *TIMP3;*
- *NPLOC4;* and
- *HSPH.*

The *C2* E318D protective allele conferred decreased risk, adjusting for other covariates.

Drusen size drivers

Drusen size increased twofold in 8 percent of eyes at five years, and 19 percent had drusen growth at 10 years. Non-genetic factors associated with higher risk of drusen progression were older age, smoking and larger drusen size at baseline.

A number of factors didn't differ between patients with and without drusen progression: gender, education level, body-mass index, history of AREDS treatment and multivitamin use.

We calculated a genetic risk score based on the 11 genetic variants in eight genes that were related to drusen growth (*Table 1*), and determined the association between drusen size growth, gene variants and adherence to the Mediterranean diet using the aMeDi score.

A higher genetic risk score was associated with drusen size progression—specifically a hazard ratio of 2.68 for each one-unit increase in score

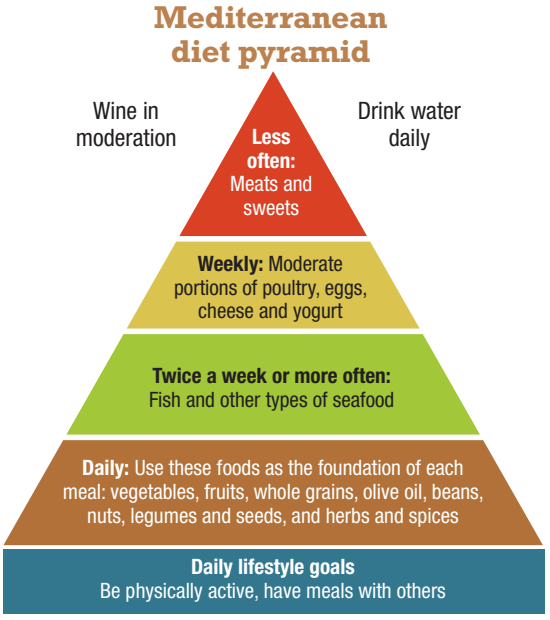

Figure 1. The Mediterranean diet emphasizes plant-based foods and fish over poultry, dairy and meat.

Table 1. Genetic factors associated with drusen size progression[12]

	Drusen size progression	
	Hazard ratio (95% CI)*	*p* value
COMPLEMENT PATHWAY		
CFH Y402H: rs1061170	1.22 (1.02 - 1.43)	0.03
CFH: rs1410996	1.22 (1.01 - 1.48)	0.04
CFH R1210C: rs121913059	5.85 (2.44 - 14.06)	<0.001
C2 E318D: rs9332739	0.44 (0.28 - 0.69)	<0.001
C3 R102G: rs2230199	1.45 (1.26 - 1.67)	<0.001
C3 K155Q: rs147859257	2.19 (0.98 - 4.88)	0.05
ANGIOGENESIS PATHWAY		
VEGF-A: rs943080	1.19 (1.04 - 1.36)	0.01
IMMUNE INFLAMMATORY PATHWAY		
ARMS2/HTRA1 A69S: rs*10490924*	1.34 (1.17 - 1.54)	<0.001
EXTRACELLULAR MATRIX		
TIMP3: rs9621532	1.52 (1.16 - 2.01)	0.003
DNA REPAIR/PROTEIN BINDING		
NPLOC4/TSPAN10: rs9895741	1.16 (1.02 - 1.32)	0.02
HSPH1/B3GALTL: rs9542236	1.21 (1.06 - 1.39)	0.005

*Hazard ratios (HR) and confidence interval (CI) for drusen size progression represent risk per allele, and are adjusted for age, gender, education, smoking, body mass index, drusen size grade at baseline, AREDS treatment and multivitamin supplement use. Eyes were used as the unit of analysis.

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(p<0.001) (*Table 2*). Likewise, adherence to the Mediterranean diet yielded a 17-percent lower risk of progression in patients with medium to high aMeDi scores.

A Kaplan-Meier analysis depicts the association with genetic risk score more clearly (*Figure 2*). Among patients with lower genetic risk scores—that is, below the median—the rates of drusen progression were 6 percent at five years, doubling to 12 percent at 10 years. However, in eyes with higher-than-median genetic risk scores, those rates were doubled or more: 12 percent at five years and 26 percent at 10 years.

Risk alleles linked to drusen growth

Our study findings elucidate the role of specific gene variants and a genetic risk score in the earlier stages of AMD. They provide further evidence that the following genes have a role in drusen progression:

• ***High-impact, rare* CFH *R1210C* mutation.** This mutation has been shown to compromise C-terminal factor H function. Our group has published studies showing the association of this variant with higher drusen burden, earlier age of AMD onset and progression to advanced disease, and also earlier age of progression to advanced stages of AMD.[10,14-17] Our most recent study found an almost sixfold greater risk (HR 5.85, p<0.001) for drusen growth among carriers of this mutation.

• ***Common* C3 *R102G and rare* C3 *K155Q variants.*** These variants impact C3 protein regulation, an implicating factor in AMD.[18,19] Ours is the first study to explore the role these variants have on drusen size progression.

• ***Common variant in the gene locus* ARMS2/HTRA1.** The role of this variant isn't understood as well as the complement pathway in AMD pathogenesis, but it has been implicated in non-advanced AMD.[8,9,11] Our previous study using optical coherence tomography found a link between this variant, along with *CFH* and larger drusen area and volume.[16]

• ***VEGF-A.*** Implicated in advanced AMD, the role of this gene in the angiogenesis pathway has been specifically linked to cell growth and vascular permeability.[20] However, its role in drusen progression is still unclear.

• **TIMP3.** TIMP3 is a tissue inhibitor of metalloproteinase-3, an extracellular matrix protein. A mutation in this gene has been reported to disrupt the retinal pigment epithelial membrane.[21]

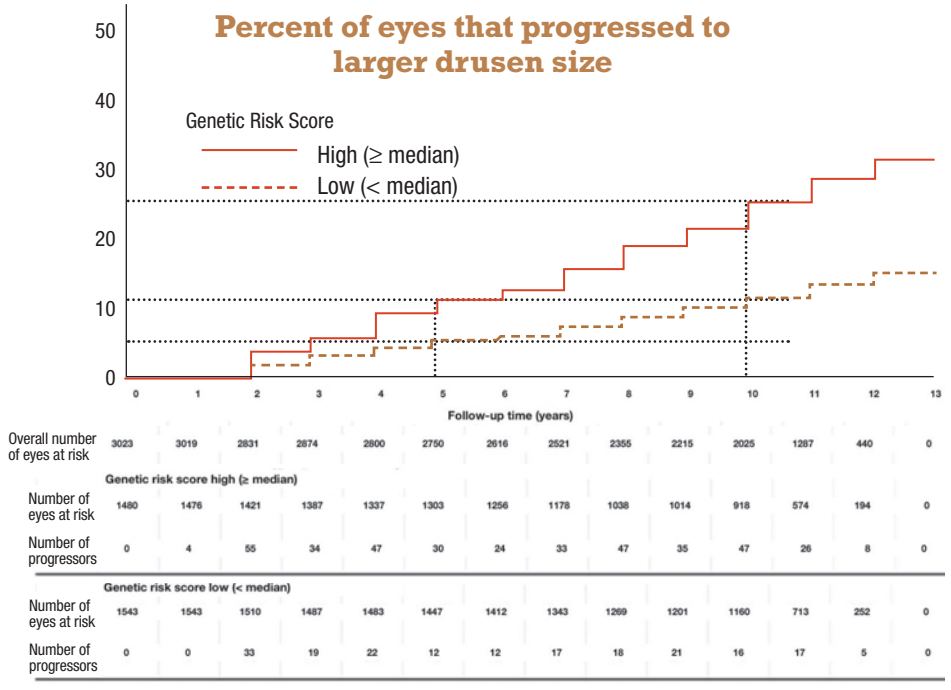

Figure 2. Kaplan-Meier curves for the probability of eyes progressing to larger drusen size (two steps) by follow-up time according to high or low Genetic Risk Score. (Reprinted with permission: Investigative Ophthalmology & Visual Science)

Dietary factors

Prospective studies in the United States and Europe have documented the protective effects of the Mediterranean diet against AMD.[5,13] The elements of the Mediterranean diet have been well documented: fish

rich in omega-3 fatty acids, fruits, vegetables, legumes, olive oil and nuts. These foods contain vitamins and minerals such as vitamins B, C and E, zinc, lutein and zeaxanthin, as well as healthy fats that nourish vision, act as antioxidants and have anti-inflammatory properties.[1,3,4,22,23]

We found lower levels of systemic inflammatory biomarker C-reactive protein in patients who consumed higher concentrations of lutein and zeaxanthin, vitamin C and fish, also supporting the anti-inflammatory role of this type of diet.[24]

Table 2. Association between drusen size progression, genetic susceptibility and Mediterranean diet score[12]

	Progressors Mean (SD)	Non-progressors Mean (SD)	Hazard ratio (95% CI)*	*p* Value
Genetic risk score †	1.06 (0.49)	0.81 (0.45)	2.68 (2.23-3.23)	<0.001
aMeDi score	**n (%)**	**n (%)**		
Low (0 to 3)	212 (21)	796 (79)	Reference	
Medium to high (4 to 9)	375 (19)	1640 (81)	0.83 (0.68-0.99)	0.049

* Hazard ratios calculated using Cox proportional hazards model adjusting for all covariates: age, sex, education, smoking, body mass index, drusen size grade at baseline, total energy intake, AREDS treatment, multivitamin supplement use, genetic risk score (continuous), aMeDi score. For genetic score, HR is the change for one-unit increase. Eyes were used as the unit of analysis.

† Gene score includes 11 variants in eight genes: *CFH Y402H, CFH rs1410996, CFH R1210C, C2, C3 R102G, C3 K155Q, ARMS2/HTRA1 A69S, TIMP3, NPLOC4/TSPAN10, VEGF-A* and *HSPH1/B3GALTL*. aMeDi: alternate Mediterranean Diet; CI: confidence interval.

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Bottom line

We've closed some of the knowledge gaps surrounding factors associated with drusen growth, and we've provided more information on genetic variants that may influence drusen growth that can lead to progression from early to advanced AMD. Recent study results underscore the role a healthy diet may have in the pathogenesis of this disease, even in the earlier stages.[12,25] These findings can help us develop strategies to better manage AMD progression in the most vulnerable patients.

REFERENCES

1. Seddon JM. Macular Degeneration Epidemiology: Nature-Nurture, Lifestyle Factors, Genetic Risk, and Gene-Environment Interactions – The Weisenfeld Award Lecture. Invest Ophthalmol Vis Sci. 2017;58:6513-6528.
2. Seddon JM, Willett WC, Speizer FE, Hankinson SE. A prospective study of cigarette smoking and age-related macular degeneration in women. JAMA. 1996;276:1141-1146.
3. Seddon JM, Ajani UA, Sperduto RD, et al. Dietary carotenoids, vitamins A, C, and E, and advanced age-related macular degeneration. Eye Disease Case-Control Study Group. JAMA. 1994;272:1413-1420.
4. Seddon JM, Cote J, Rosner B. Progression of age-related macular degeneration: Association with dietary fat, transunsaturated fat, nuts, and fish intake. Arch Ophthalmol. 2003;121:1728-1737.
5. Merle BMJ, Silver RE, Rosner B, Seddon JM. Adherence to a Mediterranean diet, genetic susceptibility, and progression to advanced macular degeneration: A prospective cohort study. Am J Clin Nutr. 2015;102:1196-1206.
6. Yu Y, Wagner EK, Souied EH, et al. Protective coding variants in CFH and PELI3 and a variant near CTRB1 are associated with age-related macular degeneration. Hum Mol Genet. 2016;25:5276-5285.
7. Fritsche LG, Igl W, Bailey JNC, et al. A large genome-wide association study of age-related macular degeneration highlights contributions of rare and common variants. Nat Genet. 2016;48:134-143.
8. Seddon JM, Rosner B. Validated prediction models for macular degeneration progression and predictors of visual acuity loss identify high-risk individuals. Am J Ophthalmol. 2019;198:223-261.
9. Yu Y, Reynolds R, Rosner B, Daly MJ, Seddon JM. Prospective assessment of genetic effects on progression to different stages of age-related macular degeneration using multistate Markov models. Invest Ophthalmol Vis Sci. 2012;53:1548-1556.
10. Seddon JM, Reynolds R, Yu Y, Rosner B. Three new genetic loci (R1210C in CFH, variants in COL8A1 and RAD51B) are independently related to progression to advanced macular degeneration. PloS One. 2014;9:e87047.
11. Seddon JM, Silver RE, Kwong M, Rosner B. Risk Prediction for Progression of Macular Degeneration: 10 Common and Rare Genetic Variants, Demographic, Environmental, and Macular Covariates. Invest Ophthalmol Vis Sci. 2015;56:2192-2202.
12. Merle BMJ, Rosner B, Seddon JM. Genetic susceptibility, diet quality, and two-step progression in drusen size. Invest Ophthalmol Vis Sci. 2020:61:17.
13. Merle BMJ, Colijn JM, Cougnard-Grégoire A, et al. Mediterranean diet and incidence of advanced age-related macular degeneration: The EYE-RISK Consortium. Ophthalmology. 2019;126:381-390.
14. Raychaudhuri S, Iartchouk O, Chin K, et al. A rare penetrant mutation in CFH confers high risk of age-related macular degeneration. Nat Genet. 2011;43:1232-1236.
15. Ferrara D, Seddon JM. Phenotypic Characterization of Complement Factor H R1210C Rare Genetic Variant in Age-Related Macular Degeneration. JAMA Ophthalmol. 2015;133:785-791.
16. Seddon JM, Dossett JP, Widjajahakim R, Rosner B. Association between perifoveal drusen burden determined by OCT and genetic risk in early and intermediate age-related macular degeneration. Invest Ophthalmol Vis Sci. 2019;60:4469-4478.
17. Seddon JM, Widjajahakim R, Rosner B. Rare and common genetic variants, smoking, and body mass index: Progression and earlier age of developing advanced age-related macular degeneration. Invest Ophthalmol Vis Sci. 2020; 61:32.
18. Seddon JM, Yu Y, Miller EC, et al. Rare variants in CFI, C3 and C9 are associated with high risk of advanced age-related macular degeneration. Nat Genet. 2013;45:1366-1370.
19. Maller JB, Fagerness JA, Reynolds RC, Neale BM, Daly MJ, Seddon JM. Variation in complement factor 3 is associated with risk of age-related macular degeneration. Nat Genet. 2007;39:1200-1201.
20. Yu Y, Bhangale TR, Fagerness J, et al. Common variants near FRK/COL10A1 and VEGFA are associated with advanced age-related macular degeneration. Hum Mol Genet. 2011;20:3699-3709.
21. Jacobson SG, Cideciyan AV, Bennett J, Kingsley RM, Sheffield VC, Stone EM. Novel mutation in the TIMP3 gene causes Sorsby fundus dystrophy. Arch Ophthalmol. 2002;120:376-379.
22. Reynolds R, Rosner B, Seddon JM. Dietary omega-3 fatty acids, other fat intake, genetic susceptibility, and progression to incident geographic atrophy. Ophthalmology. 2013;120:1020-1028.
23. Merle BMJ, Silver RE, Rosner B, Seddon JM. Dietary folate, B vitamins, genetic susceptibility and progression to advanced nonexudative age-related macular degeneration with geographic atrophy: A prospective cohort study. Am J Clin Nutr. 2016;103:1135-1144.
24. Seddon JM, Gensler G, Klein ML, Milton RC. C-reactive protein and homocysteine are associated with dietary and behavioral risk factors for age-related macular degeneration. Nutrition. 2006;22:441-443.
25. Thompson JT, Seddon JM. Eat Right For Your Sight: Simple, Tasty Recipes That Help Reduce the Risk of Vision Loss from Macular Degeneration. American Macular Degeneration Foundation. New York, NY; The Experiment, LLC; 2015.

Will biosimilars find their place in retina?

With patents expiring, an approval pending and legislation aimed at easing regulations, more biosimilars could be coming. But are retina specialists ready?

Richard Mark Kirkner, Editor

Richard Mark Kirkner, Editor

Take-home points

- Ranibizumab loses patent protection this year in the United States and next year in Europe. Aflibercept comes off patent in 2023 and 2025 in the United States and Europe, respectively.
- An application for a ranibizumab biosimilar has been submitted to the Food and Drug Administration, with another expected later in the year.
- No fewer than eight biosimilar candidates of the two leading anti-VEGF agents are in development.
- In the United States, off-label bevacizumab already provides a low-cost alternative to the approved anti-VEGF agents, a dynamic that may uniquely affect the impact of biosimilars in retina.

Biosimilars are to biologics what generics are to chemical-based drugs, but the biosimilar's clinically inactive components can differ slightly from the reference product.

As patents for ranibizumab and aflibercept approach expiration and one anti-VEGF biosimilar application awaits approval in the United States, interest in biosimilar versions of these biologic agents is peaking. Recent clinical trials of ranibizumab biosimilars have reported equivalence with the reference agent. Major pharma companies, including Novartis and Bausch + Lomb, have taken recent steps to advance their own biosimilar development programs. And President Joseph Biden recently signed legislation aimed at fixing the oft-maligned regulatory pathway for biosimilars.

Biosimilars are replicated versions of biologic agents that may be commercialized once the reference agent comes off patent. Biosimilars are to biologics what generics are to chemical-based drugs, but where the active ingredients of generics are the same as their reference brand-name drugs, the clinically inactive components of biosimilars can differ slightly from the reference product.

Ranibizumab (Lucentis, Genentech/Roche) comes off patent in the United States this year, and loses its European patent protection in 2022, while aflibercept (Eylea, Regeneron Pharmaceuticals) comes off patent in 2023 in the United States and 2025 in Europe.

Clinical trial results

No fewer than eight anti-VEGF biosimilars are under development, four referencing each aflibercept and ranibizumab. South Korea-based Samsung Bioepis and U.S. partner Biogen last year filed for Food and Drug Administration approval for its ranibizumab biosimilar candidate, SB11. This biosimilar candidate was also the subject of one of two trial results published this year.[1] In 705 patients, the trial found SB11 equivalent to the reference drug in terms of best-corrected visual acuity at eight weeks and optical coherence tomography central subfield thickness at four weeks.

The second trial, a 48-week study of FYB201 (Bioeq) in 477 patients with neovascular age-related macular degeneration, found equivalence with reference ranibizumab for BCVA improvement and ocular and systemic safety.[2]

Economics of biosimilars

The appeal of biosimilars is cost. The health information technology/clinical research company IQVIA estimates that overall savings from biosimilars could exceed $100 billion by 2024. "With an average discount range of 15 to 30 percent for the biosimilars thus far, these agents are expected to bring cost savings to some of the most common treatment options for neovascular age-related macular degeneration," says Sonia T. Oskouei, PharmD, vice president of biosimilars for the global health-care services company Cardinal Health. The cost of Lucentis and Eylea is between $1,800 and $2,000 a dose.

But in the United States, with off-label bevacizumab (Avastin, Roche/Genentech) already holding a commanding market share in retina, ophthalmology may be an anomaly among medical specialties in which biologics use is widespread. Medicare and commercial payers typically reimburse between $50 and $125 for an injection of Avastin.

For pharmaceutical companies, anti-VEGF drugs have been a big payday. Regeneron reported $4.95 billion in Eylea sales in 2020. Bayer, distributor of Eylea outside the United States, recorded $3 billion in sales of that agent in 2020. Roche, parent company of Genentech, reported U.S. sales of $1.3 billion for Lucentis last year, a decline of 16 percent from the previous year. Novartis, which holds Lucentis rights outside the United States, reported $1.93 billion in Lucentis sales in 2020.

Overcoming regulatory barriers

In the United States, the regulatory pathway for biosimilars has historically been dodgy. Congress passed the Biologics Price Competition and Innovation Act (BPCIA) in 2010 that, in effect, was supposed to create an abbreviated regulatory approval process for biologic products that are "highly similar" to and have no clinically meaningful differences from a previously approved product. But the Food and Drug Administration was slow in writing regulations. Biosimilars developers became frustrated with how the agency defined "interchangeability," which allows a pharmacist to substitute a biosimilar for the reference product. Over the years, a series of FDA commissioners pledged to fix the process, to little avail.

This spring, President Biden signed two pieces of legislation that could make biosimilars more widely available. In April he signed the Advancing Education on Biosimilars Act. Meaghan Rose Smith, executive director of the trade group Biosimilars Forum, says the law is "to

Eight biosimilars in the retina pipeline

Here's a quick look at potential biosimilars under development.

Ranibizumab biosimilars are:

- **SB11.** Samsung Bioepis and Biogen filed marketing authorization applications late last year with the Food and Drug Administration and the European Medicines Agency.
- **FYZB201.** Formycon and partner Bioeq say they intend to file with the FDA in the first half of this year.
- **ONS-5010/Lytenava.** Outlook Theraperutics in March reported positive safety outcomes of the NORSE THREE open-label study and says the Phase III NORSE TWO trial should report results in the third quarter this year. The company anticipates an FDA biologics license application by the end of the year.
- **Xlucane.** Bausch + Lomb entered into an agreement with STADA Arzneimittel of Germany and its development partner, Sbrane of Sweden, to commercialize this candidate in the United States and Canada.

Aflibercept biosimilars include:

- Sandoz, a division of Novartis, reports that it's ready to enroll the first patients in the Phase III MYLIGHT trial of its unnamed candidate.
- **ALT-L9.** South Korea-based Alteogen reported in April that it completed a Phase I trial. The findings showed equivalent efficacy in 28 patients with neovascular age-related macular degeneration. Alteogen says the findings may provide a path to a shorter Phase III trial.
- **CT-P42.** In February Celltrion initiated a Phase III trial.
- **LY9004.** Luye Pharma's biotech subsidiary Boan has licensed LY9004 to China-based Ocumension Therapeutics. The asset is in Phase III trials in China.

ensure that patients and providers have all of the educational resources and materials they need to be assured of the safety and efficacy of biosimilars." The Biosimilars Forum notes the bill requires the FDA to advance education and awareness among healthcare providers about biological products. That includes developing or improving continuing education programs.

In India, Ashish Sharma, MD, has seen the impact of biosimilars in retina, but explains why that may not translate to the United States.

The bill also empowers the FDA to host a website that provides educational materials to providers, patients and caregivers, regarding the meaning of the terms, and the standards for review and licensing of, biological products, including biosimilars.

In May Biden signed the Ensuring Education Act, which would tighten regulations on what biologics and chemical-based drugs qualify for product exclusivity protection. The Center for Biosimilars says the law would close loopholes that let pharmaceutical companies get patent protections for drugs that don't represent true innovations.

"The Advancing Education on Biosimilars Act is intended to lower healthcare costs by strengthening provider and patient confidence in biosimilars through enhanced educational efforts, thereby increasing utilization," says Cardinal Health's Dr. Oskouei.

It should, she adds, help providers better understand terms embedded in the BPCIA, such as *interchangeability* and *extrapolation* (the regulatory principle of extrapolating efficacy and safety data from one indication to another if trials show biosimilarity to the reference product).

"The bottom line is that there is an overall lack of familiarity, and therefore comfort, with biosimilars amongst ophthalmologists."
— Sonia Oskouei, PharmD

Retina specialists need some of that education

In an opinion piece for The Center for Biosimilars, Dr. Oskouei reported on results of a survey of 37 community-based retina specialists.[3] The survey found that 31 percent said they're not very familiar with biosimilars, and 55 percent said they've read research about them but aren't familiar with specifics. However, 83 percent said they thought biosimilars would fit into their treatment regimens and would help keep drug costs down, and more than half said they would consider using a biosimilar of ranibizumab or aflibercept.

"The bottom line is that there is an overall lack of familiarity, and therefore comfort, with biosimilars amongst ophthalmologists," Dr. Oskouei says. "There is a significant need for biosimilar education amongst ophthalmologists, especially as we anticipate our first ophthalmology biosimilar later this year."

The Cardinal Health survey has since been updated. Dr. Oskouei says that responses from 75 U.S. retina specialists revealed that 24 percent thought biosimilars' clinical trials aren't adequately powered to appropriately evaluate efficacy and safety. And 35 percent said they have "very limited knowledge" of what goes into designing clinical trials for biosimilars.

"When asked about primary concerns with prescribing biosimilars once available, 'uncomfortable from a clinical standpoint' and 'payer coverage concerns' were equally rated as the top answers across all respondents," she says.

Then there's the Avastin dynamic. "In addition to the clinical comfort aspect with biosimilars, there is a strong desire to understand the financial implications of these products as well, especially given common use of low cost, off-label bevacizumab currently in ophthalmology," Dr. Oskouei adds.

(Continued on page 38)

Clearing up E/M 'clarifications'

The AMA issued new evaluation and management guidelines that can be hard to appreciate.

By Ellen R. Adams, MBA

The 2021 evaluation and management guidelines from the American Medical Association have a straightforward premise: Code your visit based on problems, data and management, and don't count history and exam elements. Yet, there are some points in these guidelines that are hard to appreciate, especially in light of recent clarifications the AMA published in March.[1] I'll review them here.

Minor and major surgery

The first, and probably most confusing, statement the AMA made is that minor and major surgery aren't defined by the postoperative period. It states:

> *The classification of surgery into minor or major is based on the common meaning of such terms when used by trained clinicians, similar to the use of the term "risk." These terms are not defined by a surgical package classification.*

It seems unlikely that Medicare or other third-party payers would agree that surgery with a zero- or 10-day postoperative period could be considered "major." The Medicare Claims Processing Manual Chapter 12, §40, states, "… a national definition of a global surgery package has been established …" The remainder of this section describes in great detail billing requirements for major and minor procedures, and the associated modifiers, so Medicare will probably use these definitions and principles established in 1992 rather than overlook them.

Although a physician may argue that prophylaxis of retinal tear (67145, 90-day global period) and repair of retinal detachment by laser (67105, 10-day global) have comparable management risk profiles, how would the "common meaning" be objectively assessed and supported in the medical record?

The distinction is important because a major surgery supports a moderate management level; a major surgery with identified risk factors supports a high management level. Conversely, a minor surgery supports a low management level; minor surgery with identified risk factors supports a moderate management level.

Table 1. Examples of major ocular surgeries with identified risk factors

- Complex cataract surgery with apparent loose zonules
- Complex retinal detachment repair after severe head injury
- Eyelid surgery in patient with blood dyscrasia
- Intravitreal injection of vitreous substitute in suprachoroidal hemorrhage
- Late wound repair with apparent infection and necrosis
- Ophthalmic surgery with known abnormal anesthesia risk
- Repeat invasive glaucoma surgery (e.g., trabeculectomy)
- Repeat keratoplasty due to failed graft

Identified risk factors for surgery

All surgery has risks, but identified risk factors for surgery are those that are exceptional rather than typical, and the physician emphasizes them in the informed consent. Table 1 lists a few major procedures with identified risk factors. Table 2 (*page 36*) lists a few minor procedures with identified risk factors.

So, an office visit that concludes with a plan for an anti-VEGF injection for chronic exudative age-related macular degeneration supports a low management level because it's a minor procedure, but an anti-VEGF injection in a one-eyed patient supports a moderate level based on the additional identified risk factor.

Have a question for "Coding Commentary"? Tweet it to us at **@RetSpecMag**

Bio

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The AMA's guidelines would be easier to appreciate if they included examples. While those examples may be developed and published later on, the 2021 CPT manual doesn't contain them.

Services reported separately

The March AMA guideline further explained another complex part of E/M: services reported separately. The guideline states:

> *Any specifically identifiable procedure or service (i.e., identified with a specific CPT code) performed on the date of E/M services may be reported separately. The ordering and actual performance and/or interpretation of diagnostic tests/studies during a patient encounter are not included in determining the levels of E/M services when the professional interpretation of those tests/studies is reported separately by the physician or other qualified health care professional reporting the E/M service.*

Because ophthalmologists commonly order imaging procedures, such as scanning computerized ophthalmic diagnostic imaging, fundus photography and angiography, on the day of the visit, necessitating an interpretation and report on the same day, all of these diagnostic tests fall within the meaning of services reported separately. Thus, the level of data is none for E/M.

Only notes and diagnostic tests that "… are from an external physician, other qualified health care professional, facility, or health care organization" can count for the level of data. Furthermore, notes and diagnostic tests from a "unique source count as one element."

Data elements

The update defines "a unique source … as a physician or qualified heath care professional in a distinct group or different specialty or subspecialty, or a unique entity." For example, a new patient is referred by a comprehensive ophthalmologist in the community who's not part of your practice for E/M of AMD. The patient arrives with five years of medical records including eye exams, optical coherence tomography scans and visual fields. This counts as one data element from a single, external source.

Besides external notes and tests, data elements may also include the following:

- an independent historian, such as a parent, guardian, spouse, caregiver or witness;
- independent interpretation of a test or tests performed by another physician and not reported separately;
- orders for tests direct to other providers or facilities; and
- discussion with another physician outside of your group.

AMA provided more clarity about these discussions

Discussion requires an interactive exchange. The exchange must be direct and not through intermediaries (e.g., clinical staff or trainees). Sending chart notes or written exchanges that are within progress notes doesn't qualify as an interactive exchange. The discussion doesn't need to be on the date of the encounter, but it's counted only once and only when it's used in the decision making of the encounter. It may be asynchronous (i.e., it doesn't need to be in person), but it must be initiated and completed within a short time period (e.g., within a day or two).

As a practical matter, a claim for an office visit would typically not be held for a delayed

(Continued on page 38)

Table 2. Examples of minor ocular surgeries with identified risk factors

- Emergency laser peripheral iridotomy for angle-closure attack
- Foreign body penetrating the cornea into anterior capsule
- Intravitreal injection of anti-VEGF in patient with one eye
- Major trichiasis (five or more cilia) in ocular pemphigoid
- Photodynamic therapy for ocular tumor
- Peripheral iridotomy for rubeosis
- Probe nasolacrimal duct under general anesthesia in a child
- Panretinal photocoagulation for nystagmus
- Removal of retained foreign body in cornea with infection

How THR-149 targets alternate pathway

The plasma kallikrein inhibitor is being investigated to treat diabetic macular edema that doesn't respond to anti-VEGF therapy.

By Richard Mark Kirkner, Editor

Oxurion is in the unique position of pursuing two candidates to treat exudative retinal disease on parallel tracks: the plasma kallikrein inhibitor THR-149 for diabetic macular edema that doesn't respond to anti-VEGF therapy; and the small-molecule pan-RGD integrin antagonist THR-687, which the company says is a potential first-line treatment for DME.

The Phase II KALAHARI trial of THR-149 is currently recruiting, with a readout due later this year. Arshad Khanani, MD, MA, managing partner and director of clinical research and fellowship at Sierra Eye Associates in Reno, Nevada, and a clinical associate professor at the University of Nevada, answers questions about the trial. Dr. Khanani is a consultant to and receives research support from Oxurion.

Q Please describe the mechanism of action of THR-149 in your own words.

A THR-149 is a highly potent, subnanomolar reversible inhibitor of human plasma kallikrein (PKal). Plasma kallikrein is a serine protease, which has been implicated in many physiological and pathological processes. The plasma kallikrein kinin system (KKS) is activated during vascular injury. KKS activation leads to PKal activation, which triggers the release of the vasoactive peptide bradykinin.

Intraocular activation of the KKS has been shown to increase retinal vascular permeability and retinal thickening, and these responses are exacerbated in diabetic animals. PKal deficiency and pharmacological inhibition of PKal lowers bradykinin levels and reduces retinal edema.

Encouraging preclinical data have shown the potency and efficacy of bicyclic peptide inhibitors of PKal such as THR-149.[1]

Q What's the rationale for targeting DME in the Phase II KALAHARI trial?

A The rationale for targeting DME is twofold. On the one hand, while both vascular endothelial growth factor and PKal levels are increased in the vitreous of DME patients, their levels don't correlate. Some patients exhibit high levels of PKal but low to non-detectable levels of VEGF.[2] These observations imply that additional mechanisms beside VEGF upregulation play a role in mediating DME, and that PKal and KKS may contribute to DME in a VEGF-independent manner.

On the other hand, a significant fraction (40 percent) of the patients treated with current standard-of-care treatments such as anti-VEGF drugs respond suboptimally. Therefore, it's important to identify other targets, such as PKal, in DME. Anti-PKal therapy represents an attractive treatment option, in particular, for patients responding suboptimally to current standard-of-care treatment.

Preclinical and early clinical data strongly support the role of PKal in the development of DME.

Q Please describe the design of the Phase IIa and IIb trials.

A The Phase II study consists of two parts. Part A is a randomized, single masked, parallel group, dose-finding study including three injections of THR-149, one month apart in three dose levels (low dose 0.01 mg; medium dose 0.04 mg; and high dose 0.13 mg). Six patients will be randomized in each dose level and followed for six months. A safety monitoring committee will select the optimal dose for inclusion into the Part B of the study.

In part B, which is the randomized, double-masked, active-controlled phase of the study with two treatment arms, the selected dose of THR-149 will be compared to aflibercept in 104 patients in a 1:1 randomization ratio. Patients in each arm will receive

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three injections one month apart and will be followed for six months.

The Phase II study will evaluate THR-149 as a monotherapy in patients with persistent central involved DME despite prior treatment with anti-VEGF. The data of the Phase II study is expected to inform us on whether THR 149 can be the best second-line treatment for DME patients.

Q Where would THR-149 potentially fit in the retina specialist's toolbox?

A Subject to data, I could envision THR-149 claiming its place as a monotherapy in patients with persistent central-involved DME despite prior treatment with anti-VEGF therapy. THR-149 definitely holds potential as a first-in-class, second-line treatment for DME.

Further down the road, I could even envision the use of THR-149 in combination with anti-VEGF for treatment-naïve patients.

Q What else can you tell us about THR-149?

A It's important to look at new mechanisms of action beyond VEGF inhibition to treat our patients with DME. THR-149 fits in that category as it has a novel mechanism of action and has shown good safety and efficacy signals in the Phase I trial. I continue to be very excited about this program as an investigator and look forward to seeing the efficacy and safety results of THR-149 from the Phase II trial in the near future.

REFERENCES

1. Teufel DP, Bennett G, Harrison H, et al. Stable and long-lasting, novel bicyclic peptide plasma kallikrein inhibitors for the treatment of diabetic macular edema. J Med Chem. 2018;61:2823-2836.
2. Kita T, Clermont AC, Murugesan N, et al. Plasma kallikrein-kinin system as a VEGF-independent mediator of diabetic macular edema. Diabetes. 2015;64:3588-3599.

Clearing up E/M language

(Continued from page 36)

discussion. A discussion on the same day as the office visit is preferred. Finally, because data can come from more than one source and take different forms, the AMA further states:

> *A combination of different data elements, for example, a combination of notes reviewed, tests ordered, tests reviewed, or independent historian, allows these elements to be summed. It does not require each item type or category to be represented. A unique test ordered, plus a note reviewed and an independent historian, would be a combination of three elements.*

Experience has shown that data don't figure often in determining medical decision-making for E/M for ophthalmologists because most are for services reported separately rather than from an external source.

Bottom line

This year we will enjoy a honeymoon from payer audits of E/M as we learn and apply the new E/M guidelines. Grasping the new concepts and definitions requires study and some careful thought. Fine discrimination between the service levels will largely depend on the chart notes in the assessment and plan rather than the history and exam. It's hoped that the new guidelines will lead to greater coding accuracy. But, as I note here, a few areas of the evolving guidelines are subtle and potentially challenging.

REFERENCE

1. American Medical Association CPT Evaluation and Management Office or Other Outpatient (99202=99215) and Prolonged Services (99354, 99355, 99356, 99417) Code and Guideline Changes. January 1, 2021, updated March 9, 2021. Available at: https://www.ama-assn.org/system/files/2019-06/cpt-office-prolonged-svs-code-changes.pdf

FEATURE Biosimilars

Biosimilars in retina

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Unicorn anti-VEGF market

As a retina specialist in Coimbatore, India, Ashish Sharma, MD, has first-hand experience with anti-VEGF biosimilars. The first commercialized ranibizumab biosimilar was launched there in 2015, and he's reported on a number of biosimilar trials at U.S. meetings.

He also understands why the U.S. market is different. "In the United States, with Avastin, you have good compounding pharmacies, so that means, in the U.S. physicians' hands, Avastin is being used quite well, with a lot of safety," he says.

However, in India and other countries, anti-VEGF biosimilars hold greater promise. "In India and probably in many other developing countries, we do not have that kind of robust compounding pharmacy system," he says.

With the first biosimilar nearing approval here, U.S. retina specialists will soon find out how that fits with Avastin in their practice.

REFERENCES

1. Woo SJ, Veith M, Hamouz J, et al. Efficacy and safety of a proposed ranibizumab biosimilar product vs a reference ranibizumab product for patients with neovascular age-related macular degeneration: A randomized clinical tria JAMA Ophthalmol. 2021;139:68–76.
2. Holz FG, Oleksy P, Ricci F, Kaiser PK, Kiefer J, Schmitz-Valckenberg S. Efficacy and safety of biosimilar FYB201 compared with ranibizumab in neovascular age-related macular degeneration. Ophthalmology. Published online May 2, 2021.
3. Oskouei ST. Opinion: Is the ophthalmology market ready to embrace biosimilars? Center for Biosimilars website. Posted January 16, 2021. Available at: https://www.centerforbiosimilars.com/view/is-the-ophthalmology-market-ready-to-embrace-biosimilars- Accessed April 27, 2021.

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