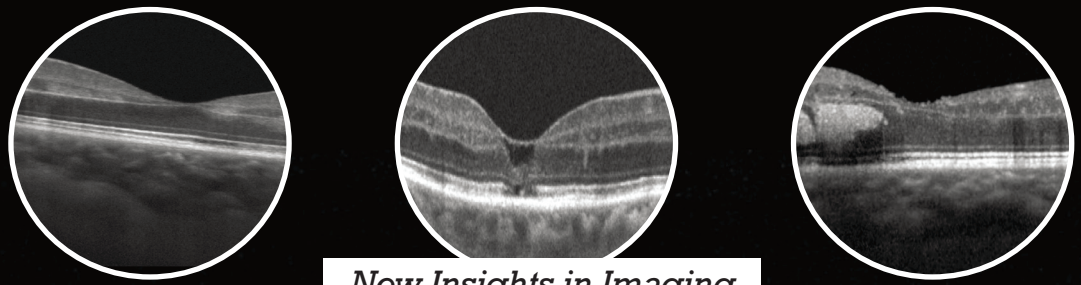
A PUBLICATION BY REVIEW of OPHTHALMOLOGY

RETINA SPECIALIST

VOL. 8, NO. 3 • MAY/JUNE 2022



New Insights in Imaging

Can you recognize these novel OCT signs?

Characteristic findings that can aid in diagnosis. *Page 18*

OCT biomarkers in uveitis: An update *Page 23*

What's the potential for home-based OCT? *Page 30*

Also Inside

VABYSMO™
faricimab-svoa injection 6 mg

NOW AVAILABLE

INDICATIONS

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

IMPORTANT SAFETY INFORMATION

Contraindications

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

Warnings and Precautions

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

Adverse Reactions

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

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

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

*Dosing Information:

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

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

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

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

References: 1. VABYSMO [package insert]. South San Francisco, CA: Genentech, Inc; 2022. **2.** Beovu® (brolucizumab) [package insert]. East Hanover, NJ: Novartis; 2020. **3.** Eylea® (aflibercept) [package insert]. Tarrytown, NY: Regeneron Pharmaceuticals, Inc; 2021. **4.** LUCENTIS® (ranibizumab) [package insert]. South San Francisco, CA: Genentech, Inc; 2018. **5.** SUSVIMO™ (ranibizumab injection) [package insert]. South San Francisco, CA: Genentech, Inc; 2021.

Genentech
A Member of the Roche Group

THE WINDOW TO CHANGE

VABYSMO™
faricimab-svoa injection 6 mg

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

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

1 INDICATIONS AND USAGE

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

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

1.2 Diabetic Macular Edema (DME)

4 CONTRAINDICATIONS

4.1 Ocular or Periocular Infections

VABYSMO is contraindicated in patients with ocular or periocular infections.

4.2 Active Intraocular Inflammation

VABYSMO is contraindicated in patients with active intraocular inflammation.

4.3 Hypersensitivity

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

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis and Retinal Detachments

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

5.2 Increase in Intraocular Pressure

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

5.3 Thromboembolic Events

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

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

The incidence of reported ATEs in the DME studies during the first year was 2% (25 out of 1,262) in patients treated with VABYSMO compared with 2% (14 out of 625) in patients treated with aflibercept *[see Clinical Studies (14.2)]*.

6 ADVERSE REACTIONS

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

- Hypersensitivity *[see Contraindications (4)]*
- Endophthalmitis and retinal detachments *[see Warnings and Precautions (5.1)]*
- Increase in intraocular pressure *[see Warnings and Precautions (5.2)]*
- Thromboembolic events *[see Warnings and Precautions (5.3)]*

6.1 Clinical Trial Experience

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

The data described below reflect exposure to VABYSMO in 1,926 patients, which constituted the safety population in four Phase 3 studies *[see Clinical Studies (14.1, 14.2)]*.

Table 1: Common Adverse Reactions (≥ 1%)

Adverse Reactions	VABYSMO		Active Control (aflibercept)	
	AMD N=664	DME N=1262	AMD N=622	DME N=625
Conjunctival hemorrhage	7%	7%	8%	6%
Vitreous floaters	3%	3%	2%	2%
Retinal pigment epithelial tear[a]	3%		1%	
Intraocular pressure increased	3%	3%	2%	2%
Eye pain	3%	2%	3%	3%
Intraocular inflammation[b]	2%	1%	1%	1%
Eye irritation	1%	1%	< 1%	1%
Ocular discomfort	1%	1%	< 1%	< 1%
Vitreous hemorrhage	< 1%	1%	1%	< 1%

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

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

6.2 Immunogenicity

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

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

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

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

Data

Animal Data

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

8.2 Lactation

Risk Summary

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

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

8.3 Females and Males of Reproductive Potential

Contraception

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

Infertility

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

8.4 Pediatric Use

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

8.5 Geriatric Use

In the four clinical studies, approximately 60% (1,149/1,929) of patients randomized to treatment with VABYSMO were ≥ 65 years of age. No significant differences in efficacy or safety of faricimab were seen with increasing age in these studies. No dose adjustment is required in patients 65 years and above.

17 PATIENT COUNSELING INFORMATION

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

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

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

M-US-00013249(v1.0) 2/22

RETINA
SPECIALIST

19 Campus Blvd., Suite 101
Newtown Square, PA 19073
Telephone (610) 492-1000
Fax (610) 492-1039

Editorial inquiries (610) 492-1000
Advertising inquiries (610) 492-1011
E-mail retinaspecialist@jobson.com

Jobson Medical Information

EDITORIAL

By Charles C. Wykoff, MD, PhD

OCT-ologists

Optical coherence tomography is indispensable for retina care delivery in the United States. *Wait*, you think to yourself, *my 78-diopter exam is pretty good!*

To quickly be reminded how desperately we need OCT to complement our examinations in order to accurately diagnose and manage our patients, try examining a few new patients before you look at their OCT.

The first commercial units were released 26 years ago, and since then the hardware and software functionalities have advanced tremendously. Currently, most clinical units use spectral-domain technology with resolution of up to 2 µm, representing 1/50th the diameter of a strand of hair, or one-quarter the width of an erythrocyte. Repeated scanning over short periods enables OCT-angiography, which is slowly being incorporated into routine practice.

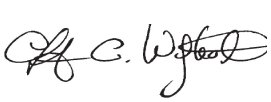
Most commonly, we utilize OCT to determine the presence, absence or change in fluid status associated with exudative retinal diseases. But, the utility of OCT extends far beyond management of these common causes of blindness. We identify nonexudative macular neovascular lesions, hunt for subtle fundings suggestive of photoreceptor dysfunction and assess vitreous status and choroidal thickness in order to inform accurate diagnoses, to name just a few additional uses.

Descriptions of OCT findings have exploded into an alphabet-soup of clinically relevant acronyms (FCE, ORT, PAMM, AMN, SIRE, etc.) and graphic metaphors of imaging patterns (flying saucer sign, pearl necklace sign, cotton ball sign, etc.). Please see Dr. Caroline Baumal's and Dr. Dilraj Grewal's pieces for excellent summaries of important and more nuanced OCT findings on pages 18 and 23.

Despite our obsession with OCT, it's notable that the Food and Drug Administration has not accepted any OCT findings as approvable clinical trial endpoints for new therapeutics. So far, visual outcomes are the primary basis for FDA approval, although a precedence for anatomic endpoints is emerging.

For example, score changes on the Diabetic Retinopathy Severity Scale have led to approvals for diabetic retinopathy. Looking ahead, we may have our first approved therapeutic for geographic atrophy in the coming months, based on anatomic assessment through longitudinal fundus autofluorescence changes.

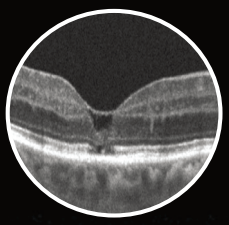
Consistent with the FDA emphasis on vision, as important as OCT is to us, we must hear our patients when they repeatedly direct us back to function. Our patients want to see better today and tomorrow, with as few interventions as possible. We must continue aspiring to connect our OCT biomarkers with functional, prognostic or diagnostic relevance in order to guide better care for our patients. RS

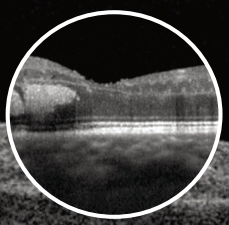


A PUBLICATION BY REVIEW of OPHTHALMOLOGY
RETINA SPECIALIST
MAY/JUNE 2022 • VOL. 8, NO. 3

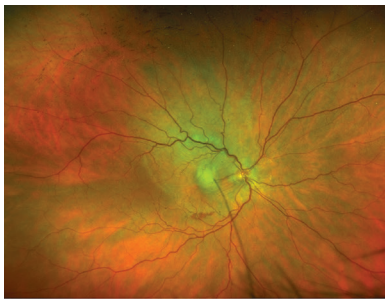
FEATURES

New Insights in Imaging





DEPARTMENTS



New DME treatment trial targets underrepresented populations

A principal investigator of a Phase IV postmarket study of Vabysmo (faricimab) in patients who have diabetic macular edema says the study aims to determine if the drug works as well in underrepresented minorities as it did in Phase III clinical trials that led to its approval by the Food and Drug Administration earlier this year.

"With this study, our goal is to see if we can improve our scientific understanding of diabetic macular edema and to improve the standard of care for all patients, not just the patients that were in the majority in previous DME clinical trials," Matthew A. Cunningham, MD, a principal study investigator at his practice, Florida Retina Institute in Orlando, tells *Retina Specialist*.

The FDA approved intravitreal Vabysmo (Genentech/Roche) for DME based on results of the YOSEMITE and RHINE trials.[1] However, Dr. Cunningham notes, the percentage of minority populations in those trials, similar to previous DME trials, "was not representative of the population at large."

Diabetes disparities

The Phase IV trial, known as Elevatum (NCT05224102), will enroll around 120 patients in the United States and globally. Eligible patients must self-identify as Black/African American, Hispanic/Latino, Native American, Native Alaskan, Native Hawaiian or Pacific Islander. They must have active DME and be treatment-naive.

Matthew A. Cunningham, MD

A study of national databases in 2017 reported the incidence of type 2 diabetes is 9 percent in Asians, 13.2 percent in African Americans, 12.8 percent in Hispanics and 7.6 percent in non-Hispanic Whites.[2] In the Native American population, incidence ranged from 6 percent in Alaskan Natives to 24.1 percent in southern Arizona Native American groups. Subgroups within those identifying as Hispanic also had wide disparities, ranging from 8.5 percent in Central/South Americans to 14.8 percent in those identifying as Puerto Rican.

"Within our underrepresented patient population, we know that this population is disproportionately affected by diabetes and, as a whole they are at a higher risk of developing diabetic macular edema," Dr. Cunningham says. "There's an historical lack of diversity in clinical trials in ophthalmology and Elevatum, to my best knowledge, is the first industry-sponsored trial to attempt to address this, specifically looking in the DME space."

Trial design

Elevatum is a multicenter, open-label, single-arm trial in which the first patient was recently dosed. The primary endpoint is change from baseline in best corrected visual acuity at week 56, as measured on the Early Treatment Diabetic Retinopathy Study chart.

Secondary endpoints include safety, the percentage of patients who achieve at least two- and three-step improvement from baseline in the ETDRS Diabetic Retinopathy Severity Scale at weeks 20 and 56, and the percentage with absence of intraretinal fluid over time. Other key secondary endpoints are changes in subretinal fluid and central subfield thickness, BCVA improvement and levels of anti-drug antibodies against Vabysmo. Results are expected in 2024.

Elevatum is using criteria for hemoglobin A1c that's broader than typical studies in diabetes, Dr. Cunningham adds. "Many studies won't include patients because their HbA1c is greater than 10 percent," he says. "In Elevatum that's been broadened

IN BRIEF

Prevent Blindness and **Regeneron Pharmaceuticals** have partnered to expand their "Diabetes and the Eyes" education program to include a video series for both English and Spanish speakers, community-level health education and support, and new materials about how the disease impacts vision.

A clinical trial of photobiomodulation to treat dry age-related macular degeneration has shown a mean increase of 5.5 letters in 91 treated eyes after 13 months. The LIGHTSITE III prospective trial is evaluating the **Valeda** light delivery system **(LumiThera).** The results were presented at the 2022 Sonoma Eye Meeting.

Apellis Pharmaceuticals reports that 18-month results from the Phase III DERBY and OAKS trials of intravitreal **pegcetacoplan** show continued reduction in geographic atrophy lesion growth. Apellis says it will submit a New Drug Application to the Food and Drug Administration by summer.

so that in up to 20 percent of participants, A1c may be up to 12 percent. That will hopefully ease one of the known barriers for clinical trial participation in this population."

He notes that his site is participating because it has a higher proportion of underserved patients than the typical retina practice. The study offers participants compensation, meal stipends and assistance with transportation. "We're trying to address some of these issues to give the patient one less thing to think about when it comes to being included or enrolled in the study," Dr. Cunningham says.

Dr. Cunningham is a paid consultant for Genentech/Roche, as well as Alimera Sciences and Allergan/AbbVie .

— Richard Mark Kirkner

REFERENCES

1. Wykoff CC, Abreau F, Adamis AP, et al. Efficacy, durability, and safety of intravitreal faricimab with extended dosing up to every 16 weeks in patients with diabetic macular oedema (YOSEMITE and RHINE): Two randomised, double-masked, phase 3 trials. Lancet. 2022:399:741-755.
2. Ferdinand KC, Nasser SA. Racial/ethnic disparities in prevalence and care of patients with type 2 diabetes mellitus. Curr Med Res Opin 2015;31:913–923

RPE patch shows survivability after two years

An allogeneic retinal pigment cell transplant developed to treat severe vision loss from geographic atrophy has been shown to survive after two years without signs of inflammation or immune rejection, according to a recent paper in the journal *Stem Cell Reports*.[1]

In earlier results from the Phase I/IIa trial, the transplantable patch, known as CPCB-RPE1 (Regenerative Patch Technologies), was shown to be safe and well-tolerated out to a year.[2]

CPCB-RPE1 is a bioengineered implant consisting of stem cell-derived, mature, polarized retinal pigment epithelial cells on a synthetic parylene membrane. It's placed in a subretinal bleb overlying the area of GA to replace damaged RPE and Bruch's membrane.

Postmortem histology

In the most recent study, researchers evaluated the implant in the eye of an 84-year-old patient who died from pneumonia two years after receiving the implant. Postmortem histology confirmed that the cells on the transplant patch had survived, that they hadn't migrated and were oriented in the optimal polarized position. Mohamed Faynus, a graduate student researcher in the laboratory of stem cell biologist Dennis O. Clegg, PhD, at the University of California Santa Barbara, says that provides evidence the cells maintained functionality.

The researchers also found that after two years, the patch hadn't triggered neovascularization or scarring that could cause a retinal detachment. They also found no clinical sign of the inflammation that would indicate an immune response to the foreign cells, even after the patient was taken off immunosuppressants two months post-implantation.

"This is the first study of its kind and it indicates that the implanted RPE cells can survive and function, even in what could be a toxic environment of a diseased eye," Dr. Clegg says.

Dr. Clegg holds equity in and is a consultant to Regenerative Patch Technologies.

REFERENCE

1. Kashani AH, Lebkowski JS, Hinton DR, et al. Survival of an HLA-mismatched, bioengineered RPE implant in dry age-related macular degeneration. Stem Cell Rep. 2022;17:448-458.
2. Kashani AH, Lebkowski JS, Rahhal FM, et al. A bioengineered retinal pigment epithelial monolayer for advanced, dry age-related macular degeneration. Sci Transl Med. 2018;10:eaao4097.

RETINA SPECIALIST

BUSINESS OFFICES
19 CAMPUS BOULEVARD, SUITE 101
NEWTOWN SQUARE, PA 19073
SUBSCRIPTION INQUIRIES (877) 529-1746
(USA ONLY); OUTSIDE USA, CALL (847) 763-9630

BUSINESS STAFF
PUBLISHER
MICHAEL HOSTER
(610) 492-1028 MHOSTER@JOBSON.COM

REGIONAL SALES MANAGER
MICHELE BARRETT
(610) 492-1014 MBARRETT@JOBSON.COM

REGIONAL SALES MANAGER
JONATHAN DARDINE
(610) 492-1030 JDARDINE@JOBSON.COM

CLASSIFIED ADVERTISING
(888)-498-1460

PRODUCTION MANAGER
FARRAH APONTE
(212) 274-7057 FAPONTE@JOBSON.COM

SUBSCRIPTIONS
US ONE YEAR: $63.00
CANADIAN ONE YEAR: $99.00
FOREIGN ONE YEAR: $158.00
SUBSCRIPTIONS E-MAIL:
SUBSCRIPTIONS@MDEDGE.COM

CIRCULATION
RETINA SPECIALIST
10255 W HIGGINS ROAD, SUITE 280
ROSEMONT, IL 60018.

DIRECTOR, CIRCULATION
JARED SONNERS
jsonners@mdedge.com

CEO, INFORMATION GROUP SERVICES
MARC FERRARA

SENIOR VICE PRESIDENT, OPERATIONS
JEFF LEVITZ

VICE PRESIDENT, HUMAN RESOURCES
TAMMY GARCIA

VICE PRESIDENT, CREATIVE SERVICES & PRODUCTION
MONICA TETTAMANZI

SENIOR CORPORATE PRODUCTION DIRECTOR
JOHN ANTHONY CAGGIANO

DIRECTOR, CIRCULATION
JARED SONNERS

Jobson Medical Information LLC,
395 Hudson Street, 3rd Floor, New York, NY 10014

A ser(i)ous detachment

How multimodal imaging and systemic examination helped uncover the underlying etiology of a longstanding choroidal neovascular membrane.

By Abtin Shahlaee, MD, and Jason Hsu, MD

Abtin Shahlaee, MD

Jason Hsu, MD

A 59-year-old Caucasian male with a history of hypertension was referred for several months of painless vision loss in the right eye. He reported having central vision loss with worsening of symptoms over the preceding month. Peripheral vision was normal in both eyes. The patient had no known refractive error or notable ocular or surgical history.

Examination and imaging

On presentation, visual acuity was hand motion in the right eye and 20/25 in the left. Intraocular pressures were normal, extraocular movements were full and the pupillary exam was intact. The anterior segment examination was unremarkable.

Fundoscopic examination of the affected eye demonstrated a large serous detachment with a subretinal white lesion in the central macula and a sliver of subretinal hemorrhage (*Figure 1*). The fellow eye had circumpapillary pigmentary changes. On intravenous fluorescein angiography, the affected eye displayed a large central focus of leakage consistent with choroidal neovascularization (*Figure 2*).

Optical coherence tomography showed marked subretinal and intraretinal fluid and a hyperreflective subretinal lesion (*Figure 3*). In the fellow eye, a focal disruption in Bruch's membrane adjacent to the disc was evident.

Fundus autofluorescence of the affected eye demonstrated a mixed stippled autofluorescence pattern, while in the fellow eye speckled radial linear hyper-autofluorescence patterns were visible emanating from the disc, consistent with angioid streaks (*Figure 4, page 10*).

On physical exam, diffuse waxy papules resembling a "plucked chicken skin" appearance were noted on the patient's neck (*Figure 5, page 10*). The patient was started on monthly intravitreal bevacizumab injections, with interval improvement in the subretinal fluid and visual acuity to counting fingers. He was referred for genetic testing in addition to cardiovascular, gastrointestinal and dermatologic evaluations.

Angioid streaks

Angioid streaks represent breaks in Bruch's membrane, appearing funduscopically as irregular, red or brown lines that radiate circumferentially from the optic nerve,[1] although, as seen in this case, clinical findings may be subtle and better captured on multimodal imaging. Angioid streaks pose an imminent risk of choroidal neovascularization. Their interplay with

Bios

Dr. Shahlaee is a vitreoretinal fellow with Mid Atlantic Retina/Wills Eye Hospital, Philadelphia.

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

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

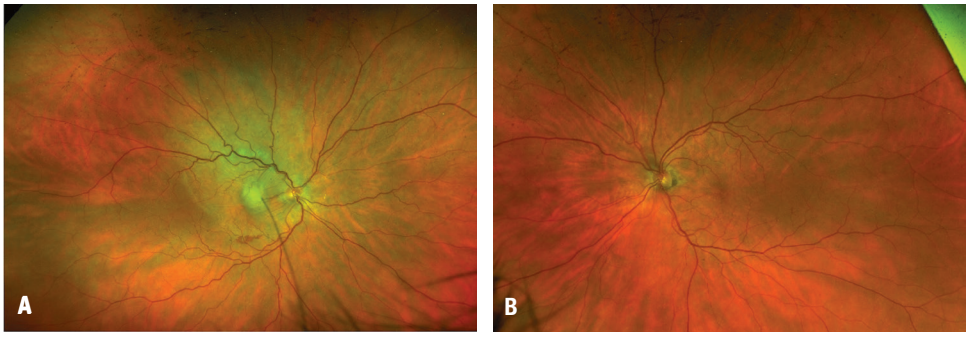


Figure 1. Color fundus imaging demonstrates (A) a large serous detachment with a subretinal white lesion and overlying striations in the central macula, along with a sliver of subretinal hemorrhage in the right eye, and (B) circumpapillary pigmentary changes in the left eye.

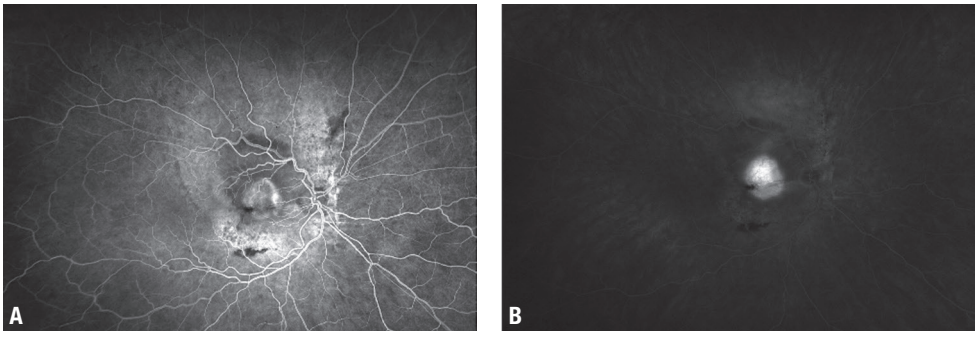


Figure 2. A) Intravenous fluorescein angiography shows a large central focus of hyperfluorescence. B) Concomitant leakage is consistent with choroidal neovascularization.

systemic disorders requires an interdisciplinary approach to diagnosis and treatment. Various associated systemic conditions include pseudoxanthoma elasticum (PXE), Ehler-Danlos syndrome, Paget's disease of bone, hematologic disorders (e.g., sickle cell disease) and diabetes mellitus.[2]

The prevalence of PXE is estimated to be 1:25,000. It has been seen in at least half of the patients with angioid streaks.[3,4] Despite the well-known association between PXE and angioid streaks, the wide array of clinical presentations for PXE—secondary to allelic heterogenicity—could make an early diagnosis challenging.[5] While there's no cure for PXE, the potential for underdiagnosis delays treatment and puts patients at serious risk for an otherwise preventable worsening of vision.[6]

The major criteria for the diagnosis of PXE include ophthalmologic, dermatologic and genetic findings, such as:

- *peau d'orange*—a French term meaning orange peel or orange skin—referring to the appearance of the fundus or presence of angioid streaks;
- the presence of yellow papules on the neck and/or flexural areas, demonstrating abnormal and calcified elastin fibers on skin biopsy; and
- a genetic analysis demonstrating a biallelic *ABCC6* mutation.[7]

The diagnosis is confirmed by the presence of two distinct categories of the three major criteria. Systemic associations include:

- premature gastrointestinal angina and/or bleeding;
- intermittent claudication of the arm and leg muscles; and
- stroke, renovascular hypertension, and cardiovascular complications, such as angina and myocardial infarction.

Depending on the patient's symptoms, cardiovascular, gastrointestinal and vascular evaluations may also be warranted.[7]

Genetic testing

While various mutational culprits for PXE exist, the mutation most commonly associated with ocular involvement is in the adenosine triphosphate (ATP)-binding cas-

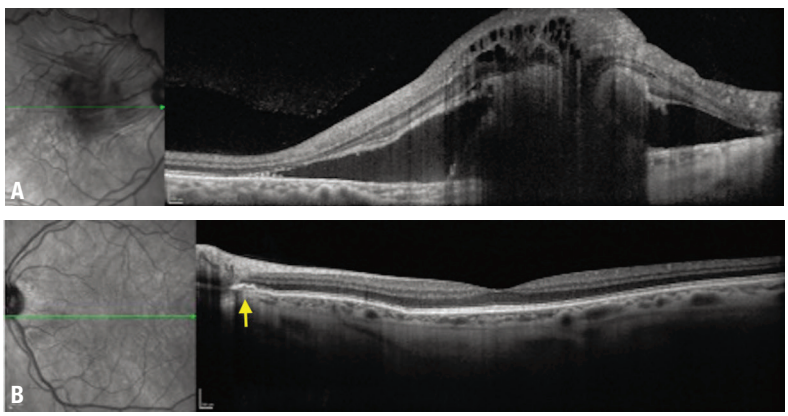


Figure 3. A) Optical coherence tomography of the right eye demonstrates marked subretinal and intraretinal fluid and a hyperreflective subretinal lesion. B) The left eye shows focal disruption in Bruch's membrane adjacent to the disc (arrow).

sette subtype C number 6 (*ABCC6*) gene on chromosome 16p13.1.8 The *ABCC6* gene encodes for a binding cassette that allows for the transcellular transport of ATP into the extracellular space, with subsequent conversion of ATP into adenosine monophosphate (AMP) and inorganic pyrophosphate.[9]

A biallelic mutation in the *ABCC6* gene disrupts this process and prevents the formation of inorganic pyrophosphate, which allows for ectopic mineralization. This induces breaks and calcification in the elastic fibers within connective tissues of the eyes, skin and peripheral arteries.[10]

In the eye, the elastic membranes of Bruch's membrane become abnormally calcified, reducing the membranes' structural integrity and resilience, with subsequent increased vulnerability to mechanical stressors. The weakened Bruch's membrane is prone to breaks, otherwise known as angioid streaks.[4] These breaks can result in endothelial dysfunction, which ultimately induces CNV via vascular endothelial growth factor activation.[11]

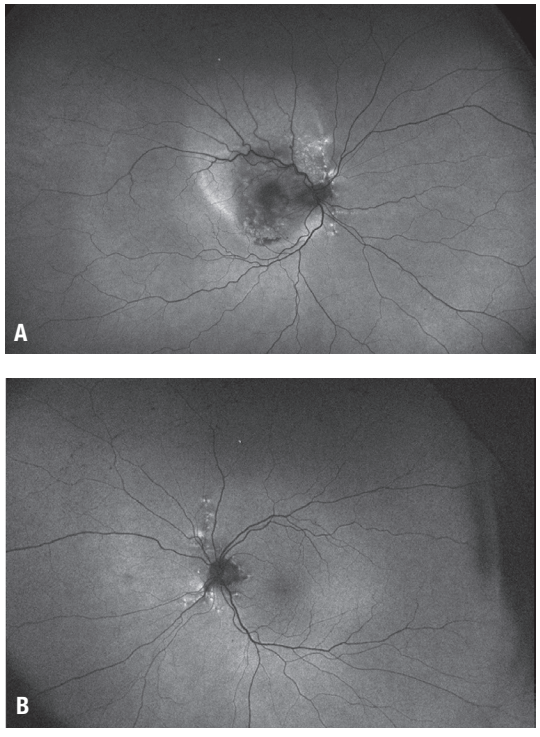


Figure 4. A) Fundus autofluorescence of the right eye shows a mixed stippled pattern. B) The left eye exhibits speckled radial linear hyper-autofluorescence patterns emanating from the disc in the left eye.

In our patient, genetic testing revealed a heterozygous mutation for *ABCC6* c.4218G>C, p.(Gln1406His), a variant of uncertain significance. There have been reports of two individuals with autosomal recessive PXE with compound heterozygosity for a different nucleotide substitution at a similar protein position (*ABCC6* c.4216C>A, p.(Gln1406Lys)).[12,13]

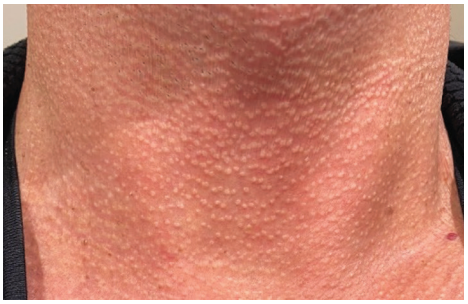


Figure 5. Inspection of the neck shows diffuse waxy, calcific papules resembling "plucked chicken skin."

Nevertheless, our patient didn't have the same substitution or evidence of compound heterozygosity because no additional pathologic variant was identified within the *ABCC6* gene. While the genetic analysis covered 100 percent of the *ABCC6* gene's target region, the patient could have an as yet unidentified variant associated with PXE, a different variant not covered by the genetic analysis, or a variant that's difficult to detect due to factors such as structural arrangements or the size of insertion-deletion mutations.

Treatment

Vascular endothelial growth factor inhibitors are the primary treatment for CNV secondary to angioid steaks in the setting of PXE. They've been shown to improve vision, especially in patients with better baseline visual acuity.[4] However, CNV recurrence or new CNV has been shown to occur frequently as early as six months after the last anti-VEGF treatment.[14]

Although photodynamic therapy and laser photocoagulation may also be used for CNV, these treatments have been associated with complications, including decreased vision, recurrence and progressive damage to the retina.[4] Overall, existing and potential studies further emphasize the importance of early diagnosis of PXE to ensure preservation of visual acuity.

(Continued on page 15)

WET AMD EYE

ANTI-VEGF

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

FELLOW EYE

20/79 VA

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

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

Detect Early. Treat Early.

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

- FDA Cleared
- Medicare Covered

ForeseeHOME™
AMD Monitoring Program

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

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

The Key to Successful Home Monitoring

NOTAL VISION MONITORING CENTER

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

NOTAL VISION™
Monitoring Center

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

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

See website for FDA Indication for Use.

SM-125. 2

GET STARTED TODAY

1-855-600-3112

Mon-Fri, 8 AM to 6 PM EST

www.foreseehome.com/doctor

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

Treating uveitic macular edema

A review of local and systemic treatments for UME and insights on when to use them.

By Parisa Emami-Naeini, MD, MPH

Parisa Emami-Naeini, MD, MPH

Uveitis is one of the major causes of vision loss among young, working- age people.[1] Visual impairment is noted in 70 percent of patients with noninfectious uveitis, with macular edema the most common etiology.[1,2] In these patients, inflammation leads to impairment of the blood-retinal barrier and increased permeability of chorioretinal vasculature, which will result in accumulation of fluid and uveitic macular edema (UME).[3] Macular edema can be seen in any type of noninfectious uveitis, but it's most commonly seen in association with intermediate, posterior or panuveitis.

Fluorescein angiography and optical coherence tomography are used to confirm the presence of vascular leakage and macular edema. Based on the location of fluid on OCT, UME can be classified into cystoid macular edema, diffuse macular edema and serous retinal detachment. Of these, diffuse edema is the most common, and cystoid macular edema has the most impact on patient's vision.[4,5]

Chronic, untreated UME may result in damage to photoreceptors and permanent vision loss. Moreover, UME can be seen even in the setting of controlled uveitis as well as a result of previous inflammation and permanent damage to the blood-retinal barrier.[6] Several systemic and local treatment options are available for UME, which we'll review here.

Local treatments

Local treatments fall into two subcategories: topical eye drops, and peri- and intraocular steroids.

Eye drops have been used extensively to control anterior uveitis. Recent studies have shown favorable intraocular penetration and effectiveness of various topical drops in the control of UME. Non-steroidal drops, including bromfenac, nepafenac and ketorolac, and steroidal drops, including prednisolone acetate and difluprednate, have been successfully used to treat UME. Corticosteroid drops have been associated with an increase in intraocular pressure and cataract formation. However, they seem to have fewer side effects than other treatment modalities. [7,8]

A number of peri- and intraocular steroids are available. They include:

• ***Triamcinolone acetonide 40 mg/ml.*** Preservative-free triamcinolone acetonide (Triesence, Novartis) is injected intravitreally and has shown to be effective for six to eight weeks, less in vitrectomized eyes. Sub-Tenon's or transseptal injection of preserved triamcinolone acetonide (Kenalog, Bristol-Myers Squibb) provides a depot of slowly releasing steroids for two to three

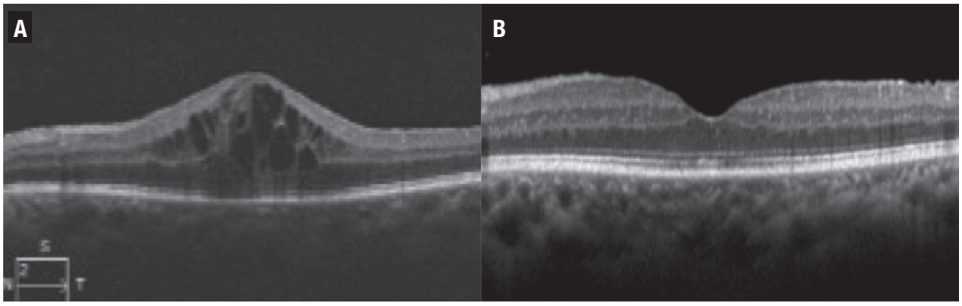


Figure 1. A) A 68-year-old woman with a history of sarcoidosis presented with leakage and uveitic macular edema (UME) in the left eye. B) After treatment with intravitreal triamcinolone acetonide, the UME resolved six weeks later.

Bio

Dr. Emami-Naeini is an assistant professor of ophthalmology at the University of California, Davis, Sacramento.

DISCLOSURE: Dr. Emami-Naeini has no relevant financial disclosures.

months. However, the duration is less predictable because of triamcinolone's variable particle size.

• ***Dexamethasone 0.7-mg implant.*** It's approved for intravitreal use in patents with uveitis and the effect lasts for three to six months. The POINT trial of Ozurdex (Allergan/AbbVie), a prospective randomized clinical study with intravitreal and periocular triamcinolone, showed that both intravitreal steroids are more potent than the periocular steroid in controlling UME and improving visual acuity, with a modest increase in intraocular pressure. No statistically significant difference was found between the two intraocular steroids[9] (*Figure 1*).

• ***Fluocinolone acetonide 0.18-mg injectable implant.*** This implant (Yutiq, EyePoint Pharmaceuticals) has shown effectiveness in controlling intraocular inflammation, decreasing flares and preventing vision loss in patients with posterior uveitis.[10] The fluocinolone acetonide 0.19-mg implant (Iluvien, Alimera Sciences) is a similar steroid with slightly different dosing. It's approved for use in diabetic macular edema in the United States and Europe, and for noninfectious uveitis in Europe.[11] Studies have demonstrated its effectiveness in managing UME.[12]

• ***Fluocinolone acetonide 0.59-mg surgical implant.*** Surgically sutured to the sclera, this implant (Retisert, Bausch + Lomb) can slowly release steroids over approximately 30 months. Its safety and efficacy have been widely studied in the landmark MUST trial and follow-up publications.[13] In this prospective, multicenter trial patients with non-infectious intermediate, posterior or panuveitis were randomized to receive the Retisert implant or were managed with systemic immunosuppressive therapy. The seven-year follow-up data showed that the implant was effective in controlling inflammation. However, patients who received systemic treatment had better visual outcomes at seven years but with high rates of cataracts and glaucoma surgery in the implant group (*Figure 2*).

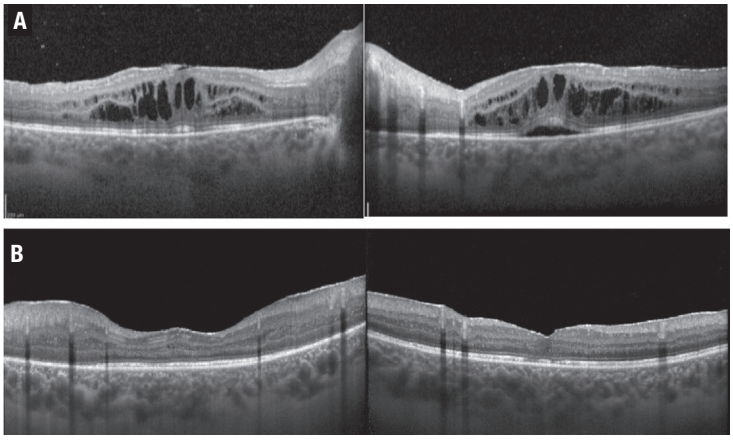


Figure 2. A) A 24-year-old woman with a history of ulcerative colitis and panuveitis was diagnosed with uveitic macular edema (UME), which failed to respond to systemic immunosuppressives. B) The fluocinolone acetonide 0.59-mg surgical implant (Retisert, Bausch + Lomb) resulted in resolution of the UME within two months after surgery.

• ***Suprachoroidal triamcinolone acetonide injectable suspension.*** This implant (Xipere, Clearside Biomedical and Bausch + Lomb) recently received Food and Drug Administration approval for use in patients with UME.[14] The efficacy and safety of this platform in UME have been studied in the Phase III PEACHTREE trial.[15] In this study, 47 percent of patients who received the suprachoroidal steroid gained >15 letters compared to only 16 percent in the sham group ($p<0.001$). The drug was well-tolerated with comparable rates of cataract and elevated intraocular pressure between the treatment and control arms.

• ***Anti-VEGF.*** Recent studies have shown that these medications can be effective in UME, as well. Ranibizumab (Lucentis, Genentech) and aflibercept (Eylea, Regeneron Pharmaceuticals) have been used successfully in treating refractory UME.[16]

Systemic treatments

Corticosteroids are effective in controlling ocular inflammation, retinal vasculitis and

UME. Their use is associated with a lower risk of local side effects, such as glaucoma and cataract. However, high rates of systemic side effects, including hypertension, diabetes, osteoporosis, mood changes, increased risk of infections and more limits their long-term use. Systemic corticosteroids are generally used for a short period of time and to control acute or breakthrough inflammation.

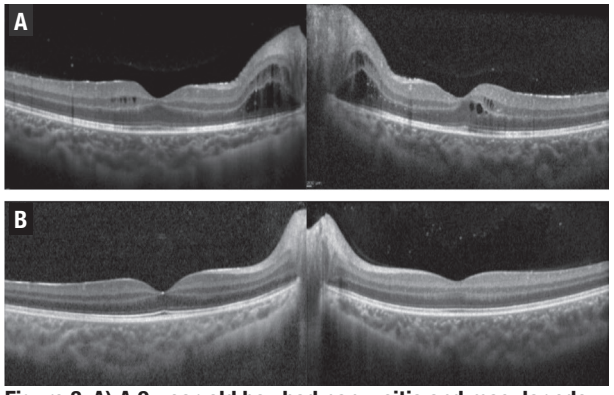


Figure 3. A) A 9-year-old boy had panuveitis and macular edema in both eyes despite topical drops. B) The macular edema resolved three months after the patient started systemic therapy with methotrexate and adalimumab (Humira, AbbVie).

So, steroid-sparing immunosuppressives are an option for longer-term therapy. They include:

• ***Antimetabolites.*** These agents include mycophenolate mofetil (Cellcept, Genentech/Roche) and methotrexate, both of which are commonly used as first-line steroid-sparing immunosuppressives in patients with uveitis, and are effective in controlling UME. The FAST trial compared the efficacy of these two medications.[17] This prospective, randomized trial showed that methotrexate is more effective in controlling posterior and panuveitis, and favored mycophenolate in controlling intermediate uveitis. The subanalysis of study data on patients with UME showed that both medications can reduce macular edema.[18] However, half of the eyes had persistent edema at 12 months. Side effects include increased risk of infection, liver failure and fatigue.

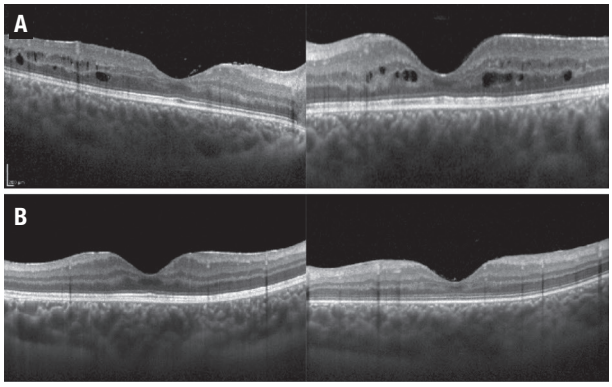


Figure 4. A 16-year-old girl had pars planitis and macular edema in both eyes. The edema (A) didn't respond well to infliximab (Remicade, Janssen Biotech) and adalimumab (Humira, AbbVie). The patient was switched to tocilizumab (Actemra, Genentech) and the macular edema resolved after two months (B).

• ***Adalimumab.*** This tumor necrosis factor (TNF) inhibitor (Humira, AbbVie) is a fully human monoclonal antibody FDA-approved for systemic use in patients with noninfectious intermediate, posterior or panuveitis (*Figure 3*).[19] This medication can reduce the rate of treatment failure by 43 to 87 percent in patients with inactive and active uveitis, respectively.

Moreover, adalimumab decreased the risk of UME formation by 67 percent and resulted in resolution of edema in up to 70 percent of cases.[20] Off-label intravitreal use of adalimumab has also shown effectiveness in reducing UME in a small retrospective series.[21] Side effects include increased risk of infection, lymphoma, heart failure and demyelinating disease.

• ***Tocilizumab.*** This monoclonal antibody (Actemra, Genentech) targets interleukin 6, and is used to control inflammation and refractory uveitis. A multicenter retrospective study compared the efficacy of tocilizumab with an anti-TNF agent, infliximab (Remicade, Janssen Biotech).[22] This study found tocilizumab to be more effective for controlling and achieving complete resolution of UME (*Figure 4*). Side effects included infections, elevated liver enzymes and hypertension.

Bottom line

Various systemic and local treatment options are available to manage uveitic macular edema, the most common cause of vision loss in these patients.

REFERENCES

1. Durrani OM, Tehrani NN, Marr JE, Moradi P, Stavrou P, Murray PI. Degree, duration, and causes of visual loss in uveitis. Br J Ophthalmol. 2004;88:1159-1162.
2. Tomkins-Netzer O, Talat L, Bar A, et al. Long-term clinical outcome and causes of vision loss in patients with uveitis. Ophthalmology. 2014;121:2387-2392.
3. Chen S, Kong J, Feng L. The trend of drug therapy on uveitic macular edema: A bibliometric analysis of the 100 most cited articles. Front Med (Lausanne). 2022;9:807319.
4. Markomichelakis NN, Halkiadakis I, Pantelia E, et al. Patterns of macular edema in patients with uveitis: Qualitative and quantitative assessment using optical coherence tomography. Ophthalmology. 2004;111:946-953.
5. Iannetti L, Accorinti M, Liverani M, Caggiano C, Abdulaziz R, Pivetti-Pezzi P. Optical coherence tomography for classification and clinical evaluation of macular edema in patients with uveitis. Ocul Immunol Inflamm. 2008;16:155-160.
6. Okhravi N, Lightman S. Cystoid macular edema in uveitis. Ocul Immunol Inflamm. 2003;11:29-38.
7. Goldhardt R, Rosen BS. Uveitic Macular edema: Treatment update. Curr Ophthalmol Rep. 2016;4:30-37.
8. Feiler DL, Srivastava SK, Pichi F, Bena J, Lowder CY. Resolution of noninfectious uveitic cystoid macular edema with topical difluprednate. Retina. 2017;37:844-850.
9. Thorne JE, Sugar EA, Holbrook JT, et al. Periocular triamcinolone vs. intravitreal triamcinolone vs. intravitreal dexamethasone implant for the treatment of uveitic macular edema: The PeriOcular vs. INTravitreal corticosteroids for uveitic macular edema (POINT) Trial. Ophthalmology. 2019;126:283-295.
10. Jaffe GJ, Foster CS, Pavesio CE, Paggiarino DA, Riedel GE. Effect of an injectable fluocinolone acetonide insert on recurrence rates in chronic noninfectious uveitis affecting the posterior segment: Twelve-month results. Ophthalmology. 2019;126:601-610.
11. Alimera Sciences receives acceptance of filing to obtain approval for Iluvien uveitis indication in Europe [press release]. Atlanta, GA:Alimera Sciences; March 25, 2019. https://investors.alimerasciences.com/prviewer/release_only/id/3700779 Accessed April 18, 2022.
12. Studsgaard A, Clemmensen K, Nielsen MS. Intravitreal fluocinolone acetonide 0.19 mg (Iluvien) for the treatment of uveitic macular edema: 2-year follow-up of 20 patients. Graefes Arch Clin Exp Ophthalmol. 2022;260:1633-1639.
13. Writing Committee for the Multicenter Uveitis Steroid Treatment (MUST) Trial and Follow-up Study Research Group; Kempen JH, Altaweel MM, Holbrook JT, Sugar EA, Thorne JE, Jabs DA. Association between long-lasting intravitreous fluocinolone acetonide implant vs systemic anti-inflammatory therapy and visual acuity at 7 years among patients with intermediate, posterior, or panuveitis. JAMA. 2017;317:1993-2005.
14. Bausch + Lomb and Clearside Biomedical announce FDA approval of Xipere (triamcinolone acetonide injectable suspension) for suprachoroidal use for the treatment of macular edema associated with uveitis [press release]. Laval, QC, and Alpharetta, GA: Bausch Health Companies and Clearside Biomedical; October 25, 2021. https://www.prnewswire.com/news-releases/bausch--lomb-and-clearside-biomedical-announce-fda-approval-of-xipere-triamcinolone-acetonide-injectable-suspension-for-suprachoroidal-use-for-the-treatment-of-macular-edema-associated-with-uveitis-301407260.html Accessed April 18, 2022.
15. Yeh S, Khurana R, Shah M, et al. Efficacy and safety of suprachoroidal CLS-TA for macular edema secondary to noninfectious uveitis: Phase 3 randomized trial. Ophthalmology. 2020;127:948-955.
16. Staurenghi G, Lai TYY, Mitchell P, et al. Efficacy and safety of ranibizumab 0.5 mg for the treatment of macular edema resulting from uncommon causes: Twelve-month findings from PROMETHEUS. Ophthalmology. 2018;125:850-862.
17. Rathinam SR, Gonzales JA, Thundikandy R, et al. Effect of corticosteroid-sparing treatment with mycophenolate mofetil vs methotrexate on inflammation in patients with uveitis: A randomized clinical trial. JAMA. 2019;322:936-945.
18. Tsui E, Rathinam SR, Gonzales JA, et al. Outcomes of uveitic macular edema in the first-line antimetabolites as steroid-sparing treatment uveitis trial. Ophthalmology. Published online February 8, 2022.
19. AbbVie's HUMIRA (adalimumab) receives U.S. Food and Drug Administration approval to treat adults with non-infectious intermediate, posterior and panuveitis [press release]. North Chicago, IL; AbbVie News Center: Jun 30, 2016. https://news.abbvie.com/news/abbvies-humira-adalimumab-receives-us-food-and-drug-administration-approval-to-treat-adults-with-non-infectious-intermediate-posterior-and-panuveitis.htm Accessed April 18, 2022.
20. Suhler EB, Thorne JE, Mittal M, et al. Corticosteroid-related adverse events systematically increase with corticosteroid dose in noninfectious intermediate, posterior, or panuveitis: Post hoc analyses from the VISUAL-1 and VISUAL-2 trials. Ophthalmology. 2017;124:1799-1807.
21. Hamam RN, Barikian AW, Antonios RS, et al. Intravitreal adalimumab in active noninfectious uveitis: A pilot study. Ocul Immunol Inflamm. 2016;24:319-326.
22. Leclercq M, Andrillon A, Maalouf G, et al. Anti-tumor necrosis factor α versus tocilizumab in the treatment of refractory uveitic macular edema: A multicenter study from the French Uveitis Network. Ophthalmology. Published Online November 16, 2021.

A ser(i)ous detachment

(Continued from page 10)

Racquet and contact sports carry an increased risk for ocular and head trauma, both of which have been reported to precipitate CNV in patients with angioid streaks. Patients with angioid streaks should be discouraged from participating in such activities. Individuals with PXE who participate in sports and physical recreation should wear appropriate protective eyewear, such as polycarbonate sports goggles and/or protective helmets with eye shields.[8]

Bottom line

The pathophysiology, clinical presentation and treatment of PXE have been well described in the peer-reviewed literature. However, the varying clinical and mutational features among different patients make a timely diagnosis more elusive. A diagnostic delay may have negative consequences, particularly with regards to visual outcomes. Here, we emphasize the importance of using multimodal imaging and a systematic approach to uncover the cause of the CNV.

REFERENCES

1. Gliem M, Finger RP, Fimmers R, Brinkmann CK, Holz FG, Issa PC. Treatment of choroidal neovascularization due to angioid streaks: A comprehensive review. Retina. 2013;33:1300-1314.
2. Georgalas I, Papaconstantinou D, Koutsandrea C, et al. Angioid streaks, clinical course, complications, and current therapeutic management. Ther Clin Risk Manag. 2009;5:81-89.
3. Chassaing N, Martin L, Calvas P, Le Bert M, Hovnanian A. Pseudoxanthoma elasticum: A clinical, pathophysiological and genetic update including 11 novel ABCC6 mutations. J Med Genet. 2005;42:881-892.
4. Connor Jr PJ, Juergens JL, Perry HO, Hollenhorst RW, Edwards JE. Pseudoxanthoma elasticum and angioid streaks: A review of 106 cases. Am J Med. 1961;30:537-543.
5. Chassaing N, Martin L, Mazereeuw J, Barrie L, Nizard S, Bonafe J-L, et al. Novel ABCC6 mutations in pseudoxanthoma elasticum. J Invest Dermatol. 2004;122:608-613.
6. Finger RP, Issa PC, Schmitz-Valckenberg S, Holz FG, Scholl HN. Long-term effectiveness of intravitreal bevacizumab for choroidal neovascularization secondary to angioid streaks in pseudoxanthoma elasticum. Retina. 2011;31:1268-1278.
7. Germain DP. Pseudoxanthoma elasticum. Orphanet J Rare Dis. 2017;12:85.
8. Uitto J, Jiang Q, Váradi A, Bercovitch LG, Terry SF. Pseudoxanthoma elasticum: Diagnostic features, classification and treatment options. Expert Opin Orphan Drugs. 2014;2:567-577.
9. Jansen RS, Duijst S, Mahakena S, Sommer D, Szeri F, Váradi A, et al. ABCC6–mediated ATP secretion by the liver is the main source of the mineralization inhibitor inorganic pyrophosphate in the systemic circulation—brief report. Arterioscler Thromb Vasc Biol. 2014;34:1985-1989.
10. Kranenburg G, de Jong PA, Bartstra JW, et al. Etidronate for prevention of ectopic mineralization in patients with pseudoxanthoma elasticum. J Am Coll Cardiol. 2018;71:1117-1126.
11. Yeo NJY, Chan EJJ, Cheung C. Choroidal neovascularization: Mechanisms of endothelial dysfunction. Front Pharmacol. 2019;10:1363.
12. Le Boulanger G, Labreze C, Croue A, et al. An unusual severe vascular case of pseudoxanthoma elasticum presenting as generalized arterial calcification of infancy. Am J Med Genet A. 2010;152:118-123.
13. Hosen MJ, Van Nieuwerburgh F, Steyaert W, Deforce D, Martin L, Leftheriotis G, et al. Efficiency of exome sequencing for the molecular diagnosis of pseudoxanthoma elasticum. J Invest Dermatol. 2015;135:992-998.
14. Sawa M, Gomi F, Tsujikawa M, Sakaguchi H, Tano Y. Long-term results of intravitreal bevacizumab injection for choroidal neovascularization secondary to angioid streaks. Am J Ophthalmol. 2009;148:584-590.

Department Editor ***Paul Hahn, MD, PhD***

Subretinal blebs, sans retinotomy

This atraumatic technique uses a soft-tip on proportional reflux for creating subretinal fluid blebs.

By Gregory Lee, MD

Gregory Lee, MD

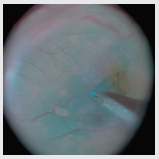
Refractory macular holes or failed hole closures are inevitable, although infrequent. I've tried various techniques with varying success. Free flaps are difficult to maneuver and keep in place. Brushing the nerve fiber layer with a diamond-dusted scraper seems to induce more damage than it creates elasticity.

I had better outcomes with perifoveal subretinal balanced salt solution injections, particularly in cases with smaller holes (<500 µm) than the chronic large holes that might require retinal transplant or amniotic membrane graft.

However, I wondered if it was really necessary to pierce the retina with a subretinal cannula. I thought if you could aspirate subretinal perfluoro-n-octane through an area of peeled internal limiting membrane transretinally (i.e., without a retinotomy), it should work in the reverse: to inject BSS transretinally without a retinotomy to create a subretinal bleb.

Promising closure rates have been reported with macular detachment with subretinal fluid injections (80 to 90 percent).[1-2] Creating increased elasticity of the perifoveal macula allows for the retinal tissue immediately adjacent the hole to close. This can be combined with scaffold techniques.

View the Video



Dr. Lee demonstrates his technique for creating subretinal blebs without a retinotomy to repair recalcitrant or chronic full-thickness macular holes.
Available at: https://bit.ly/VideoPearl_029

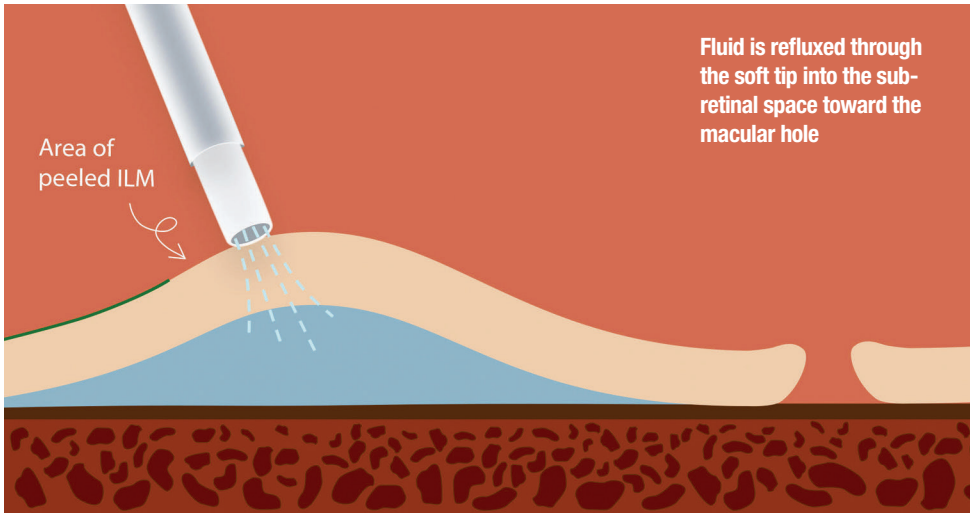
Surgical technique

The technique uses a standard vitrectomy set up. The soft tip is connected to the extrusion line, which has been primed with BSS. The amount of fluid in the tubing varies between manufacturers, but it's typically >10cc.

If not already done, then the ILM must be peeled to facilitate transretinal fluid passage. The extrusion line with the soft tip is then set to proportional reflux (standard settings on Alcon Constellation are 0 to 120 mmHg) and checked to make sure no air, hemorrhage or dye is in the cannula or line.

The soft tip is then placed over the target area, approximately 1 disc diameter from the

(Continued on page 37)



Bios

Dr. Lee is a vitreoretinal surgeon at Georgia Retina in the greater Atlanta area.

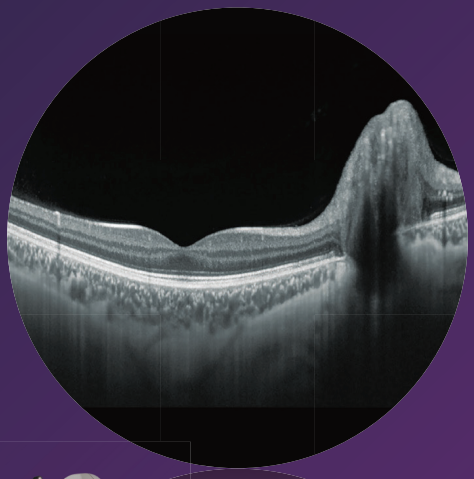
Dr. Hahn is a partner at New Jersey Retina in Teaneck.

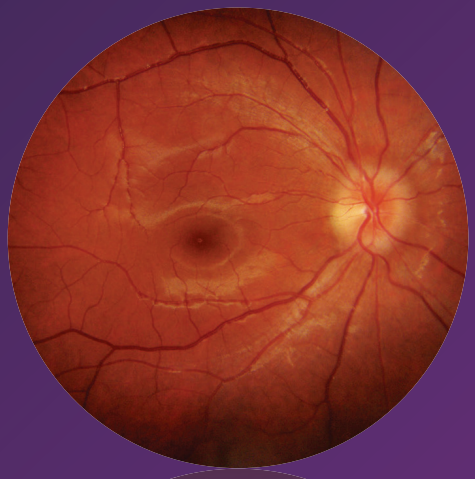
DISCLOSURES: Dr. Lee reports financial relationships with Allergan/AbbVie, Alimera Sciences, Apellis Pharmaceuticals and EyePoint Pharmaceuticals.

Dr. Hahn is a consultant to DORC.

ONE CLICK
IS ALL YOU NEED

Triton™ Swept Source OCT + Fundus Camera





Acquire a true color fundus photo, 10-Line HD Raster and 256-line 3D Widefield cube in less than 3 seconds.[1] One-page report shows reference data for Optic Nerve, RNFL, GCC, and macular thickness at a glance.

Stunningly detailed images with **100K A-scans/sec.** and **1,050nm wavelength**

Deep penetration through media opacities such as cataracts

Multimodal Imaging. SS-OCT, non-mydriatic true color fundus imaging, FA, and FAF[2]

Invisible scan beam allows patients to focus on the fixation target and **reduce involuntary eye movement**

1. CAUTION: Please note that the acquisition time will vary depending on the patient and usage environment.
2. FA and FAF available on DRI OCT Triton Plus model only.

TOPCON Healthcare
SEEING EYE HEALTH DIFFERENTLY

New Insights in Imaging

Can you recognize these novel OCT signs?

A review of characteristic optical coherence tomography findings that can help narrow or even confirm a novel diagnosis.

Caroline R. Baumal, MD

By Caroline R. Baumal, MD

Take-home points

- Optical coherence tomography angiography and en face OCT patterns, described as fern-like, arteriolar and globular, have been used to further characterize paracentral acute middle maculopathy (PAMM).
- Acute macular neuroretinopathy is rarer than PAMM and warrants an appropriate history and focused systemic evaluation.
- In macular telangiectasia type 2, OCT may show degenerative hyporeflective retinal cyst (or cavitation) at various retinal depths along with asymmetry or irregularity of the fovea contour.
- Clinical findings of Henle fiber layer hemorrhage demonstrate deep hemorrhages that may exhibit a feathery margin and petaloid pattern radiating from the fovea or have a rounder appearance when located peripheral to the macula.

Optical coherence tomography imaging of the retina has come a long way since the first prototype OCT device was used to evaluate patients in the 1990s in a collaboration between James Fujimoto's lab at Massachusetts Institute of Technology and clinicians at the New England Eye Center.[1]

In the 25-year journey of commercial OCT machines in the ophthalmology clinic, the images acquired have drastically improved with current spectral-domain and swept-source devices. This has given us better diagnostics and an increased understanding of disease pathogenesis, and enabled OCT to direct our therapeutic decisions.

For example, use of the grayscale over the false color OCT imaging has improved visualization of subtle reflectivity that may be associated with retinal disorders. Multimodal imaging using complementary technologies has confirmed OCT findings of retinal disorders.[2]

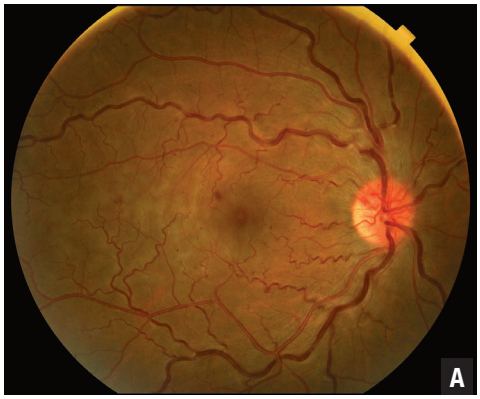
Characteristic OCT findings have emerged that can help narrow or even confirm a novel diagnosis. Last year we reviewed some of these findings.[3] This article will highlight some of them, including paracentral acute middle maculopathy (PAMM), acute macular neuroretinopathy (AMN), macular telangiectasia (MacTel) type 2 and hemorrhage in the Henle fiber layer. Table 1 lists some novel findings.

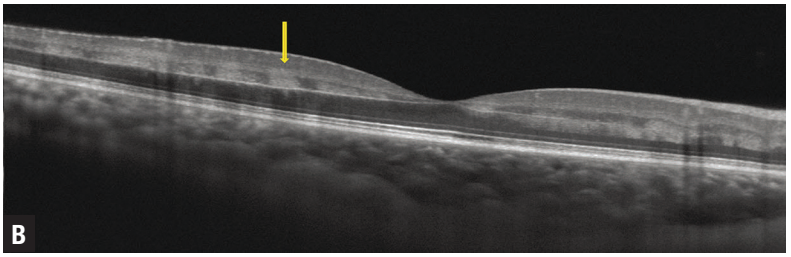
Paracentral acute middle maculopathy

PAMM refers to a SD-OCT finding characterized by hyperreflective discontinuous band like lesions, primarily located in the inner nuclear layer (INL).[4] It's hypothesized that these lesions result from ischemia or insult to the intermediate and deep retinal capillary plexus.[5]

Bio
Dr. Baumal is professor of ophthalmology at New England Eye Center, Tufts Medical Center, Boston.

DISCLOSURES: Dr. Baumal is a consultant to Genentech, Ora, Novartis and EyePoint Pharmaceuticals, and a speaker for Regeneron Pharmaceuticals and Carl Zeiss Meditec.





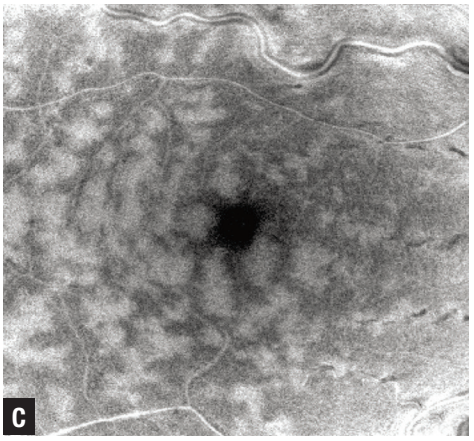


Figure 1. In central retinal vein occlusion with paracentral acute middle maculopathy (PAMM), color fundus photography (A) shows retinal venous tortuosity, small-dot retinal hemorrhages and optic nerve hyperemia. Note the deep retinal whitening adjacent the retinal veins temporal to the fovea. B) Hyperreflective focal band-like lesions (yellow arrow) in the middle retina (inner nuclear layer, inner plexiform, outer plexiform layers) on spectral-domain optical coherence tomography are consistent with PAMM. C) Distinct en face OCT appearance with a perivenular pattern described as fern-like PAMM.

The OCT features of PAMM are distinctive (*Figure 1*), and are more readily recognized when clinicians realize that structural grayscale SD-OCT images offer greater visibility of subtle OCT reflectivity compared to the false color scale.

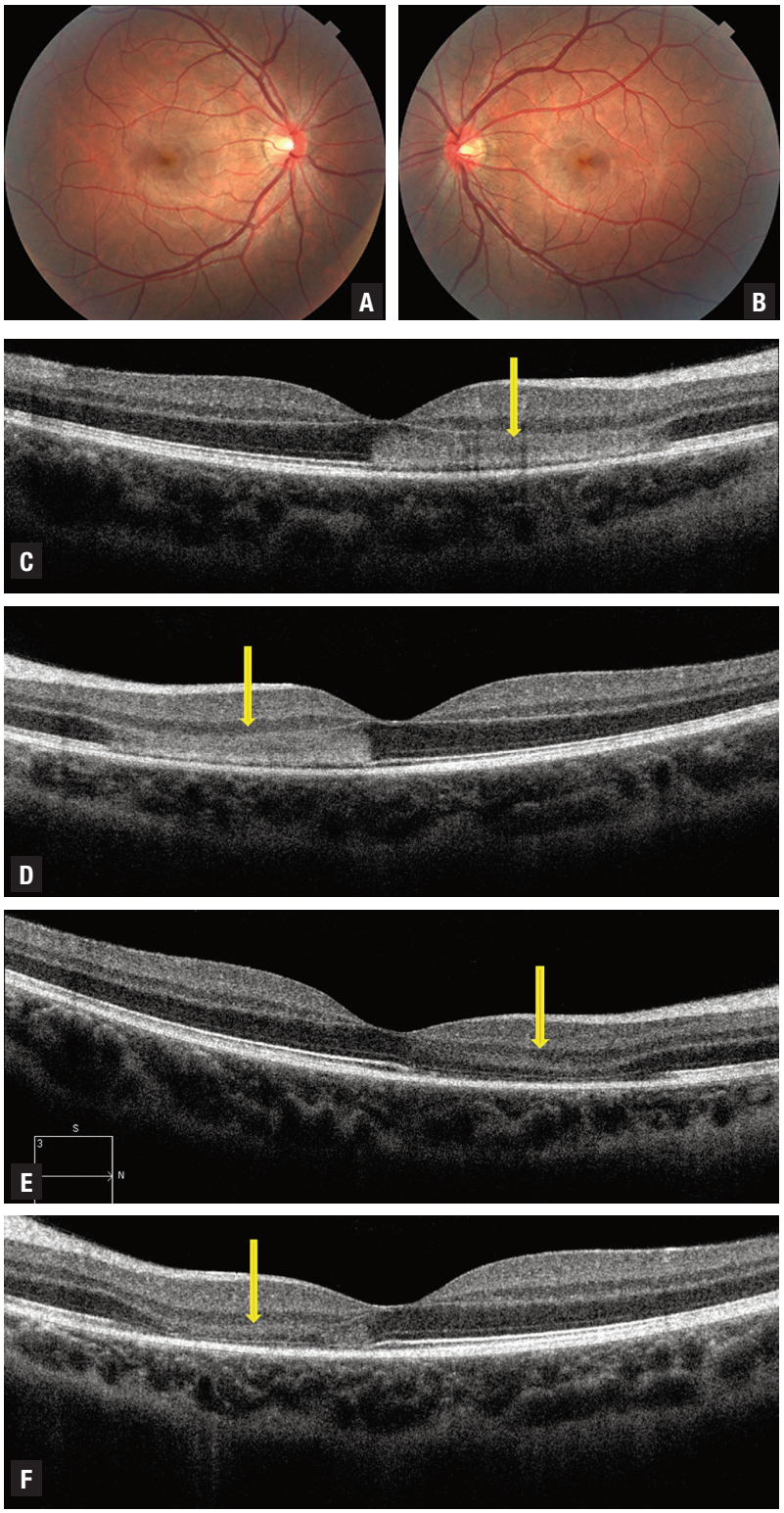
PAMM represents an imaging finding that may help narrow the diagnostic spectrum, rather than suggest a single diagnosis. PAMM was initially described in isolation, but subsequently it has been observed in conjunction with many other disorders, most prominently retinal vascular and systemic disorders, including branch retinal artery occlusion, central retinal artery occlusion, central retinal vein occlusion, diabetic retinopathy, sickle cell retinopathy and Purtscher retinopathy.[6-9]

OCT angiography and en face OCT patterns, described as fern-like, arteriolar and

Table 1. Novel optical coherence tomography findings

- ILM drape
- SIRE (Double layer sign)
- Subretinal hyperreflective material (SHRM)
- Flying saucer sign
- Dome shaped macula
- Disorganization of retinal inner layer (DRIL)
- Bacillary detachment
- Hyperreflective spots (HRS)
- Outer retinal tubulation
- Outer retina-choroid complex (ORCC) splitting
- Brush border pattern or elongation of photoreceptor outer segment
- POHMS (peripapillary hyperreflective ovoid mass-like structures)
- Sponge sign
- Omega sign
- Henle layer hyperreflectivity
- Henle hemorrhage
- Focal ellipsoid loss
- Diffuse outer retinal loss/vitreous inflammation
- Pearl necklace sign
- Foveal pseudocyst
- Focal choroidal excavation (FCE)
- Choroidal macrovessel
- Choroidal caverns
- Choroidal rift
- Pachychoroid/peripapillary pachychoroid syndrome
- Dipping sign
- Plume
- Fuzzy border
- Cotton ball sign
- Needle sign

Adapted from Baumal C. Novel OCT findings. Paper presented at American Academy of Ophthalmology 2021 Retina Subspecialty Day; New Orleans, LA; November 13, 2022.



globular, have been used to further characterize PAMM.[10] Diagnosis of PAMM warrants a directed history to identify potential causes and a systemic evaluation to exclude vascular risk factors. An underlying cause may not be identified.

Acute macular neuroretinopathy

In contrast to PAMM, AMN in the acute phase features a horizontal band of hyperreflectivity anterior to the RPE between the outer plexiform and outer nuclear layers (*Figure 2*).[11] Thus, the anatomic location of hyperreflectivity differs between AMN and PAMM. Where the hyperreflectivity in PAMM is more anterior at the level of the INL, eyes with AMN also demonstrate bilateral subtle dark gray wedge-shaped lesions on near infrared reflectance or en face OCT, corresponding to red-brown lesions on color fundus photography.

The acute phase of the OCT hyperreflective band in AMN may be brief. By the time the patient presents complaining of paracentral scotomas, the OCT may show the later findings of thinning, and disruption of the outer retina and ellipsoid/interdigitation zones.[12,13]

AMN is rarer than PAMM. An appropriate history and focused systemic evaluation are indicated to assess for potential associations, which may include oral contraceptives, epinephrine use, hypotension, trauma, flu-like syndrome and systemic lupus.

Figure 2. In acute macular neuroretinopathy, color fundus photography (A,B) reveals reddish-brown petaloid (∩ on elevated) perifoveal lesions with the tip pointed toward the fovea in a young woman presenting with bilateral scotomas. C,D) Spectral-domain optical coherence tomography (C right eye, D left) acutely through the lesion reveals a horizontal band of hyperreflectivity anterior to the retinal pigment epithelium between the outer plexiform and outer nuclear layers corresponding to the lesions. E,F) SD-OCT (E right eye, F left) two weeks after presentation shows disruption and loss of the ellipsoid and interdigitation zones corresponding to the acute lesions.

Macular telangiectasia type 2

In MacTel type 2, OCT may show degenerative hyporeflective outer retinal cyst (or cavitation) located at various retinal depths along with asymmetry or irregularity of the fovea contour (*Figure 3*).[13] Other findings include hyperreflectivity at the middle retinal layers, outward bending of inner retinal layers, retinal pigment clumps with shadowing of the deep retina, superficial retinal crystals, vitelliform lesion, internal limiting membrane drape and disruption of the external limiting membrane, ellipsoid and interdigitation zones.[14-16]

ILM drape is described as a thin layer of ILM over a superficial retinal lucency, which may represent residual foot plates of Muller cells. Vision loss may be related to ILM drape and outer retinal degeneration. Macular hole and choroidal neovascularization may ultimately develop.

MacTel type 2 affects the macular Müller cells and capillary network, leading to the anatomical changes in the inner and outer retinal structure.[17] Multimodal imaging, including OCT angiography and fluorescein angiography, may corroborate the diagnosis and exclude choroidal neovascularization.

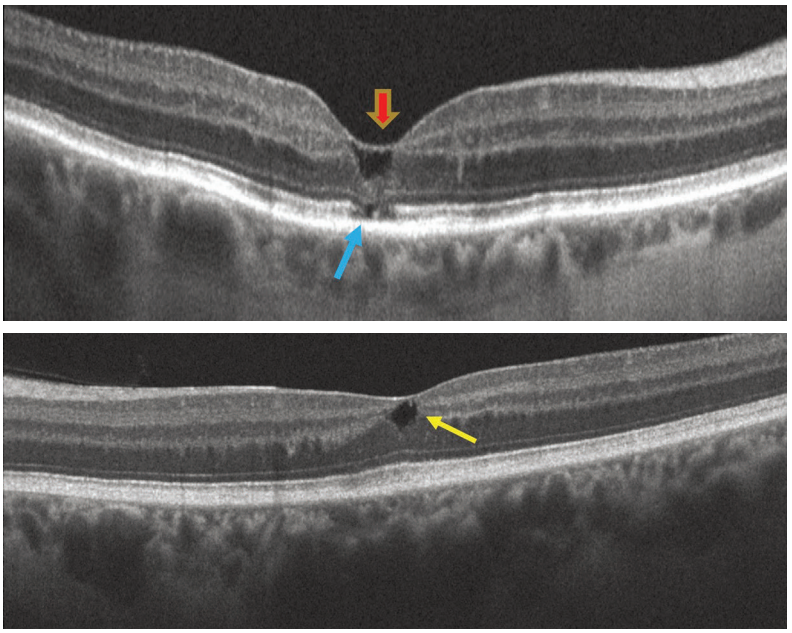


Figure 3. In macular telangiectasia type 2, spectral-domain optical coherence tomography of the right eye (A) shows internal limiting membrane drape (red arrow), outward collapse of the retinal layers and external limiting membrane, ellipsoid, interdigitation zone loss (blue arrow). B) SD-OCT of the left eye reveals an inner retinal degenerative cystic space. The fovea contour is irregular in both eyes.

Henle fiber layer hemorrhage

OCT findings of blood located within Henle fiber layer (HFL), referred to as Henle fiber layer hemorrhage or HH, have been described as characteristic hyperreflectivity from the hemorrhage delineated by the obliquely oriented fibers in the Henle layer (*Figure 4*).[18] Clinical findings demonstrate deep hemorrhages that may exhibit a feathery margin and petaloid pattern radiating from the fovea or have a rounder appearance when located peripheral to the macula.

The HFL consists of long, cylindrical, unmyelinated cone and rod axons that synapse in the outer plexiform layer. The fibers are radially orientated around the fovea due to the embryologic development of the foveal pit. The oblique orientation of fibers in HFL coursing at an angle account for the petaloid shape of Henle hemorrhages as well as the feathery margins when located around the fovea.

Henle hemorrhage may result from a wide variety of pathologies (*Table 2, page 22*) and can be classified as secondary to local vascular abnormalities of the deep capillary plexus, choroidal vascular abnormalities or

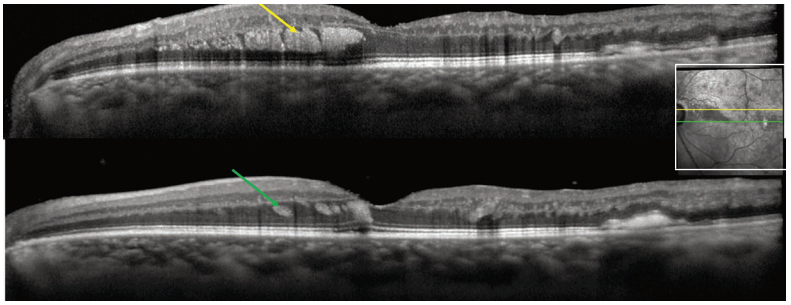


Figure 4. In Henle nerve fiber layer hemorrhage in a branch retinal vein occlusion, spectral-domain optical coherence tomography of the left eye shows oblique hyperreflectivity (yellow/green arrows) separated by hyporeflective striations corresponding to deep retinal hemorrhages in Henle fiber layer. The inset shows the near-infrared image. (*Courtesy David Sarraf, MD*)

Table 2. Etiology of Henle fiber layer hemorrhage

Systemic central venous pressure (CVP) abnormality
- Terson's syndrome
- Trauma
- Valsalva maneuver
- Epidural injection
- Whiplash maculopathy
- General anesthesia

Local retinovascular abnormality affecting the deep capillary plexus
- Retinal vein occlusion (branch or central)
- Decompression maculopathy
- Blunt globe trauma
- Face down positioning with expansile gas after vitrectomy
- Macular telangiectasia type 2
- Retinal artery macroaneurysm

Choroidal vascular abnormality with breakthrough into Henle fiber layer
- Polypoidal choroidal vasculopathy (aneurysmal type 1 neovascularization)
- Neovascular age-related macular degeneration
- Myopic degeneration +/- type 2 choroidal neovascularization

Adapted from Baumal CR, Sarraf D, Bryant T, et al. Henle fibre layer haemorrhage: Clinical features and pathogenesis. Br J Ophthalmol. 2021;105:374-380

Even though optical coherence tomography has been available in the clinic for more than two decades, novel findings continue to be described that may be based on OCT appearance, a description of the anatomy or disease pathogenesis.

disorders affecting central venous pressure. Henle hemorrhage has been described in association with MacTel type 2, where the source of the blood likely originates from the deep retinal capillary plexus as it's positioned adjacent to the HFL.[19]

Bottom line

Even though OCT has been available in the clinic for more than two decades, novel findings continue to be described that may be based on OCT appearance, a description of the anatomy or disease pathogenesis. Table 1 (*page 19*) describes a miniscule number of these novel findings from the recent literature. With careful observation, many of these findings can be observed and more novel OCT findings will be uncovered.

REFERENCES

1. Fujimoto J, Brezinski M, Tearney G. et al. Optical biopsy and imaging using optical coherence tomography. Nat Med. 1995;1: 970–972
2. Novais EA, Baumal CR, Sarraf D, Freund, KB, Duker JS. Multimodal imaging in retina disease: A consensus definition. OSLI Retina. 2016;47:201-205.
3. Baumal C. Novel OCT findings. Paper presented at American Academy of Ophthalmology 2021 Retina Subspecialty Day; New Orleans, LA; November 13, 2022.
4. Sarraf D, Rahimy E, Fawzi AA, et al. Paracentral acute middle maculopathy: a new variant of acute macular neuroretinopathy associated with retinal capillary ischemia. JAMA Ophthalmol. 2013;131:1275-1287.
5. Bakhoum MF, Freund KB, Dolz-Marco R, et al. Paracentral acute middle maculopathy and the ischemic cascade associated with retinal vascular occlusion. Am J Ophthalmol. 2018;195:143-153.
6. Rahimy E, Sarraf D, Dollin ML, Pitcher JD, Ho AC. Paracentral acute middle maculopathy in nonischemic central retinal vein occlusion. Am J Ophthalmol. 2014;158:372-380.
7. Casalino G, Williams M, McAvoy C, Bandello F, Chakravarthy U. Optical coherence tomography angiography in paracentral acute middle maculopathy secondary to central retinal vein occlusion. Eye (Lond). 2016;30:888-893.
8. Chen X, Rahimy E, Sergott RC, et al. Spectrum of retinal vascular diseases associated with paracentral acute middle maculopathy. Am J Ophthalmol. 2015;160:26-34.e1
9. Chen X, Baumal CR. Paracentral middle acute maculopathy in pregnancy. Retina Cases Brief Rep. 2020;14:221-223.
10. Sridhar J, Shahlaee A, Rahimy E, et al. Optical coherence tomography angiography and en face optical coherence tomography features of paracentral acute middle maculopathy. Am J Ophthalmol. 2015;160:1259-1268.
11. Monson BK, Greenberg PB, Greenberg E, et al. High-speed, ultra-high-resolution optical coherence tomography of acute macular neuroretinopathy. Br J Ophthalmol. 2007;19:119-120.
12. Dansingani KK, Freund KB. Paracentral acute middle maculopathy and acute macular neuroretinopathy: Related and distinct entities. Am J Ophthalmol. 2015;160:1-3.e2.
13. Rahimy E, Kuehlewein L, Sadda SR, Sarraf D. Paracentral acute middle maculopathy: What we knew then and what we know now. Retina. 2015;35:1921-1930.
14. Venkatesh R, Reddy NG, Mishra Pm et al. Spectral domain OCT features in type 2 macular telangiectasia (type 2 MacTel): Its relevance with clinical staging and visual acuity. Int J Retin Vitr. Published online April 5, 2022. doi: 10.1186/s40942-022-00378-0
15. Gass JD, Blodi BA. Idiopathic juxtafoveolar retinal telangiectasis. Update of classification and follow-up study. Ophthalmology. 1993;100:1536–1546.
16. Yannuzzi LA, Bardal AMC, Freund KB, Chen K-J, Eandi CM, Blodi B. Idiopathic macular telangiectasia. Arch Ophthalmol. 2006;124:450–460.
17. Charbel Issa P, Pauleikhoff D, Holz FG. Macular telangiectasia type 2: The international MacTel project. Ophthalmologe. 2014;111:817–818.
18. Baumal CR, Sarraf D, Bryant T, et al. Henle fiber layer haemorrhage: clinical features and pathogenesis. Br J Ophthalmol. 2021;105:374-380.
19. Au A, Hou K, Baumal CR, Sarraf D. Radial hemorrhage in Henle layer in macular telangiectasia type 2. JAMA Ophthalmol. 2018;136:1182-1185.

New Insights in Imaging

OCT biomarkers in uveitis: An update

A review of currently used findings that can help predict disease activity and functional respose.

By Dilraj S. Grewal, MD

Dilraj S. Grewal, MD

Take-home points

- The ideal biomarker for uveitis would be reliable, noninvasive and easy to acquire in routine clinical practice, with large clinical databases available for validation.
- Optical coherence tomography plays a critical role in fulfilling the need for an objective anatomic biomarker because it provides a quantitative way to assess inflammation.
- Central subfield thickness represents an important secondary anatomic endpoint and a component of retreatment criteria in clinical trials for uveitic macular edema.
- Eyes with normal central subfield ellipsoid zones experience greater improvement in visual acuity and EZ status.

Uveitis assessment is complex because of the heterogeneity across the different uveitic phenotypes, and fluctuations with disease severity and flares. This increases the need for a reliable anatomic biomarker to predict disease activity and functional response.

Use of appropriate biomarkers is also imperative in clinical trials. For example, vitreous haze, a commonly used endpoint in uveitis clinical trials, is limited by poor intergrader agreement, even among experts.[1] This is important as clinical trial failure may be due to limitations of the endpoint rather than the drug. The Food and Drug Administration mandates a trial endpoint to be "well-defined and reliable," with treatment benefit being a measure of how a patient functions.

A surrogate uveitic biomarker should thus be "biologically relevant" to the disease pathophysiology, and "functionally relevant" with a quantifiable effect on visual function.[2] So, the ideal biomarker would be reliable, noninvasive and easy to acquire in routine clinical practice, with large clinical databases available for validation.

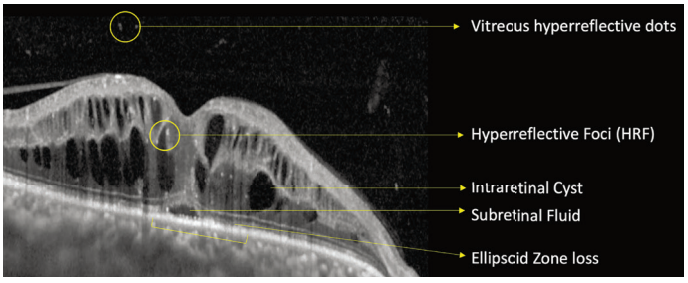


Figure 1. Optical coherence tomography showing uveitic macular edema with various anatomical parameters that are useful biomarkers, including vitreous hyperreflective dots, hyperreflective foci, intraretinal cysts, subretinal fluid and ellipsoid zone loss.

Bio

Dr. Grewal is a vitreoretinal and uveitis specialist at Duke Health and an associate professor of ophthalmology at Duke Eye Center in Durham, North Carolina.

DISCLOSURE: Dr. Grewal serves as a consultant to Allergan/AbbVie, EyePoint Pharmaceuticals and Genentech.

Optical coherence tomography plays a critical role in fulfilling the need for an objective anatomic biomarker because it provides a quantitative way to assess inflammation. Being ubiquitous in modern ophthalmic practices, and often considered as an "ocular vital sign," OCT is ideally suited to provide structural, noninvasive, repeatable measures.[2] Here, we review some of the currently used OCT biomarkers in uveitis.

Uveitic macular edema and central subfield thickness

Uveitic macular edema (UME) is the most important reversible cause of sight-loss in uveitis that's amenable to pharmacological treatment. The neurosensory retina has a degree of elasticity. Within limits, the continuity of bipolar cells is maintained even with fluid buildup and the connections between the photoreceptor and ganglion cell layers remain viable.

However, if the edema exceeds these elastic limits, bipolar axons snap, irreparably compromising this transmission pathway. This explains why visual acuity may not fully recover to baseline even after UME resolves.[3] Features of UME associated with visual acuity include intraretinal cystoid spaces and subretinal fluid (*Figure 1*). Larger cysts have a greater impact.[4]

Even in the absence of cystoid spaces and SRF, retinal thickness and perivascular thickening are valuable markers of disease activity on OCT.[5] "Non-cystic thickening," which is often monitored using the central subfield thickness, as well as perivascular thickening, can be a valuable continuous marker of disease activity (*Figure 2*). CST represents an important secondary anatomic endpoint and a component of retreatment criteria in clinical trials for UME.

Elizabeth Sugar, PhD, and colleagues demonstrated that each 100-µm reduction in CST equaled a 6.5-letter increase in visual acuity. A sensitivity analysis suggested that a 20-percent reduction in CST should be used as a clinically meaningful improvement in visual acuity.[6] In rare conditions, such as autoimmune retinopathy, macular edema

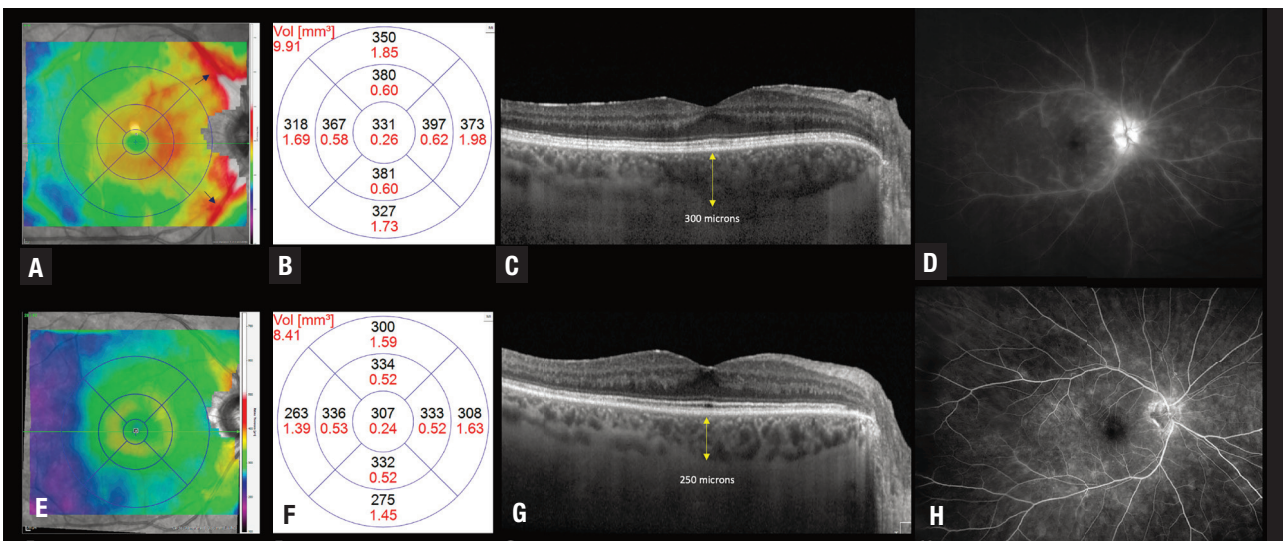


Figure 2. Optical coherence tomography thickness map (A) shows thickening in the macula along with perivascular thickening along the arcades in an eye with active birdshot chorioretinopathy that (D) corresponds to perivascular leakage seen on the fluorescein angiogram. C) OCT shows thickening of the choroid, with a subfield choroidal thickness of 300 µm. After immunomodulatory treatment, the thickness map shows marked reduction in noncystic thickening and perivascular thickening. This corresponds to improved leakage on the fluorescein angiogram, with improvement in central subfield thickness from 331 µm (B) to 307 µm (F) and a reduction in choroidal thickness to 250 µm.

is a biomarker for more severe disease, associated with decreased electroretinogram amplitudes and greater velocity of ellipsoid zone loss.[7]

Persistent cystoid macular edema may lead to irreversible disruption of the retinal neural network, gliosis or atrophy, and permanent visual acuity loss.[4] Early anatomic response based on CST is associated with a greater 24-week improvement in VA compared with those without an early response.[8]

In the Multicenter Uveitis Steroid Treatment (MUST) trial, visual acuity had a moderate negative correlation with CST at baseline (r=–0.56), and change in VA showed a moderate negative correlation with change in CST at six months (r=–0.46).[6] Using data from the Phase III PEACHTREE and AZALEA trials evaluating suprachoroidal triamcinolone in UME, structure-function correlation analyses demonstrated that eyes with center-involving cystoid spaces and subretinal fluid at baseline had greater VA improvement at 24 weeks.

Unique to this investigation, a longitudinal response model using this dataset showed that maximal VA improvement can lag peak anatomical improvement by up to six weeks, which provides valuable information for the temporal structure-function correlation and is very helpful in counseling patients on their timeline for improvement in VA.[8]

Other uveitic biomarkers

• ***Integrity of the ellipsoid zone.*** EZ integrity reflects the anatomic arrangement of photoreceptor outer segments, and has functional correlations in UME. After adjusting for CST and age, EZ integrity has been shown to account for 29 percent of the total variation in visual acuity in UME compared to intraretinal cystoid spaces, which account for 17.4 percent, and SRF, which accounts for 15 percent. Eyes with normal central subfield EZ experience greater improvement in VA. Improvement in EZ status corresponds to greater VA gains.[8]

• ***Hyperreflective foci***. The presence of HRF in the inner and outer retina is associated with worse VA.[4] Whether these also predict poor treatment response is as yet unclear. Mathias Bolz, MD, and colleagues first described HRF as deposits located within the walls of intraretinal microaneurysms and scattered throughout all retinal layers, forming confluent plaques in the outer plexiform layers. These are thought to be inflammatory in origin in uveitis.[9,10]

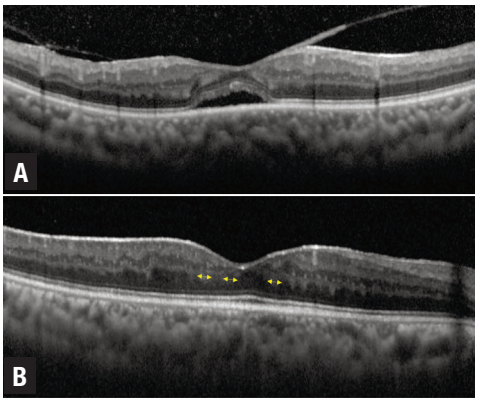


Figure 3. A) Optical coherence tomography showing uveitic macular edema (UME) with subretinal fluid and an overlying epiretinal membrane. Resolution of UME and subretinal fluid occurs after starting treatment. B) However, patches of derangement of the normal laminar inner retinal architecture emerge, which are prognostic for poor long-term visual acuity.

• ***Disorganization of retinal inner layers.*** Known as DRIL, this is defined as derangement of the normal laminar inner retinal structure. This is a robust and easy-to-obtain surrogate marker of VA in UME.[4] Foveal DRIL (*Figure 3*) is associated with worse VA at baseline and follow-up visits. The horizontal and vertical extent of DRIL strongly correlates with worse visual acuity and the association of DRIL with visual acuity is robust across a wide spectrum of UME severity.[4] There's a potential of reversibility with DRIL; improvement in DRIL corresponds to long-term improved visual acuity.

• ***Anterior chamber cells.*** Sumit Sharma, MD, and colleagues defined a continuous measure of anterior chamber inflammation as cells per millimeter cubed.[11] OCT automated quantification of AC cells may be superior to clinical grading systems, but this still requires significant validation.

• ***Choroidal biomarkers.*** Choroidal inflammation due to infiltration of immune cells and their effects on choroidal tissue is considered to reflect an increase in choroi-

WHAT ANATOMIC RESULTS COULD HE SEE THIS YEAR?

Of 134 patients treated in a DR clinical trial

80% SAW A ≥2-STEP DRSS IMPROVEMENT[1]

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

Inspired by a real patient with DR.

PANORAMA study design: Multicenter, double-masked, controlled clinical study in which patients with moderately severe to severe NPDR (ETDRS-DRSS: 47 or 53) without CI-DME (N=402; age range: 25-85 years, with a mean of 56 years) were randomized to receive 1 of 2 EYLEA dosing regimens or sham. Protocol-specified visits occurred every 28±7 days for the first 5 visits, then every 8 weeks (56±7 days). During Year 2 (Weeks 52-96), patients randomized to one of the EYLEA arms received a different dosing regimen.[1]

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.

REGENERON

777 Old Saw Mill River Road, Tarrytown, NY 10591

STARTING EYLEA EARLIER MAY HELP PREVENT DR PROGRESSION

Primary Endpoint (Year 1)		Secondary Endpoint (Year 1)	
Proportion of patients with a ≥2-step DRSS improvement[1,2,*]		Reduction in the risk of developing PDR or ASNV or CI-DME[2,*,†]	
EYLEA Q8 (n=134)	EYLEA Q16 (n=135)	EYLEA Q8 (n=134)	EYLEA Q16 (n=135)
80% vs 15% in the sham group (n=133)	**65%** vs 15% in the sham group (n=133)	**79% Risk Reduction** **Event rate:** 11% vs 42% in the sham group (n=133)	**82% Risk Reduction** **Event rate:** 10% vs 42% in the sham group (n=133)

P<0.01 vs sham.

- The recommended dose for EYLEA in DR is 2 mg (0.05 mL) administered by intravitreal injection Q4 (≈every 28 days, monthly) for the first 5 injections, followed by 2 mg Q8 (every 2 months)[1]
- Although EYLEA may be dosed as frequently as 2 mg Q4 (≈every 25 days, monthly), additional efficacy was not demonstrated in most patients when EYLEA was dosed Q4 compared with Q8. Some patients may need Q4 (monthly) dosing after the first 20 weeks (5 months)[1]

*Full analysis set.
†Event rate was estimated using the Kaplan-Meier method. Composite endpoint of developing PDR, ASNV was diagnosed by either the reading center or investigator.

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

anti-VEGF; anti–vascular endothelial growth factor; ASNV, anterior segment neovascularization; CI-DME, central-involved Diabetic Macular Edema; ETDRS-DRSS, Early Treatment Diabetic Retinopathy Study–Diabetic Retinopathy Severity Scale; PDR, proliferative diabetic retinopathy; Q4, every 4 weeks; Q8, every 8 weeks; Q16, every 16 weeks.

WARNINGS AND PRECAUTIONS (continued)

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

ADVERSE REACTIONS

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

INDICATIONS

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

References: 1. EYLEA® (aflibercept) Injection full U.S. Prescribing Information. Regeneron Pharmaceuticals, Inc. August 2019. **2.** Wykoff CC. Intravitreal aflibercept for moderately severe to severe non-proliferative diabetic retinopathy (NPDR): 2-year outcomes of the phase 3 PANORAMA study. Data presented at: Angiogenesis, Exudation, and Degeneration Annual Meeting; February 8, 2020; Miami, FL.

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

03/2021
EYL.21.02.0049

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

dal thickness, which is measured from the retinal pigment epithelium to the choroidal-scleral interface as a hyporeflective band. Choroidal thickness is a useful measurement in the acute stage of stromal choroiditis (i.e., in Vogt-Koyanagi-Harada disease) and for monitoring inflammatory activity.

Metrics such as the choroidal vascularity index (CVI), defined as the ratio of vascular area to the total choroidal area—that is, the percentage of the choroid that is vascular—can also be helpful. An increase in CVI is an indicator of inflammatory activity.[12,13] Enhanced-depth OCT imaging of features of choroidal lesions and granulomas, such as lobulated and nonhomogenous internal patterns, can differentiate etiologies such as tuberculosis, sarcoidosis and VKH.

Biomarkers in infectious uveitis

OCT signs of infectious uveitis include posterior hyaloid face precipitates and vitreous hyperreflective dots, which are often greater in areas overlying the primary chorioretinal focus.[14] Retinal lesions in infectious retinitis, such as fungal endophthalmitis, can be seen as hyperreflective, round-shaped lesions in the inner retinal layers extending toward the preretinal space and vitreous.

In placoid syphilis, a characteristic feature is EZ loss with rapid reconstitution after starting penicillin (*Figure 4*). In toxoplasma chorioretinitis, there's often marked choroidal thickening under the retinitis area that's usually not seen in viral retinitis.

Bottom line

Validated quantitative and qualitative biomarkers in uveitis remain an unmet need. OCT plays a critical role in achieving the goal of objective instrument-based quantification to provide a continuous measure of inflammatory activity and determine severity, progression and response to treatment.

We still need to collect more data for validation of these biomarkers, ideally in a prospective, multicenter, standardized manner with planned, prospective OCT imaging using standardized scan patterns. This is critical for further development and validation of OCT biomarkers in uveitis from patient care, research and clinical trial standpoints.

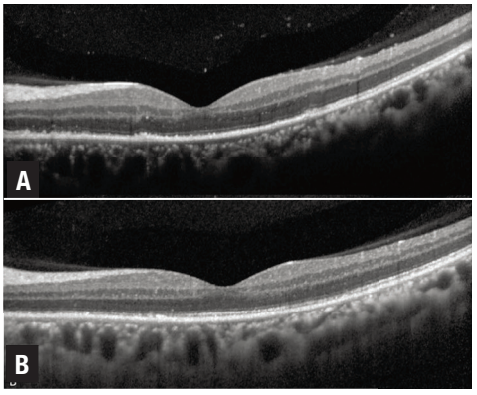


Figure 4. Marked ellipsoid layer loss with preserved external limiting membrane in an eye with syphilitic uveitis with significant reconstitution of the ellipsoid zone following penicillin treatment.

REFERENCES

1. Hornbeak DM, Payal A, Pistilli M, et al. Interobserver agreement in clinical grading of vitreous haze using alternative grading scales. Ophthalmology. 2014;121:1643-1648.
2. Denniston AK, Keane PA, Srivastava SK. Biomarkers and surrogate endpoints in uveitis: The impact of quantitative imaging. Invest Ophthalmol Vis Sci. 2017;58:BIO131-BIO140.
3. Pelosini L, Hull CC, Boyce JF, McHugh D, Stanford MR, Marshall J. Optical coherence tomography may be used to predict visual acuity in patients with macular edema. Invest Ophthalmol Vis Sci. 2011;52:2741-2748.
4. Grewal DS, O'Sullivan ML, Kron M, Jaffe GJ. Association of disorganization of retinal inner layers with visual acuity in eyes with uveitic cystoid macular edema. Am J Ophthalmol. 2017;177:116-125.
5. Thomas AS, Hatef AL, Stinnett SS, Keenan RT, Jaffe GJ. Perivascular thickening on optical coherence tomography as a marker of inflammation in birdshot retinochoroiditis. Retina. 2019;39:956-963.
6. Sugar EA, Jabs DA, Altaweel MM, et al. Identifying a clinically meaningful threshold for change in uveitic macular edema evaluated by optical coherence tomography. Am J Ophthalmol. 2011;152:1044-1052.e1045.
7. Finn AP, Thomas AS, Stinnett SS, Keenan RT, Grewal DS, Jaffe GJ. The role of cystoid macular edema as a marker in the progression of non-paraneoplastic autoimmune retinopathy. Graefes Arch Clin Exp Ophthalmol. 2018;256:1867-1873.
8. Ciulla TA, Kapik B, Barakat MR, et al. Optical coherence tomography anatomic and temporal biomarkers in uveitic macular edema. Am J Ophthalmol. 2021;237:310-324.
9. Bolz M, Schmidt-Erfurth U, Deak G, Mylonas G, Kriechbaum K, Scholda C. Optical coherence tomographic hyperreflective foci: A morphologic sign of lipid extravasation in diabetic macular edema. Ophthalmology. 2009;116:914-920.
10. Keane PA, Allie M, Turner SJ, et al. Characterization of birdshot chorioretinopathy using extramacular enhanced depth optical coherence tomography. JAMA Ophthalmol. 2013;131:341-350.
11. Sharma S, Lowder CY, Vasanji A, Baynes K, Kaiser PK, Srivastava SK. Automated analysis of anterior chamber inflammation by spectral-domain optical coherence tomography. Ophthalmology. 2015;122:1464-1470.
12. Agrawal R, Salman M, Tan KA, et al. Choroidal vascularity index (CVI)—A novel optical coherence tomography parameter for monitoring patients with panuveitis? PLoS One. 2016;11:e0146344.
13. Agrawal R, Weng RC, Fonollosa A, et al. Outcome measures for disease monitoring in intraocular inflammatory and infectious diseases (OCTOMERIA): Understanding the choroid in uveitis with optical coherence tomography (OCT). Ocul Immunol Inflamm. Published online February 24, 2022. doi: 10.1080/09273948.2022.2026414
14. Pichi F, Curi ALL, Vasconcelos-Santos DV, et al. Optical coherence tomography findings in infectious posterior uveitis. Ocul Immunol Inflamm. Published online February 28, 2022. doi: 10.1080/09273948.2022.2032197.

New Insights in Imaging

What's the potential for home-based OCT?

A feasibility study showed patients could set up the device themselves and capture quality scans.

Nancy Holekamp, MD

By Nancy Holekamp, MD

Take-home points

- A feasibility study of home-based optical coherence tomography found that patients could set up the device and self-capture high-quality daily scans.
- The device could potentially change the treatment paradigm from fixed-interval or treat-and-extend regimens.
- The future could include using this platform in diabetes and diabetic macular edema and retinal vascular occlusive disease.

Home-based, patient-operated optical coherence tomography seems to be not only feasible, but the typical patient with age-related macular degeneration can obtain high-quality scans, results of a pilot study showed.[1]

The recent study essentially proves that you can drop ship an OCT device to someone's home. They can take it out of the box and set it up themselves. They can self-image, producing very high-quality scans of the central macula. Those images can be successfully uploaded to the cloud, and doctors can, from a laptop, access those images to review them—and the images are of sufficient quality that they can also be analyzed by artificial intelligence.

What's noteworthy is that these are all AMD patients. Their median age was 75 years, a group that's thought not to be savvy with technology. This shows that the device really is simple and straightforward to use.

Study design and results

The Home OCT Performance Study was a feasibility study of 15 patients who obtained on average 5.7 (±0.9) scans per week over three months. The study was conducted from December 2020 to August 2021. After a baseline OCT was obtained in the office, participants were sent the Notal Vision Home OCT device and a printed detailed guide via courier—the first time they got to see the device.

All 15 patients completed the study. Ninety-five percent of the scans were obtained successfully. Among all the acquired scans, an average of 76 scans, or 93 percent, were eligible for fluid grading analysis by the Notal OCT Analyzer or NOA (*Figure*). The study used a manufacturer signal quality index (MSI) to quantify image quality. The average MSI among all home-acquired scans was 4.5 (±1.1), and 97 (±6) percent of scans had MSI >2, the recommended threshold for satisfactory imaging. Over the course of the study, the duration of the self-imaging sessions decreased from a median of 45.4 to 38 seconds to scan a single eye.

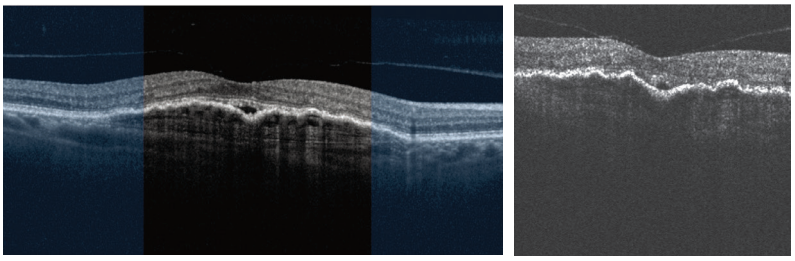
We also know from the study that there

Bio
Dr. Holekamp is director of retina services at Pepose Vision Institute, St. Louis.

DISCLOSURE: Dr. Holekamp is a consultant to and contract researcher for Notal Vision.

was a positive patient experience. Patients took a survey at the conclusion, and they gave it high marks. That resonates with my own experience. I now have had approximately 20 patients on this device through my experience in early phase clinical trials and patients love it.

In our study, the cutoff for vision was 20/200, but we also found out that patients with vision as poor as 20/320 can image themselves.



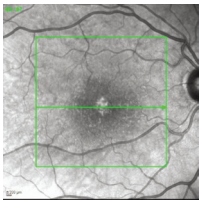


Image quality comparison of in-office Heidelberg Engineering Spectralis optical coherence tomography scan (left) and patient-operated unsupervised, at-home self-imaging with Notal Home OCT (right).

Future studies

A second study is under way. The goal is to demonstrate that the quality of scan is clinically equivalent to what we can obtain in the office. If that study proves to be positive, it could lead to Food and Drug Administration approval. Then I think the next step would be to have studies showing that the Home OCT can reliably decrease the treatment burden or the visit burden.

A key to acceptance of this technology will be physicians' willingness to change their current treatment paradigm. Change is always difficult, but if physicians can learn to trust a validated, highly sophisticated device, then patients can image themselves at home.

The physician can go to the cloud and look at the image and also set thresholds for retinal fluid. If the patient's OCT exceeds those thresholds, an alert can notify the physician that the patient needs a treatment, and the patient just comes in for a shot. It's possible that the patient wouldn't even need an OCT in the office that day because an OCT was obtained at home, and the physician has access to it.

It's also possible that the patient wouldn't have to be on a fixed-interval dosing or even a treat-and-extend regimen, as we currently use. The patient could just come in whenever their fluid reaches the treatment threshold set by the physician.

Potential for home-based OCT

This would be a real change in the treatment paradigm. It could allow for more individualization of treatment, for a lower utilization of resources, and it could ideally cut health-care costs—not only the direct costs of monitoring in the office, but the indirect costs of patients coming to the office, driving several hours, having a family member or caregiver take off work. There are many indirect costs associated with the heavy visit burden and monitoring burden of AMD.

We've learned so much about nAMD by performing OCT daily on patients receiving anti-VEGF therapy. We've learned that there's a wide variety of treatment response and reaccumulation of fluid. We've learned about differences between fluid compartments and how they present in patients, such as subretinal fluid and intraretinal fluid.

In our current practice, we're getting an OCT at day one and day 28, but with Home OCT we can fill in all the other days. We're learning a lot more about this disease than we ever knew before because we have a new way of collecting additional data.

And Home OCT will likely be useful for any retinal disease in which fluid needs to be monitored. The future could include use for diabetes and diabetic macular edema and retinal vascular occlusive disease. So, it has the potential to be a very important and useful research tool. RS

With home-based optical coherence tomography, it's possible that patients wouldn't have to be on a fixed-interval or even a treat-and-extend regimen. They could just come in whenever their fluid reaches the threshold set by the physician.

REFERENCE

1. Liu Y, Holekamp NLM, Heier JS. Prospective, longitudinal study: Daily self-imaging with home OCT in neovascular age-related macular degeneration. Ophthalmol Ret. 2022: doi.org/10.1016/j.oret.2022.02.011.

What's coming in therapies for diabetic retinopathy

Dosing tweaks, emerging delivery systems, biosimilars and gene therapy are changing the treatment paradigm.


Vlad Matei, MD


Geeta Lalwani, MD

By Vlad Matei, MD, and Geeta Lalwani, MD

Take-home points

- Anti-VEGF agents will likely remain a mainstay treatment for diabetic retinopathy and diabetic macular edema for years to come, with different doses, routes of delivery and molecular configurations continuing to evolve.
- Delivery of anti-VEGF agents via an adeno-associated virus vector promises to increase the durability of treatment over conventional direct intravitreal delivery, but the increased risk of intraocular inflammation remains a concern.
- Drug delivery to the suprachoroidal space is an evolving technology that may achieve similar efficacy to intravitreal delivery while averting some of the risks of the latter.
- Laser photocoagulation and pars plana vitrectomy continue to be the only non-pharmacological treatments effective for diabetic retinopathy.

Bio

Dr. Matei is an associate vitreoretinal surgeon at Rocky Mountain Retina Associates, based in Boulder, Colorado.

Dr. Lalwani is a vitreoretinal surgeon and founder and president of Rocky Mountain Retina Associates.

DISCLOSURES: Dr. Matei is a consultant to Carl Zeiss Meditec.

Dr. Lalwani is a consultant to Carl Zeiss Meditec, Genentech and Regeneron Pharmaceuticals.

The relentlessly increasing worldwide burden of diabetic retinopathy continues to fuel strong interest in improving the efficacy and durability of therapy. Beginning in the 1970s, for about 30 years laser photocoagulation was the only therapy for DR. Subsequently, intravitreal steroids were the only pharmacological treatment until intravitreal anti-VEGF agents became widely available.

Anti-VEGF agents were a game-changer and they've been the mainstay of DR/diabetic macular edema treatment for about 15 years. Various types of molecules with different vascular endothelial growth factor isomer affinities have been developed in this time. The recent approval of intravitreal faricimab, an inhibitor of both vascular endothelial growth factor A and angiopoietin-2, was a milestone in the mechanism of action of commercially available DR therapeutics. In light of the hastening pace of DR therapy evolution, we provide an update on emerging therapies for DR.

When considering upcoming treatments, it's helpful to first recognize some of the basic strategies for expanding the repertoire of pharmacologic treatment. Besides targeting various molecular pathways, options include repurposed therapies effective for other diseases, different doses or combinations of existing treatments, alternative pharmacologic vehicles and alternative routes of delivery. In addition, new surgical technologies and techniques can also be developed. DR therapy is evolving on nearly all of these fronts.

Evolution of anti-VEGF therapies

Ranibizumab, the monoclonal antibody fragment that binds to all isomers of VEGF-A, has more recently been incorporated into a sustained-delivery device, surgically implanted through the sclera, for long-term intravitreal drug delivery. This

Port Delivery System, or Susvimo (Genentech/Roche), is refillable in the clinic. On the heels of its approval for neovascular age-related macular degeneration, the Phase III Pagoda and Pavilion trials are evaluating its use for DME and DR, respectively.[1,2] These trials are comparing monthly ranibizumab with PDS refilled every 24 weeks after a monthly loading-dose regimen. The primary endpoint is best-corrected visual acuity. Results are expected in October.

Aflibercept binds to all isomers of VEGF-A as well as VEGF-B and placental growth factor. In the wake of the VIVID, VISTA and DRCR Retina Network Protocol T trials,[3,4] it remains a mainstay of DR therapy. As with other anti-VEGF agents, many retina specialists have anecdotally observed that a higher dose of intravitreal aflibercept seems to improve its efficacy against DME compared to the Food and Drug Administration-approved 2-mg dose. The Phase II/III PHOTON trial in DME is comparing 8-mg aflibercept injections q12 or q16 weeks (each in separate arms) with 2-mg injections q8 weeks. The primary outcome is BCVA change at 48 weeks.[5]

Biosimilars emerge

While ranibizumab and aflibercept are very effective for treating DR, one ongoing drawback is their high costs. The U.S. patent for ranibizumab expired in 2020, while aflibercept's will expire in 2023.

As a result, several companies outside the United States have developed biosimilars for ranibizumab, which are intended to provide the same therapeutic benefit at reduced cost. Per the World Health Organization, biosimilars are biotechnical products comparable in quality and performance to already approved reference products. Unlike generic drugs, which are chemically synthesized according to a drug's established formula, biosimilars are manufactured with living cells according to a reverse-engineered representation of the original drug.[6] Hence, biosimilars may be more immunogenic; their inherent deviation from the original synthetic process may lead to variations in quality.

Since the approval last year of the ranibizumab biosimilar SB11, now known as Byooviz (Samsung Bioepis) for nAMD, macular edema due to retinal vein occlusion and myopic choroidal neovascularization, we expect to see FDA-approved biosimilars for DR in the near future. A number of other biosimilars for nAMD are in development, and one biosimilar developer, Celltrion Healthcare, has initiated a trial of CT-P42, an aflibercept biosimilar, in DME.[7]

Gene therapy

This has been a very active area for investigative treatment to treat exudative disease, as the following programs illustrate.

• ***ADVM-022.*** Using gene therapy to potentially increase the durability of intravitreally administered anti-VEGF agents, ADVM-022 (Adverum Biotechnologies) is an adeno-associated virus vector capsid (AAV.7m8) carrying an aflibercept coding sequence controlled by an expression cassette. It's designed to be delivered as a one-time intravitreal injection.

INFINITY is a Phase II trial evaluating the safety and efficacy of ADVM-022 for DME, in which patients received a single intravitreal injection of aflibercept 2 mg on day one, followed an ADVM-022 injection one week later. They were also prophylactically treated with topical difluprednate for 10 weeks.[8] There were 12, 13 and nine patients in high-dose ADVM-022, low-dose ADVM-022, and control (serial aflibercept injections only) arms, respectively. The 24-week primary endpoint was time to worsening of DME activity (that is, time to requiring a supplemental aflibercept injection). By 24 weeks, only 25 percent of the high-dose and 39 percent of the low-dose groups required any supplemental aflibercept.

However, unfortunately, more than 80 percent of the low-dose and 90 percent of the high-dose patients had intraocular inflammation, including around 10 percent of whom had posterior IOI—although none had vasculitis. More than half of the patients

As with other anti-VEGF agents, many retina specialists have anecdotally observed that a higher dose of intravitreal aflibercept seems to improve its efficacy against DME compared to the approved 2-mg dose.

treated with ADVM-022 had iris-related events, including transillumination defects and synechiae, and a quarter of high-dose patients had hypotony.[9] INFINITY is expected to conclude by year-end.

• ***RGX-314.*** Representing innovations in both gene therapy and alternative routes of drug delivery, RGX-314 (RegenxBio) is an AAV8 vector encoding an anti-VEGF monoclonal antibody fragment that is being studied for subretinal or suprachoroidal delivery. Based on Phase I and II results in nAMD, the Phase II ALTITUDE trial is evaluating RGX-314 on the Diabetic Retinopathy Severity Scale at 48 weeks in patients with nonproliferative DR or mild proliferative DR without center-involved DME.[10]

The trial, expected to be completed in early 2023, is evaluating two doses of RGX-314 delivered suprachoroidally using the RegenxBio Suprachoroidal Space (SCS) Microinjector, which could be employed for in-office injections. Results from the first cohort of 15 patients getting the lower dose of RGX-314, compared to five controls, suggest good tolerability of RGX-314, with a few reports of conjunctival hyperemia or hemorrhage. One patient developing mild episcleritis; none developed IOI.[11] Treated patients demonstrated stable BCVA and one-third had at least a two-step improvement in DRSS.

While these results are encouraging, some authors propose that suprachoroidal AAV8 may induce a different immune response than intravitreal therapy, with a greater potential for vitritis and chorioretinitis.[12]

While results with suprachoroidal AAV8 therapy are encouraging, some authors propose that it may induce a different immune response than intravitreal therapy, with a greater potential for vitritis and chorioretinitis.

• ***Other gene candidates.*** Several additional molecular pathways relevant to DR are being studied, but few of the corresponding drugs have reached or shown positive results at the Phase II stage. OPT-302 (Opthea) is an intravitreally injected anti-VEGF R3 receptor fusion protein that acts as a "trap" molecule to block VEGF-C and VEGF-D. A Phase IIa trial evaluated a combination of OPT-302 and aflibercept in patients with persistent CI-DME following aflibercept monotherapy. At 12 weeks, patients in the combination therapy group gained a mean of 6.6 letters in BCVA vs. a mean of 3.4 letters in patients receiving a combination of sham with aflibercept.[13]

Fenofibrate

While these novel therapies are exciting, there may also be some benefit to repurposing fenofibrate, an established drug for hyperlipidemia, in the treatment of DR. Several studies have proposed that fenofibrate may slow the progression of DR, including by such mechanisms as reducing blood-retina-barrier breakdown.

Most recently in a multicenter cohort study based on a claims database, 5,835 NPDR patients without DME who were taking fenofibrate were found to have a lower incidence of PDR or a composite endpoint of PDR and DME (but not DME alone), when compared with 144,417 NPDR patients who were not taking the drug.[14]

On the basis of this and other hypothesis-generating studies, the DRCR Retina Network is recruiting for a trial comparing fenofibrate and placebo in the prevention of DR worsening over a four-year follow-up in patients with mild to moderately severe NPDR and no CI-DME at baseline.[15]

Nonpharmacologic treatments

Unfortunately, the pipeline of nonpharmacologic treatments for DME hasn't been as fruitful. Photobiomodulation, the irradiation of tissue by far-red to near-infrared light (630-900 nm), demonstrated favorable effects in animal and *in-vitro* studies, including reduced apoptosis, oxidative stress, leukostasis and expression of pro-inflammatory molecules upregulated in DR. DRCR Protocol AE was a Phase II trial of diabetic adults with CI-DME, visual acuity >20/25 and no or minimal prior DME treatment, and compared the effect of PBM to that of an identical-appearing placebo device after four months of follow-up.[16]

Despite a high study completion rate and

no adverse effects among the 69 patients in each of the treatment and placebo arms, PBM did not demonstrate any significant effect on CI-DME compared with placebo. Based on this outcome, DRCR decided not to pursue a Phase III trial. Laser photocoagulation and pars plana vitrectomy remain the only validated surgical options for DR.

Early treatment

Perhaps the most impactful therapy may be disease prevention. Detecting and treating DR at an earlier stage leads to better visual outcomes. Because of the overwhelming number of diabetic patients compared to providers, teleretinal screening has become essential in detecting DR, and artificial intelligence will continue to be a key technology in the evolution of teleretinal screening.

A multicenter, head-to-head, real-world retrospective study of more than 20,000 Veterans Affairs patients with type 2 diabetes compared seven different artificial intelligence algorithms to human graders for detecting DR in fundus photos. The human grader demonstrated 100 percent sensitivity for detecting moderate or worse NPDR, while three of the AI algorithms showed the same sensitivity.[17] Increasingly, refined AI algorithms may compensate for both the interpretation errors and short supply of human graders, making teleretinal screening more effective and accessible.

Bottom line

We've covered several therapies on the horizon for DR, including alternate doses of familiar anti-VEGF agents and biosimilars. Stem cell transplantation is yet another exciting strategy with potential applications in DR, but at this time most of the studies in this arena relevant to DR are still in the basic-science research phase.[18]

Overall, DR treatments in the pipeline have the potential to improve upon the efficacy and durability of existing treatments, although it remains to be seen how these benefits will be offset by safety risks.

REFERENCES

1. ClinicalTrials.gov. Identifier: NCT04108156. This study will evaluate the efficacy, safety, and pharmacokinetics of the port delivery system with ranibizumab in participants with diabetic macular edema compared with intravitreal ranibizumab (Pagoda). Updated April 21, 2022. https://clinicaltrials.gov/ct2/show/NCT04108156?term=NCT04108156&draw=2&rank=1 Accessed March 24, 2022
2. ClinicalTrials.gov Identifier: NCT04503551. A multicenter, randomized study in participants with diabetic retinopathy without center-involved diabetic macular edema to evaluate the efficacy, safety, and pharmacokinetics of ranibizumab delivered via the port delivery system relative to the comparator arm (Pavilion). Updated February 17, 2022. https://clinicaltrials.gov/ct2/show/NCT04503551?term=NCT04503551&draw=2&rank=1 Accessed March 24, 2022.
3. Heier JS, Korobelnik J-F, Brown DM, et al. Intravitreal aflibercept for diabetic macular edema: 148-week results from the VISTA and VIVID studies. Ophthalmology 2016;123:2376-2385.
4. Wells JA, Glassman AR, Ayala AR, et al. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema: two-year results from a comparative effectiveness randomized clinical trial. Ophthalmology 2016;123:1351-1359.
5. ClinicalTrials.gov Identifier: NCT04429503. Study of a high-dose aflibercept in participants with diabetic eye disease (PHOTON). Updated September 2, 2021. https://clinicaltrials.gov/ct2/show/NCT04429503?term=NCT04429503&draw=2&rank=1 Accessed March 3, 2022.
6. Kapur M, Nirula S, Naik MP. Future of anti-VEGF: biosimilars and biobetters. Int J Retina Vitreous 2021;8:2.
7. ClinicalTrials.gov Identifier: NCT04739306. Study to compare efficacy and safety of CT-P42 in comparison with Eylea in patients with Diabetic Macular Edema. Updated August 2, 2021. https://clinicaltrials.gov/ct2/show/NCT04739306?term=NCT04739306&draw=2&rank=1 Accessed April 23, 2022.
8. ClinicalTrials.gov Identifier: NCT0441842. ADVM-022 intravitreal gene therapy for DME (INFINITY). Updated January 11, 2022. https://clinicaltrials.gov/ct2/show/NCT04418427?term=NCT04418427&draw=2&rank=1 Accessed April 22, 2022.
9. Boyer DS. Results from a Phase 2 study of ADVM-022 intravitreal gene therapy for diabetic macular edema: the INFINITY trial. Paper presented at the American Academy of Ophthalmology Retina 2021 Subspecialty Day; November 12, 2021; New Orleans, LA.
10. ClinicalTrials.gov Identifier: NCT04567550. RGX-314 gene therapy administered in the suprachoroidal space for participants with diabetic retinopathy without center-involved diabetic macular edema (ALTITUDE). Updated March 29, 2022. https://clinicaltrials.gov/ct2/show/NCT04567550?term=NCT04567550&draw=2&rank=1 Accessed April 22, 2022
11. Avery RL. Two-year results from the subretinal RGX-314 gene therapy phase 1/2a study for the treatment of nAMD and an update on suprachoroidal trials. Paper presented at the American Academy of Ophthalmology Retina 2021 Subspecialty Day; November 12, 2021; New Orleans, LA.
12. Chung SH, Mollhoff IN, Mishra A, et al. Host immune responses after suprachoroidal delivery of AAV8 in nonhuman primate eyes. Hum Gene Ther 2021;32:682-693.
13. Opthea. Phase 1B/2A DME Clinical Trial: OPT-302-1003 (COMPLETED). https://opthea.com/dme-clinical-trial/ Accessed March 3, 2022.
14. Meer E, Bavinger JC, Yu Y, et al. Association of fenofibrate use and the risk of progression to vision-threatening diabetic retinopathy. JAMA Ophtalmol. Published online April 7, 2022. doi: 10.1001/jamaophthalmol.2022.0633.
15. ClinicalTrials.gov Identifier: NCT04661358. Fenofibrate for prevention of diabetic retinopathy worsening (Protocol AF). Updated January 27, 2022. https://clinicaltrials.gov/ct2/show/NCT04661358?term=NCT04661358&draw=2&rank=1 Accessed April 18, 2022.
16. Kim JE, Glassman AR, Josic K, et al. A randomized trial of photobiomodulation therapy for center-involved diabetic macular edema with good visual acuity (Protocol AE). Ophthalmol Retina. 2022;6:298-307.
17. Lee AY, Yanagihara RT, Lee CS, et al. Multicenter, head-to-head, real-world validation study of seven automated artificial intelligence diabetic retinopathy screening systems. Diabetes Care. 2021;44:1168-1175.
18. Li X-J, Li C-Y, Bai D, et al. Insights into stem cell therapy for diabetic retinopathy: A bibliometric and visual analysis. Neural Regen Res. 2021;16:172-178.

While these novel therapies are exciting, there may also be some benefit to repurposing fenofibrate, a long established drug for hyperlipidemia, in the treatment of diabetic retinopathy.

How not to suffer retractions

Fastidious preoperative documentation will prove to payers you did the surgery.

By Ellen R. Adams, MBA

Retinal surgery is often needed to prevent permanent vision loss. The nature of retinal disease means retinal surgery is often urgent or, in the mind of the surgeon and patient, nonelective.

However, "urgent" doesn't mean you can neglect documenting medical necessity. Payers expect your documentation to support medical necessity as well as the patient's informed consent for treatment. It's important you be familiar with any payer policies for the procedures you perform and apply the same documentation principles to procedures that don't have policies.

Making sense of policies

You're no doubt aware that payer policies vary widely. The Centers for Medicare and Medicaid Services develops National Coverage Determinations (NCDs). Individual Medicare Administrative Contractors (MAC) have Local Coverage Determinations (LCDs). And commercial carriers develop policies that may be vaguely worded or that deem newer procedures "experimental."

Some, like the Medicare NCD for vitrectomy,[1] lack specific documentation requirements. The policy simply lists covered diagnoses and states the need to document medical necessity.

Commercial carriers can be even more challenging. Although a policy may seem quite extensive, the opening salvo can be unnerving, as you can see in this example, including the asterisks and all caps, from Blue Cross/Blue Shield of Illinois' policy for photodynamic therapy (PDT) for choroidal neovascularization: "Coverage: *CAREFULLY CHECK STATE REGULATIONS AND/OR THE MEMBER CONTRACT*"[2]

Since you won't be able to investigate every insurance contract your patients may have, the importance of standardized, comprehensive documentation is clear.

Quotable

Any ophthalmic imaging that demonstrates a worsening disease state or prior procedures that were ineffective or only partially effective will support additional treatments or surgery.

There's some guidance if one reviews a policy like the one from CGS Administrators, the MAC for Region J15. CGS provides a local coverage policy, "Pan Retinal Photocoagulation (PRP) Documentation Requirements," that provides a good starting point to standardize your surgical documentation.[3] The policy states:

The patient's medical record should include but is not limited to:

- *The assessment of the patient by the ordering provider* as it relates to the complaint *(emphasis added) of the patient for that visit.*
- *Relevant medical history.*
- *Results of pertinent tests/procedures.*
- *Signed and dated office visit record/operative report.*

Patient complaint is key

You might think the patient complaint is irrelevant for a procedure such as PRP, retinal cryopexy or vitrectomy. However, all payers require a chief complaint to support surgery. In the case of PRP, the chief complaint may be "poor vision for all activities due to episodic vitreous hemorrhaging, right eye." If the patient has no subjective

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

Bio
Ms. Adams is a consultant with Corcoran Consulting Group. She can be reached at 1-800-399-6565 or at www.corcoranccg.com.

visual complaints, it's important to document the severity of the disease, including likelihood of vision loss, due to the retinal condition.

The patient's medical history should be relevant to the procedure under consideration. Thus, poorly controlled diabetes is significant for diabetic retinopathy; anticoagulation therapy may be relevant in determining the need to move forward with subretinal hemorrhage evacuation.

Recall that the new Evaluation and Management (E/M) exam code rules don't require a full review of systems. (Avoid box-checking!) Conversely, the eye codes require a *relevant* medical history. Obtaining a concise, useful history will streamline the workup, declutter your documentation and meet the payer policy for the majority of surgeries you perform.

Also, the impact of testing is important for determining medical necessity for surgery. Any ophthalmic imaging that demonstrates a worsening disease state or prior procedures that were ineffective or only partially effective will support additional treatments or surgery.

Use a checklist

Both simple and complex tasks, such as documenting a surgical admit, can benefit from a checklist. For your surgical admits, a documentation checklist should include:

- Patient chief complaint with history of present illness.
- Review of medical history relevant to the exam.
- Clear patient-stated effect on activities of daily living when there's a decrease in vision or if the surgery is elective (e.g., epiretinal membrane peel, vitrectomy for floaters).
- Assessment clearly stating the impact of the disease on vision (e.g., "the vitreous hemorrhage is the cause of decreased vision OD") if there's:
  - more than one reason for decreased vision, a clear indication justifying the surgery under consideration; or
  - no current impact on vision (e.g., retinal hole or tear; neovascularization), which is the probable course if the disease isn't treated.
- Clearly documented discussion of the specific risks, benefits and alternative treatments, including no treatment (a consent form doesn't replace the surgeon-patient discussion).
- If applicable, the rationale for scheduling urgent or emergent surgery (e.g., "recommend surgery within 24 hours to prevent further retinal detachment and potential loss of central vision").

Bear in mind that the insurance company paying the claim doesn't share your expertise in retinal disease and surgery. Weak documentation can result in a payer considering a surgery unnecessary. The stronger your documentation, the less likely you'll suffer retractions. Remember, as with all areas of chart documentation, if you didn't write it down, you didn't do it.

REFERENCES

1. Centers for Medicare & Medicaid Services. National Coverage Determination (NCD) Vitrectomy. Publication number 100-3; Manual section number 80.11. https://www.cms.gov/medicare-coverage-database/view/ncd.
2. Blue Cross Blue Shield of Illinois. Medical Policies: Photodynamic therapy (PDT) for choroidal neovascularization (CNV). Number:OTH903.015 http://www.medicalpolicy.hcsc.net/medicalpolicy/activePolicyPage?lid=kx37biep&corpEntCd=IL1 Effective January 1, 2022.
3. Centers for Medicare & Medicaid Services. Medicare Coverage Determination: Billing and Coding: PANRETINAL (Scatter) Laser Photocoagulation. Article ID A56594. https://www.cms.gov/medicare-coverage-database/view/article.

Subretinal blebs

(Continued from page 16)

fovea. The soft tip is positioned to just touch the retinal surface. The fluid is then refluxed with increasing pressure until a bleb of desired size is created (*Figure, page 16*). Generally the amount of pressure needed is 30 to 40 mmHg (25 percent pedal depression). Alternatively, you can set the high end of reflux to 40 mmHg (full pedal depression) to avoid theoretical retinal pigment epithelium trauma from a high-pressure jet stream.

I typically place blebs superotemporally and inferotemporally. I aim to create a bleb that just lifts the edge of the hole rather than refluxing through the hole. This technique can also be performed with a subretinal needle on the extrusion line and requires less pressure since the jet stream of fluid is stronger with a smaller diameter.

For chronic, large holes

This is a helpful adjunctive technique for treating chronic, large holes. My partners at Georgia Retina and I have had good success for >700-µm holes thus far with a 90 percent closure rate and no complications.

In addition to avoiding a retinotomy, this technique uses readily available equipment without the additional cost of a subretinal needle and/or VFC pack. For cases of holes that fail to close after standard initial macular hole surgery, this can be a useful technique as a second surgery prior to plug techniques (e.g., autologous graft or amniotic membrane).

REFERENCES

1. Meyer CH, Szurman P, Haritoglou C, et al. Application of subretinal fluid to close refractory full thickness macular holes: Treatment strategies and primary outcome: APOSTEL study. Graefes Arch Clin Exp Ophthalmol. 2020;258:2151–2161.
2. Felfeli T, Mandelcorn ED. Macular hole hydrodissection: surgical technique for the treatment of persistent, chronic, and large macular holes. Retina. 2019;39:743-752.

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

Burnish your online presence

A look at three essential tools that can boost your social media productivity.

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

A question I've frequently been asked concerns what productivity tools and applications I routinely recommend. Whether you're a relative novice or an advanced user, I'm going to review the three tools I consider invaluable for ophthalmologists and retina specialists on social media.

Platform: Twitter

As I wrote back in October 2019 (www.retina-specialist.com/article/twitter-as-a-microblog), Twitter is the logical starting point for any physician or practice. Twitter is your "microblog" and provides a platform to highlight your brand and connect with colleagues, patients, and others in an easily digestible and enjoyable form.

With a limit of 280 characters or less, Tweets don't require significant time expense, and anyone can read them. Although only registered users can post Tweets and comments, anyone with an internet connection can view your Tweets, allowing colleagues and patients without a Twitter account to still be able to access your professional and practice message.

Since a record of all Tweets is stored on your home page, patients can review your Twitter profile as it provides text, images, and videos that may be of relevance to readers.

News aggregator: Feedly

So, you decided to use Twitter as your predominant platform, but how do you curate content to post and comment on? Feedly (feedly.com) is a news aggregator application for web and mobile devices that allows you to customize compilations of content from various trusted online sources.

Feedly has grown from 500,000 users in 2013 to more than 14 million today and is currently the largest RSS (Really Simple Syndication) reader available.

I routinely use Feedly to facilitate up-to-date content. It provides the ability to categorize multiple RSS feeds into similar topics or folders. For example, you can have a collection on "retina" or "therapeutics" from your favorite publications, blogs and websites. In my opinion, the primary benefit of Feedly is that it provides an efficient source of relevant curated content that can be shared on your social media accounts directly from the Feedly dashboard.

Social media scheduler: Buffer

Whereas Feedly is a content curator and Twitter is the platform for posting that content, you need the ability to organize and manage your social media posts. Buffer (buffer.com) is a social media management tool that allows you to schedule your content and supports Twitter, Facebook, LinkedIn, Instagram and Pinterest.

The Buffer software provides you with tools to create a personalized schedule for posting your content. Moreover, the intuitive interface and browser extensions are ideal for scheduling content from the web. (It works with Chrome, Firefox, Opera and Safari browsers.) Buffer also provides you with analytics and other advanced features for those that desire it.

Bottom line

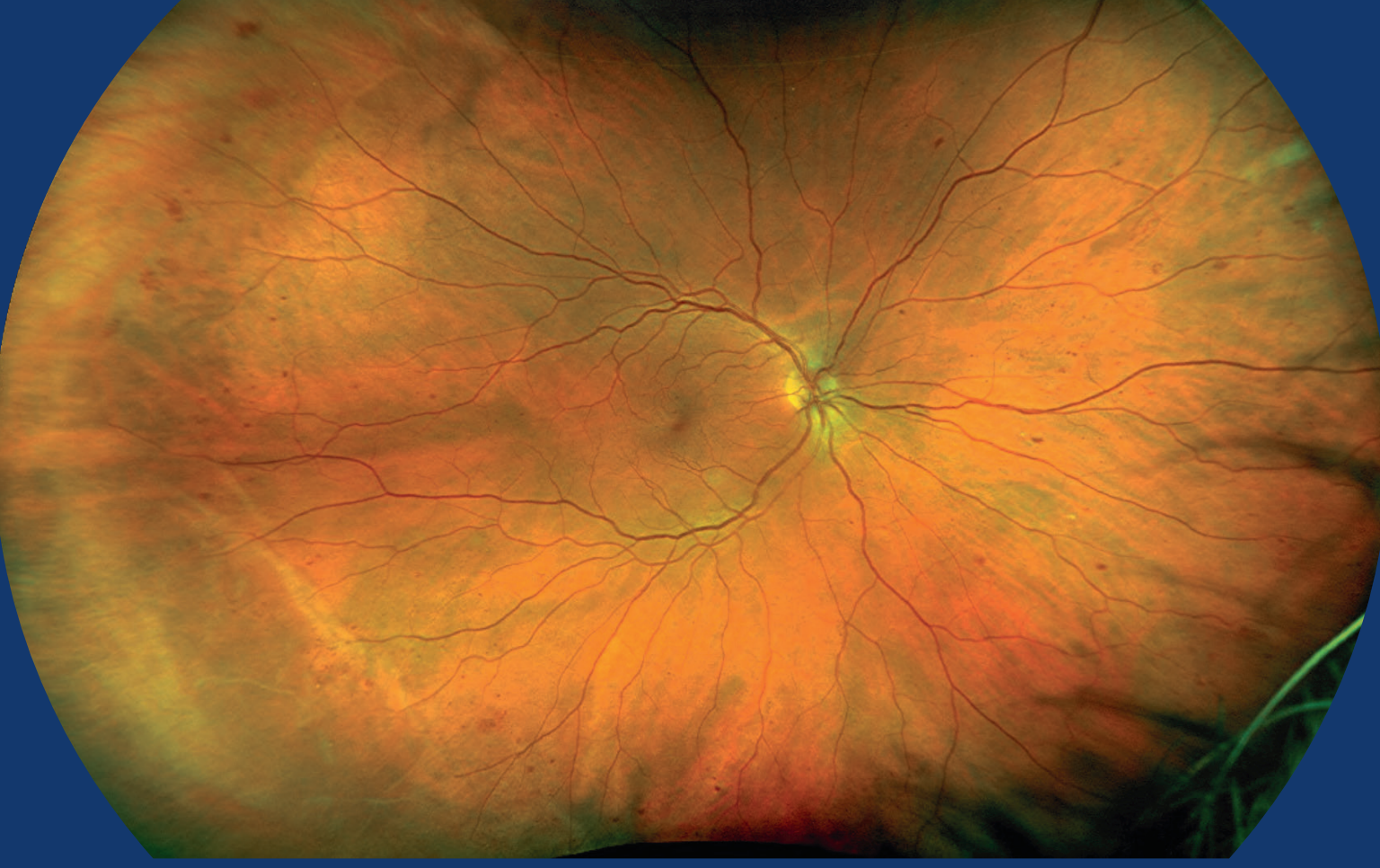
These three productivity tools provide you with the "what" (content curation via Feedly), the "how" (social media post organization with Buffer) and the "where" (Twitter social media platform) for your retina social media presence. The "why" remains up to you.

Bio

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

DISCLOSURE: Dr. Almeida reports no relevant financial relationships.

- Twitter: @davidalmeidamd
- Email: drpa@pm.me.



optomap® Improves Efficiency

The **ONLY** single-capture ultra-widefield retinal image, **opto**map improves practice flow and supports patient engagement.

Decrease patient visit time 33%[1]

66% MORE **Find 66% more pathology[2]**

See 7% more patients[3]

www.optos.com

1. Successful interventions to improve efficiency and reduce patient visit duration in a retina practice; Retina, 2021. 2. Comparison of image-assisted versus traditional fundus examination; Eye and Brain, 2013. 3. The Impact of Ultra-widefield Retinal Imaging on Practice Efficiency; US Ophthalmic Review, 2017.

Nikon

optos®

Apellis is exploring the role of complement in Geographic Atrophy[1]

C3 is the linchpin of complement overactivation in GA.[2-7]

All three complement pathways converge at C3 and it drives multiple downstream effects — inflammation, opsonization, and formation of the membrane attack complex — all of which can ultimately lead to retinal cell death. Increased levels of complement activity have been found not just in the lesion itself, but also in the area just outside the lesion, known as the pre-lesion.[2-9]

Scan the code to explore new territory with us at pre-lesion.com

Apellis

1. Katschke KJ Jr, et al. *Sci Rep*. 2018;8(1):13055. 2. Mastellos DC, et al. *Trends Immunol*. 2017;38(6):383-394. 3. Ricklin D, et al. *Immunol Rev*. 2016;274(1):33-58. 4. Heesterbeek TJ, et al. *Opthalmol Vis Sci*. 2020;61(3):18. 5. Seddon JM, et al. *Nat Genet*. 2013;45:1266-1370. 6. Yates JRW, et al. *N Engl J Med*. 2007;357(6):553-561. 7. Smailhodzic D, et al. *Ophthalmology*. 2012;119(2):339-346. 8. Boyer DS, et al. *Retina*. 2017;37:819-835. 9. Park DH, et al. *Front Immunol*. 2019;10:1007.