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**HOW IMAGING IS ADVANCING MANAGEMENT OF DRY AMD**

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

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- Imaging biomarkers and precision medicine – page 23
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- Will biosimilars find their place in retina? – page 32
- Clinical Trial Closeup: PKal inhibitor THR-149 – page 37

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- Pearls for epiretinal membrane peeling – page 16
• Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments.

• 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.

**CONTRAINDICATIONS**

• Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA. 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.

• Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA. Patients may experience temporary visual disturbances after an intravitreal injection with EYLEA and the associated eye catarract, vitreous detachment, vitreous floaters, and intraocular pressure increased.

**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.

• Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with VEGF inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately.

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

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777 Old Saw Mill River Road, Tarrytown, NY 10591
EYLEA ACHIEVED RAPID, SUSTAINED OUTCOMES IN DME

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

Mean change in BCVA (ETDRS letters) at Year 1 from baseline⁴⁻⁵,₆

<table>
<thead>
<tr>
<th>Initial Gains (Month 5)</th>
<th>Primary Endpoint (Year 1)</th>
<th>Prespecified Exploratory Endpoint (Year 3)</th>
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<tbody>
<tr>
<td>VISTA</td>
<td>VISTA</td>
<td>VISTA</td>
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<tr>
<td>EYLEA Q4</td>
<td>+10.3 (n=154)</td>
<td>+12.5 (n=154)</td>
</tr>
<tr>
<td></td>
<td>(n=136)</td>
<td>(n=136)</td>
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<tr>
<td></td>
<td>*Last observation carried forward; full analysis set. *Following 5 initial monthly doses.</td>
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<tr>
<th>VVID</th>
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<tbody>
<tr>
<td>EYLEA Q8†</td>
<td>+9.9 (n=151)</td>
<td>+10.7 (n=151)</td>
</tr>
<tr>
<td></td>
<td>(n=135)</td>
<td>(n=135)</td>
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<td>+0.2 (n=154)</td>
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<td>+1.6 (n=154)</td>
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<td></td>
<td>(n=132)</td>
<td>(n=132)</td>
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P<0.01 vs control at Year 1.

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

Year 2 data was consistent with results seen in Year 1.⁴⁻⁵

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

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

See what EYLEA could do for your patients with DME at HCP.EYLEA.US

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

ADVERSE REACTIONS

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

INDICATIONS

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


Please see Brief Summary of Prescribing Information on the following page.
Injection site hemorrhage 1% 2% 2% 2%

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

Injection site pain 3% 3% 3% 4%

Intraocular pressure increased 5% 7% 7% 11%

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M/a.altnufactured by:

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

EYL.20.09.0052

In the days following EYLEA administration, patients are at risk of developing endophthalmitis or retinal detachment. If the vision of the affected eye does not improve within 1 to 2 weeks of EYLEA administration, further evaluation by an ophthalmologist is strongly recommended.

Less common adverse reactions reported in <1% of the patients treated with EYLEA were hypotension, retinal detachment, vitreous detachment, and vitreous hemorrhage.

Macular Edema Follow-up Retinal Vein Occlusion (RVO). The data described below reflect exposure to EYLEA in 570 patients with RVO treated with the 2-mg dose in 2 double-masked, controlled clinical studies (VOY and VOXD from baseline to week 52 and from baseline to week 100.

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

Baseline to Week 100

Adverse Reactions

EYLEA (N=1570)

Control (N=1570)

Baseline to Week

EYLEA (N=578)

Control (N=578)

Conjunctival hemorrhage 2% 1% 3% 1%

Retinal detachment 1% <1% 2% <1%

Retinal hemorrhage 2% 1% 3% 1%

Conjunctival hemorrhage 1% 0% 1% 0%

Retinal detachment 1% <1% 1% <1%

Retinal hemorrhage 3% 1% 0% 0%

Retinal detachment 1% <1% 2% <1%

Retinal hemorrhage 2% 1% 3% 1%

Conjunctival hemorrhage 3% 2% 0% 0%

Retinal detachment 3% 2% 2% 1%

Retinal hemorrhage 1% 1% 0% 0%

Retinal detachment 2% 1% 0% 0%

Retinal hemorrhage 1% 1% 0% 0%

Retinal detachment 1% <1% 1% <1%

Retinal hemorrhage 1% 1% 0% 0%

Conjunctival hemorrhage 1% 1% 0% 0%

Retinal detachment 1% <1% 1% <1%

Retinal hemorrhage 0% <1% 0% <1%

Retinal detachment 1% <1% 1% <1%

Retinal hemorrhage 1% <1% 0% <1%

Conjunctival hemorrhage <1% <1% 0% <1%

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Retinal detachment <1% <1% 0% <1%

Retinal hemorrhage <1% <1% 0% <1%

Conjunctival hemorrhage <1% <1% 0% <1%

Retinal detachment <1% <1% 0% <1%

Retinal hemorrhage <1% <1% 0% <1%
Untapped insights

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

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

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

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

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

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

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

## How imaging is advancing management of dry AMD
Emerging modalities and deep learning are helping to expose an old foe in non-neovascular age-related macular degeneration: reticular pseudodrusen.
By Jorge Orellana-Rios, MD, Yuehong Tong, PhD, Nayanika Challa, BS, and Roland Theodore Smith, MD, PhD

## Imaging biomarkers and precision medicine
Advances in technology are creating new opportunities for understanding disease mechanisms.
By Gagan Kalra, MD, and Justis P. Ehlers, MD

## Where genetics, diet and drusen size intersect
A close look at research into how diet may reverse the effect of genetic susceptibility in drusen size progression in AMD.
By Johanna Seddon, MD, ScM

## Will biosimilars find their place in retina?
With patents expiring, an approval pending and legislation aimed at easing regulations, are retina specialists ready?
By Richard Mark Kirkner

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Untapped insights
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NEI-supported group is tackling ophthalmology’s diversity problem

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Retinal sequelae of novel oncology drugs
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Taking treatment beyond adalimumab
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NEI-supported group is tackling ophthalmology’s diversity problem

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

Last month, as Medscape reported, a coalition of Black physicians met with the American Medical Association to press the case for anti-racism initiatives in medicine. The studies of the lack of diversity in ophthalmology defined minority groups traditionally underrepresented in medicine, known as URM. That includes Black, Hispanic, Native American, and Native Hawaiian or Pacific Islander. U.S. Census data shows these URM groups make up 33.4 percent of the population.

**Rabb-Venable Program**

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

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

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

**Improving diversity in retina**

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

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

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

“One of the barriers is not having institutional support or support from advisers in school to pursue this particular field,” Dr. Miller-Ellis says. That gets to high school counselors and American Society of Retina Specialists to engage minority trainees.

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

REFERENCES


For the record

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

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

—Keith H, retinal prosthesis recipient

WE’RE SEEING AMAZING RESULTS. AND SO ARE THEY.

At the Foundation Fighting Blindness our mission is everybody’s vision. Our work shines a light on the darkness of inherited retinal diseases (IRDs).

We’re the world’s leading organization searching for treatments and cures. We need your help to fuel the discovery of innovations that will illuminate the future for so many. We have robust disease information, a national network of local chapters and support groups, local educational events, and our My Retina Tracker® Registry to help keep your patients connected with clinical and research advancements.

Help accelerate our mission by donating at ECPs4Cures.org.

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

**Work-up and imaging findings**

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

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

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

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

**Additional history and diagnosis**

The patient’s Erdheim-Chester disease (ECD) had been resistant to multiple therapies. However, before the onset of visual symptoms, he had started treatment with the BRAF enzyme inhibitor vemurafenib (marketed as Zelboraf), followed by the MEK inhibitor cobimetinib. (MEK stands for MAPK/ERK kinase, or mitogen-activated protein kinases [MAPKs], including extracellular signal-regulated kinases [ERKs].) After he started the cobimetinib, the patient noticed changes in his vision. Given this history and the constellation of imag-
Although we counseled the patient that there was no definitive ocular indication to stop the MEK inhibitor, he was very bothered by the visual changes. After consulting with his oncologist, he decided to discontinue the cobimetinib. Four weeks after the initial visit, his visual acuity had improved to 20/40 OU.

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

**Novel treatments, novel side effects**

After clinical trials reported that trametinib increased patient survival, this MEK inhibitor was the first medication of its class approved to treat metastatic melanoma in 2013. The RAS-RAF-MEK-ERK signal-
In the MEK pathway, cell cycle progression is regulated, and dysregulation of this cascade sequence is widely implicated in malignant cell proliferation. Within this sequence, MEKs phosphorylate and activate MAPK/ERK. By blocking downstream effects, MEK inhibitors block tumor growth and induce cell death via apoptosis.

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

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

Clinical characteristics of MEKAR

The understanding of MEKAR has evolved from case reports and case series. SRF has been noted on examination in up to 90 percent of patients undergoing treatment with a MEK inhibitor. When it occurs, it’s bilateral in more than 90 percent of cases. Intensive monitoring of some clinical trial patients have shown rapid accumulation of SRF (within three hours of administration of the MEK inhibitor) followed by even more rapid resolution (by the fourth hour), although a large portion of patients continue to have SRF at their final follow-up.
As this patient demonstrated, in spite of the SRF, fluorescein angiography doesn’t demonstrate pooling or leakage in MEKAR.

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

MEKAR has been termed CSR-like, but there are important differences between these two conditions. MEKAR is bilateral more than 90 percent of the time, while CSR is bilateral in less than half.14 MEKAR is also frequently multifocal, involves the posterior pole at the fovea and along the arcades, and has no gravitational effect on the fluid as is seen in CSR.13 Furthermore, the pigment epithelial detachments and increased choroidal thickness commonly observed in CSR don’t necessarily occur in MEKAR.14

Treatment

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

Bottom line

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

REFERENCES

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

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

Tumor necrosis factor inhibitors

TNF inhibitors are the most broadly utilized and effective class of biologics for the treatment of uveitis, and adalimumab remains the most widely used. Standard adalimumab dosing is a subcutaneous injection of 40 mg every two weeks after a loading dose of 80 mg followed by 40 mg one week later; loading doses are deferred in children. Although highly effective, about 40 to 60 percent of patients on this regimen will develop treatment failure at one year, according to the VISUAL I and II studies.3 Treatment failure can often be attributed to the development of anti-adalimumab neutralizing antibodies, although insufficient serum levels of adalimumab, or simply non-responsiveness to TNF blockade can also contribute. Testing for the presence of serum anti-adalimumab antibodies can help guide treatment decisions in cases of loss of response. If anti-adalimumab antibodies are absent, increasing the serum level of adalimumab by switching to weekly dosing has been shown to improve uveitis control in about 60 percent of patients.3

Five alternative TNF inhibitors

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

• Infliximab. Of the alternatives, this is the most-studied TNFi in uveitis. The efficacy of infliximab for the treatment of uveitis is likely similar to that of adalimumab.3,5 Unlike adalimumab, which is a fully human monoclonal antibody, infliximab is a...
chimeric human/mouse antibody leading to a higher immunogenicity and greater risk of forming anti-drug antibodies. For this reason, many practitioners recommend concurrent use of an antimetabolite to reduce antibody formation.

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

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

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

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

**Interleukin-6 inhibitors**

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

The APTITUDE trial evaluating tocilizumab in TNFi-refractory JIA uveitis failed to meet its primary endpoint of inflammatory control, although about 30 percent of patients showed improvement when switched from a TNFi to tocilizumab.11 Tocilizumab does appear to be effective for the treatment of retinal vascular leakage, with 83 percent of patients showing improvement in angiographic inflammation (Figure 1).12 Tocilizumab has also proven to be highly effective in the treatment of uveitic macular edema, with early studies showing a dramatic response to treatment (Figure 2).13 Sarilumab (Kevzara, Regeneron Pharmaceuticals) is an alternative to IL-6 inhibition. It has similarly shown efficacy in posterior segment disease, particularly uveitic macular edema.14

**CD-20 inhibitors**

Rituximab is a monoclonal antibody against the CD-20 antigen found on B-lymphocytes. Administered as an IV infusion every six to 12 months, rituximab leads to a depletion of the B-cell population. Compared with the other biologics, the long-lasting effect of rituximab increases its immunosuppressive risk. Although effective in the treatment of orbital inflammatory disease, (Continued on page 17)
Vitreoretinal surgeons are often tasked with peeling visually significant epiretinal membranes off of the macula. Particularly adherent ERM can be difficult to remove entirely, posing a greater risk of iatrogenic trauma and/or postoperative recurrence. Here, we discuss some tips and tricks that can help ensure a complete and successful ERM peel.

**Initiating the peel**

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

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

**Triamcinolone vs. BBG (or ICG)**

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

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

**Four steps for performing an easier epiretinal membrane peeling.**

A) Initiate the peel at the ERM edge with the internal limiting membrane forceps after triamcinolone administration. B) Following Brilliant Blue G staining, align the forceps parallel to and over the edge of membrane, avoiding a deep pinch. C) Pull the initiated flap tangentially along the retinal surface. D) Extend the flap edge circumferentially.
ing” obvious to the surgeon. We prefer BBG and achieve a very effective stain by injecting under direct visualization with a soft-tip cannula aimed over the macula but away from the fovea. We hold the light pipe and the injection cannula in place for one minute to avoid inadvertent dye washout, as the dye settles over the macular area because of its high specific gravity. We then proceed with aspiration of the dye using the vitrector.

Keep forceps tangential to the surface

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

Consider taking the ILM

When confronted with a particularly adherent ERM, we may opt to also peel the underlying ILM. Restaining after ERM peeling can ensure that residual ILM is appropriately visualized and removed. Often, ILM may already have been appropriately visualized and removed. The ILM forceps to tangentially peel is only 27 percent of patients.16

Bottom Line

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

Beyond adalimumab

(Continued from page 15)

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

Other anti-inflammatory biologics

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

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

Bottom line

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

REFERENCES

Imaging in dry AMD

How imaging is advancing management of dry AMD

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

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

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

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

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

New understanding of AF principles

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

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

Currently, the confocal scanning laser ophthalmoscope (cSLO) attains a higher-quality RPE image than the conventional fundus camera. The FAF is the highest at 10 degrees from fovea, but diminishes at the fovea because of obstruction from the...
macular pigment, although FAF is relatively homogeneous over the remainder of the posterior pole and retinal periphery. Hence, FAF follows the distribution of rods. The outer segments of these photoreceptors are the primary precursors of lipofuscin-derived RPE fluorophores.3

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

Subtypes of FAF imaging

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

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

Total ultrastructural reconstruction of adult human perifoveal RPE indicates that there are more than 1,400 organelles significant to imaging.6 At least half are L or ML capable of generating FAF. Some of these organelles, specifically the melanosomes,
preferentially localize to the apical processes of RPE cells. They not only shadow more posteriorly localized fluorophores, but they also may contribute their own FAF signal.\(^7\)

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

**Exposing an old foe: Reticular pseudodrusen**

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

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

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

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

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

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

**Potential role of AI**

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

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

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

**Possible CVD-RPD connection**

Additionally, growing evidence is linking cardiovascular disease (CVD) and RPD. Patients with coronary artery disease (CAD) have reticular macular disease more often
than those who don’t,\textsuperscript{14} and definitely have thinner choroids.\textsuperscript{15} RPD are associated with decreased longevity,\textsuperscript{16} with CVD long suspected as the culprit. This theory of CVD causality received recent striking support from a histopathology of 1,777 study eyes.\textsuperscript{17}

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

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

**Next-gen AF assessment in AMD**

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

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

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

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

**Growing evidence is linking cardiovascular disease and reticular pseudodrusen.** Patients with coronary artery disease have reticular macular disease more so than those without CAD, and they definitely have thinner choroids.
The fluorescence lifetime is the average amount of time a fluorophore remains in the excited state following excitation. The FLIO device is also based on an OCT system. Autofluorescence lifetimes are excited at 473 nm and recorded in two spectral wavelengths channels. Typically, mean autofluorescence lifetimes in a 30-degree retinal field are investigated. For example, in non-nAMD, ring patterns of prolonged FLIO lifetimes 1.5 to 3 mm from the fovea can be appreciated.

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

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

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

We also studied the drusen spectral signature at \(\lambda_{\text{ex}} 450\) nm excitation and demonstrated that it also has a peak at 510 nm and a similar shape to that at \(\lambda_{\text{ex}} 436\) nm.

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

(Continued on page 27)
Imaging biomarkers and precision medicine

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

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

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

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

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

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

Visualizing enhanced anatomy on OCT
The incredible anatomic details that spectral-domain OCT and swept-source OCT provide have revolutionized the field through their impact on diagnosis, disease surveillance and assessment of therapeutic response. Qualitative feature assessment of...
specific retinal layers and zones has been linked to functional impact and outcomes, including location of retinal fluid and integrity of outer retinal bands. Historically, many of these assessments of retinal integrity were primarily qualitative and often binary. The inability to quantify these features limited the widespread impact of these assessments.

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

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

**Transformative OCT advances**

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

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

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

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

**Biomarkers in AMD, GA**

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

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

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

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

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

Vascular biomarkers on UWFA, OCTA

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

The labor-intensive nature of manual feature assessment had been a barrier to more widespread use. Recently, methods and systems have been developed to provide important context, they limit the resolution of comparative evaluation between other key features of interest.
in-depth evaluation of leakage features, microaneurysm counts, ischemic burden and vascular characteristics (Figure 4).15,16 Machine learning systems have provided the ability to perform enhanced vascular segmentation, feature extraction, and more efficient methods for evaluating imaging characteristics.17-19 The binary depth-encoded nature of OCTA has also provided a new frontier in quantitative feasibility of vascular analysis.

**Vascular biomarkers in DR, DME**

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

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

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

One study of swept-source OCTA found the foveal avascular zone to be significantly higher in diabetic eyes than controls.29 In addition, eyes with DR had larger mean perifoveal intercapillary area (PIA) than controls.20 Utilizing quantitative OCTA parameters, novel classification systems for DR have also been proposed using features such as blood vessel tortuosity, vascular caliber, vessel perimeter index, blood vessel density, FAZ area and FAZ contour irregularity.30,31

**Bottom line**

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

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

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

By Johanna Seddon, MD, ScM

Take-home points

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

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

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

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

Evaluating the role of diet

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

- vegetables (excluding potatoes);
- fruits;
• legumes;
• whole grains;
• nuts;
• fish;
• red and processed meats;
• alcohol consumption; and
• the ratio of monounsaturated to saturated fatty acid (MUFA:SFA).
Scores of 1 or 0 were assigned depending on intake of these components. A score of 9 represents perfect adherence; 0 represents complete non-adherence. For our purposes, we categorized aMeDi scores in two categories: low (0 to 3); and medium-high (4 to 9).

Genotype data
We found that the following genetic variants in the complement pathway were significantly associated with a two-step progression in drusen size, adjusting for other covariates:
• CFH Y402H;
• CFH rs1410996;
• CFH R1210C;
• C2 E318D;
• C3 R102G; and
• C3 K155Q.
Variants in the following genes were also significantly associated with a two-step progression in drusen size:
• ARMS2/HTRA1;
• VEGF-A;
• TIMP3; 
• NPLOC4; and
• HSPH.

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

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

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

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

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

Table 1. Genetic factors associated with drusen size progression12

<table>
<thead>
<tr>
<th>Drusen size progression</th>
<th>Hazard ratio (95% CI)*</th>
<th>p value</th>
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</tr>
<tr>
<td>C2 E318D: rs9332739</td>
<td>0.44 (0.28 - 0.69)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>C3 R102G: rs2230199</td>
<td>1.45 (1.26 - 1.67)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>C3 K155Q: rs147859257</td>
<td>2.19 (0.98 - 4.88)</td>
<td>0.05</td>
</tr>
<tr>
<td><strong>ANGIOGENESIS PATHWAY</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VEGF-A: rs943080</td>
<td>1.19 (1.04 - 1.36)</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>IMMUNE INFLAMMATORY PATHWAY</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARMS2/HTRA1 A69S: rs10490924</td>
<td>1.34 (1.17 - 1.54)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>EXTRACELLULAR MATRIX</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIMP3: rs9621532</td>
<td>1.52 (1.16 - 2.01)</td>
<td>0.003</td>
</tr>
<tr>
<td><strong>DNA REPAIR/PROTEIN BINDING</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPLOC4/TSPAN10: rs9895741</td>
<td>1.16 (1.02 - 1.32)</td>
<td>0.02</td>
</tr>
<tr>
<td>HSPH1/B3GALTL: rs9542236</td>
<td>1.21 (1.06 - 1.39)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

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

Percent of eyes that progressed to larger drusen size

Risk alleles linked to drusen growth

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

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

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

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

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

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

Dietary factors

Prospective studies in the United States and Europe have documented the protective effects of the Mediterranean diet against AMD.3,13 The elements of the Mediterranean diet have been well documented: fish
rich in omega-3 fatty acids, fruits, vegetables, legumes, olive oil and nuts. These foods contain vitamins and minerals such as vitamins B, C and E, zinc, lutein and zeaxanthin, as well as healthy fats that nourish vision, act as antioxidants and have anti-inflammatory properties.1-3,12,23

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

**Bottom line**

We’ve closed some of the knowledge gaps surrounding factors associated with drusen growth, and we’ve provided more information on genetic variants that may influence drusen growth that can lead to progression from early to advanced AMD. Recent study results underscore the role a healthy diet may have in the pathogenesis of this disease, even in the earlier stages.12-23 These findings can help us develop strategies to better manage AMD progression in the most vulnerable patients.25

**REFERENCES**


**Table 2. Association between drusen size progression, genetic susceptibility and Mediterranean diet score**

<table>
<thead>
<tr>
<th></th>
<th>Progressors Mean (SD)</th>
<th>Non-progressors Mean (SD)</th>
<th>Hazard ratio (95% CI)*</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genes score †</td>
<td>1.06 (0.49)</td>
<td>0.81 (0.45)</td>
<td>2.68 (2.23-3.23)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>aMeDi score</td>
<td>n (%)</td>
<td>n (%)</td>
<td>375 (19)</td>
<td>0.83 (0.68-0.99)</td>
</tr>
<tr>
<td>Low (0 to 3)</td>
<td>212 (21)</td>
<td>796 (79)</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Medium to high (4 to 9)</td>
<td>375 (19)</td>
<td>1640 (81)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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


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Will biosimilars find their place in retina?

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

Richard Mark Kirkner, Editor

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

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

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

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

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

Clinical trial results
No fewer than eight anti-VEGF biosimilars are under development, four referencing each aflibercept and ranibizumab. South Korea-based Samsung Bioepis and U.S. partner Biogen last year filed for Food and Drug Administration approval for its ranibizumab biosimilar candidate, SB11. This biosimilar candidate was also the subject of one of two trial results published this year. In 705 patients, the trial found SB11 equivalent to the reference drug in terms of best-corrected visual acuity at eight weeks and optical coherence tomography central subfield thickness at four weeks.
The second trial, a 48-week study of FYB201 (Bioeq) in 477 patients with neovascular age-related macular degeneration, found equivalence with reference ranibizumab for BCVA improvement and ocular and systemic safety.2

**Economics of biosimilars**

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

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

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

**Overcoming regulatory barriers**

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

This spring, President Biden signed two pieces of legislation that could make biosimilars more widely available. In April he signed the Advancing Education on Biosimilars Act. Meaghan Rose Smith, executive director of the trade group Biosimilars Forum, says the law is “to
ensure that patients and providers have all of the educational resources and materials they need to be assured of the safety and efficacy of biosimilars.” The Biosimilars Forum notes the bill requires the FDA to advance education and awareness among healthcare providers about biological products. That includes developing or improving continuing education programs.

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

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

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

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

Retina specialists need some of that education

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

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

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

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

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

(Continued on page 38)
The 2021 evaluation and management guidelines from the American Medical Association have a straightforward premise: Code your visit based on problems, data and management, and don’t count history and exam elements. Yet, there are some points in these guidelines that are hard to appreciate, especially in light of recent clarifications the AMA published in March. I’ll review them here.

Minor and major surgery

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

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

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

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

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

Identified risk factors for surgery

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

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

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

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

By Ellen R. Adams, MBA

**Bio**

Ms. Adams is a consultant with Corcoran Consulting Group. She can be reached at 1-800-399-6565 or at www.corcoranccg.com.
The AMA’s guidelines would be easier to appreciate if they included examples. While those examples may be developed and published later on, the 2021 CPT manual doesn’t contain them.

**Services reported separately**

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

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

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

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

**Data elements**

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

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

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

**AMA provided more clarity about these discussions**

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

As a practical matter, a claim for an office visit would typically not be held for a delayed (Continued on page 38)
How THR-149 targets alternate pathway

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

REFERENCES

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

REFERENCE
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