Emerging imaging methods may help catch diseases earlier.

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iCare EIDON FA

Dynamic perspective of retinal vasculature

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I’ve been preparing a talk on practical tips for treating geographic atrophy. Ever since wet age-related macular degeneration therapies became available, many patients have been clamoring for a GA treatment. Now, we have two Food and Drug Administration-approved drugs, pegectacoplain (Syfovre, Apellis) and avacincaptad pegol (Izervay, Astellas), both of which have shown modest but significant reductions in GA growth over the course of two years but without any prespecified visual benefits.

So, a debate rages as to whether we should be treating these patients.1,2

On the pro side are several important points: 1) less GA progression will save more overall vision; 2) we don’t have the proper tests to assess visual function or the studies didn’t look at the right endpoints, which is why no visual benefit has been seen; 3) we should be treating even sooner when the atrophy is small and farther from the foveal center; 4) with more time, we will eventually see a vision benefit since the effect of the drugs improves the longer a patient is on it; and 5) this is the best thing available now and will help bridge the gap until something better comes out.

Arguments against include: 1) without a definite vision benefit, it doesn’t make sense to treat; 2) these drugs are slowing down atrophy growth marginally when you delve into the numbers and they may just be delaying clearance of cells that are already not functioning, which explains the disconnect with lack of visual benefit; 3) the potential side effects are serious, including endophthalmitis, increased macular neovascularization risk and inflammation, of which occlusive retinal vasculitis is most concerning; 4) we shouldn’t make assumptions about potential visual benefits with earlier or longer treatment courses without solid evidence; and 5) the treatment carries a significant burden for patients and providers with ongoing monthly or bimonthly injections and may have a serious impact on health-care spending with unclear benefits.

One of the difficulties is that we don’t really know who will benefit from these treatments. We are left looking at each individual and assessing current vision, location and size of GA, fellow eye status, etc.

The second issue is that we currently have no good way to tell if the treatment is helping. Looking at the post-hoc vision loss analyses, it looks like these drugs may be slowing things down by a few months at best.

There’s no question that we need better tools to guide our decision-making. Imagine an algorithm that can project GA growth into the future and then being able to superimpose the effect of treatment on altering that course.

However, we ultimately need high-quality studies, not just post-hoc analyses, to convince us whether there’s indeed a functional benefit and quell this debate. ☹️

REFERENCES

2. Del Priore UV. To treat or not to treat geographic atrophy – that is the question. Ophthalmol Retina. 2018;3:517-20.
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SYFOVRE® (pegcetacoplan injection) 15 mg / 0.1 mL

SAFETY AND EFFICACY INFORMATION

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

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS
- SYFOVRE is contraindicated in patients with ocular or periocular infections, and in patients with active intraocular inflammation

WARNINGS AND PRECAUTIONS
- Endophthalmitis and Retinal Detachments
  - Intraocular injections, including those with SYFOVRE, may be associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering SYFOVRE to minimize the risk of endophthalmitis. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately.
- Retinal Vasculitis and/or Retinal Vascular Occlusion
  - Retinal vasculitis and/or retinal vascular occlusion, typically in the presence of intraocular inflammation, have been reported with the use of SYFOVRE. Cases may occur with the first dose of SYFOVRE and may result in severe vision loss. Discontinue treatment with SYFOVRE in patients who develop these events. Patients should be instructed to report any change in vision without delay.
- Neovascular AMD
  - In clinical trials, use of SYFOVRE was associated with increased rates of neovascular (wet) AMD or choroidal neovascularization (12% when administered monthly, 7% when administered every other month and 3% in the control group) by Month 24. Patients receiving SYFOVRE should be monitored for signs of neovascular AMD. In case of increased Intraocular Pressure, anti-Vascular Endothelial Growth Factor (anti-VEGF) is required, it should be given separately from SYFOVRE administration.

ADVERSE REACTIONS
- Most common adverse reactions (incidence ≥5%) are ocular discomfort, neovascular age-related macular degeneration, vitreous floaters, conjunctival hemorrhage.

The CMS-assigned permanent J-code for SYFOVRE is J2781—effective 10/1/23

SYFOVRE achieved continuous reductions in mean lesion growth rate* vs sham pooled from baseline to Month 24.4

- Monthly
  - OAKS trial (mm²): 3.11 vs 3.98 22%
  - DERBY trial (mm²): 3.28 vs 4.00 18%
- Every Other Month (EOM)
  - OAKS trial (mm²): 3.26 vs 3.98 18%
  - DERBY trial (mm²): 3.31 vs 4.00 17%

SE in trials (monthly, EOM, sham pooled):
- OAKS: 0.15, 0.13, 0.14; DERBY: 0.13, 0.13, 0.17.

* Slope for baseline to Month 24 is an average of slope of baseline to Month 6; Month 6 to Month 12; Month 12 to Month 18, and Month 18 to Month 24.

Based on a mixed effects model for repeated measures assuming a piecewise linear trend in time with knots at Month 6, Month 12, and Month 18.

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

References:
SYFOVRE® (pegcetacoplan injection), for intravitreal use

**BRIEF SUMMARY OF PRESCRIBING INFORMATION**

Please see SYFOVRE full prescribing information for details.

**INDICATIONS AND USAGE**

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

**CONTRAINDICATIONS**

Ocular or Pericellular Infections
SYFOVRE is contraindicated in patients with ocular or pericellular infections.

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

**WARNINGS AND PRECAUTIONS**

Endophthalmitis and Retinal Detachments
Intravitreal injections, including those with SYFOVRE, may be associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering SYFOVRE in order to minimize the risk of endophthalmitis. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately.

Retinal Vascularitis and/or Retinal Vascular Occlusion
Retinal vasculitis and/or retinal vascular occlusion, typically in the presence of intraocular inflammation, have been reported with the use of SYFOVRE. Cases may occur with the first dose of SYFOVRE and may result in severe vision loss. Discontinue treatment with SYFOVRE in patients who develop these events. Patients should be instructed to report any change in vision without delay.

Neovascular AMD
In clinical trials, use of SYFOVRE was associated with increased rates of neovascular (wet) AMD or choroidal neovascularization (12% when administered monthly, 7% when administered every other month and 3% in the control group) by Month 24. Patients receiving SYFOVRE should be monitored for signs of neovascular AMD. In case anti-Vascular Endothelial Growth Factor (anti-VEGF) is required, it should be given separately from SYFOVRE administration.

Intraocular Inflammation
In clinical trials, use of SYFOVRE was associated with episodes of intraocular inflammation including: vitritis, vitreal cells, iridocyclitis, uveitis, anterior chamber cells, iritis, and anterior chamber flare. After inflammation resolves patients may resume treatment with SYFOVRE.

Increased Intraocular Pressure
Acute increase in IOP may occur within minutes of any intravitreal injection, including with SYFOVRE. Persuasion of the optic nerve head should be monitored following the injection and managed as needed.

**ADVERSE REACTIONS**

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

A total of 830 patients with GA in two Phase 3 studies (OAKS and DERBY) were treated with intravitreal SYFOVRE, 15 mg (0.1 mL of 150 mg/mL solution). Four hundred nineteen (419) of these patients were treated in the affected eye monthly and 420 were treated in the affected eye every other month. Four hundred seventeen (417) patients were assigned to sham. The most common adverse reactions (≥5%) reported in patients receiving SYFOVRE were ocular discomfort, neovascular age-related macular degeneration, vitreous floaters, and conjunctival hemorrhage.

**Table 1: Adverse Reactions in Study Eye Reported in ≥2% of Patients Treated with SYFOVRE Through Month 24 in Studies OAKS and DERBY**

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>PM (N = 419)</th>
<th>PEOM (N = 420)</th>
<th>Sham Pooled (N = 417)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ocular discomfort*</td>
<td>13</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>Neovascular age-related macular degeneration*</td>
<td>12</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Vitreous floaters</td>
<td>10</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Conjunctival hemorrhage</td>
<td>8</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Vitreous detachment</td>
<td>4</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Retinal hemorrhage</td>
<td>4</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Punctate keratitis*</td>
<td>5</td>
<td>3</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Posterior capsule opacification</td>
<td>4</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Intraocular inflammation*</td>
<td>4</td>
<td>2</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Intraocular pressure increased</td>
<td>2</td>
<td>3</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

**PM:** SYFOVRE monthly, **PEOM:** SYFOVRE every other month

*The following reported terms were combined:

Ocular discomfort included: eye pain, eye irritation, foreign body sensation in eyes, ocular discomfort, abnormal sensation in eye.

Neovascular age-related macular degeneration included: exudative age-related macular degeneration, choroidal neovascularization.

Punctate keratitis included: punctate keratitis, keratitis

Intraocular inflammation included: vitritis, vitreal cells, iridocyclitis, uveitis, anterior chamber cells, iritis, anterior chamber flare

Endophthalmitis, retinal detachment, hyphema and retinal tears were reported in less than 1% of patients. Optic neuropathy was reported in 1.7% of patients treated monthly, 0.2% of patients treated every other month and 0.0% of patients assigned to sham.Deaths were reported in 6.7% of patients treated monthly, 3.6% of patients treated every other month and 3.8% of patients assigned to sham. The rates and causes of death were consistent with the elderly study population.

**Postmarketing Experience**

The following adverse reactions have been identified during postapproval use of SYFOVRE.

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Eye disorders: retinal vasculitis with or without retinal vascular occlusion.

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

**Risk Summary**

There are no adequate and well-controlled studies of SYFOVRE administration in pregnant women to inform a drug-associated risk. The use of SYFOVRE may be considered following an assessment of the risks and benefits.

Systemic exposure of SYFOVRE following ocular administration is low. Subcutaneous administration of pegcetacoplan to pregnant monkeys from the mid gestation period through birth resulted in increased incidences of abortions and stillbirths at systemic exposures 1040-fold higher than that observed in humans at the maximum recommended human ophthalmic dose (MRHOD) of SYFOVRE (based on the area under the curve (AUC) systemically measured levels). No adverse maternal or fetal effects were observed in monkeys at systemic exposures approximately 470-fold higher than that observed in humans at the MRHOD.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2.4% and 15-20%, respectively.

**Lactation**

**Risk Summary**

It is not known whether intravitreal administered pegcetacoplan is secreted in human milk or whether there is potential for absorption and harm to the infant. Animal data suggest that the risk of clinically relevant exposure to the infant following maternal intravitreal treatment is minimal. Because many drugs are excreted in human milk, and because the potential for absorption and harm to infant growth and development exists, caution should be exercised when SYFOVRE is administered to a nursing woman.

**Females and Males of Reproductive Potential**

**Contraception**

Female: It is recommended that women of childbearing potential use effective contraception methods to prevent pregnancy during treatment with intravitreal pegcetacoplan. Advise female patients of reproductive potential to use effective contraception during treatment with SYFOVRE and for 40 days after the last dose. For women planning to become pregnant, the use of SYFOVRE may be considered following an assessment of the risks and benefits.

**Geriatric Use**

In clinical studies, approximately 97% (813/839) of patients randomized to treatment with SYFOVRE were ≥ 65 years of age and approximately 72% (607/839) were ≥ 75 years of age. No significant differences in efficacy or safety were seen with increasing age in these studies. No dosage regimen adjustment is recommended based on age.

**PATIENT COUNSELING INFORMATION**

Advise patients that following SYFOVRE administration, patients are at risk of developing endophthalmitis, retinal detachments, retinal vasculitis with or without retinal vascular occlusion and neovascular AMD. If the eye becomes red, sensitive to light, painful, or if a patient develops any change in vision such as flashing lights, blurred vision or metamorphopsia, instruct the patient to seek immediate care from an ophthalmologist. Patients may experience temporary visual disturbances associated either with the intravitreal injection with SYFOVRE or the eye examination. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

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In the past few years, the FDA has approved several novel hypoglycemic medications, such as GLP-1 agonists (e.g., Ozempic) or SGLT-2 inhibitors (e.g., Farxiga and Jardiance), indicated for patients with diabetes to help improve glucose control, consequently helping stave off disease-related complications like diabetic retinopathy. While keeping blood sugars in range reduces long-term risks of microvascular complications in diabetes mellitus, research is conflicting regarding the specific effects of these popular new drugs on DR progression. To investigate, the authors of a new clinical cohort study evaluated the effects of both GLP-1 agonists and SGLT-2 inhibitors on DR and its progression using a large, diverse, real-world population database. Their findings, described below, were recently published in the *American Journal of Ophthalmology*.

Included patients had an ICD-10 code of non-proliferative DR and monotherapy treatment, excluding insulin, with GLP-1 agonists or SGLT-2 inhibitors. Those with a history of PDR were excluded. The researchers compared the rate of progression to PDR and rate of development of diabetic macular edema between patients on GLP-1 agonists vs. those on SGLT-2 inhibitors. After propensity score matching, a total of 6,481 patients were identified in each medication group.

The results showed that patients on monotherapy with GLP-1 agonists had a higher rate of progression to PDR compared to those on SGLT-2 inhibitors, demonstrated at year one and year three after initiation of therapy. The GLP-1 agonist group also had a higher rate of new-onset DME than the SGLT-2 inhibitor group, observable at multiple time points, including three months, six months, one year and three years after initiation of therapy. Importantly, the researchers also pointed out in their paper, “This class-specific difference in developing vision-threatening complications appeared to be more pronounced over time.”

Study co-author Ehsan Rahimy, MD, of Stanford University, notes that the results didn’t exactly come as a surprise. “Our working hypothesis is that the cases that get worse are likely patients who don’t have good A1C to begin with and they go on these GLPs and get this massive reduction—almost like their sugar level crashes,” he says. “Just imagine that delta—that change—where the velocity of the correction is somewhat disrupting the homeostasis of the retinal microvasculature environment. The reason I say it doesn’t surprise us that much is there have been case examples of this in the past, such as when patients were getting gastric banding or bariatric surgery. Those were other examples of an extreme where some patients just stopped eating and lost so much weight that their A1C levels crashed and we’d see a worsening of the retinopathy.

“This is not to say anything negative about this class of medications,” Dr. Rahimy continues. “I’ve seen patients do well on them. They’re truly revolutionary agents, as we’re seeing their application across so many other areas of medicine. We need to better understand which patients we potentially need to monitor more closely, and to come up with better guidelines as eye-care providers on how we want to screen, especially in new starts on these meds or patients already on them.”

There was no significant difference in mean HbA1c levels or the need for secondary interventions such as intravitreal anti-VEGF injections, panretinal laser photocoagulation or pars plana vitrectomy between the GLP-1 agonist group and the SGLT-2 inhibitor group, except for a slightly higher need for anti-VEGF agents in the GLP-1 agonist group at three years.

The researchers concluded, “Our large retrospective cohort study found that GLP-1 agonists carried a higher rate of progression to PDR and DME compared to SGLT-2 inhibitors.” They encouraged clinicians “to be aware of these potential effects and to consider the current retinopathy status when initiating treatment with newer hypoglycemic agents to ensure these patients are appropriately monitored for developing potential vision-threatening complications.”

**REFERENCE**

The Verdict on Aspirin and AMD Prevention

Although treatments that restore vision lost from age-related macular degeneration have flourished in the nearly two decades since the advent of anti-VEGF agents, there remains no proven intervention that can prevent onset on a widespread scale. Clinicians are left to advising patients on lifestyle modifications, including dietary changes and considerations of AREDS supplements when appropriate. Aspirin, it seems, will be no help either.

That intervention was explored in a new study published yesterday in *JAMA Ophthalmology.* Researchers looked at data from a large double-masked, placebo-controlled trial called Aspirin in Reducing Events in the Elderly (ASPREE), jointly conducted in the United States and Australia from 2014 to 2018 that tested for efficacy of low-dose aspirin to prolong disability-free survival of older adults. An offshoot of the main study called ASPREE-AMD looked specifically at aspirin’s influence on the course of the disease.

This substudy enrolled a total of 4,993 Australian individuals in ASPREE aged 70 or older without dementia, independence-limiting physical disability, cardiovascular disease, or chronic illness limiting five-year survival and withgradable retinal images at baseline. Participants either received 100 mg per day of aspirin or a placebo for three years. At trial termination, retinal follow-up data were available for 3,208 patients, with 3,171 being analyzed for AMD incidence and progression. This resulted in a median age of 73.3 years of age and median follow-up time was 3.1 years.

The aspirin group saw a cumulative AMD incidence of 19.4 percent (195 of 1,004) while the placebo group’s AMD rate was 19.1 percent (187 of 979). Cumulative progression from early/intermediate AMD to late AMD rates were also similar; the aspirin group rate was 2.3 percent (14 of 615) and the placebo group was 3.1 percent (18 of 573).

It should be noted that the ASPREE trial was terminated early and thus captured fewer cases of AMD progression. However, there was also no subgroup of participants for which the effects were different from the main results. That is, aspirin’s impact on AMD was not affected by age, use of alcohol or smoking, sex, BMI, hypertension or use of statins. As well, no evidence suggested that late AMD was more likely to occur in the group randomized to low-dose aspirin.

The study authors relay in their journal article that aspirin was proposed as an intervention for AMD because of its anti-inflammatory property, since inflammation likely plays a role in AMD pathogenesis. These suggestions that aspirin may be beneficial for reducing either AMD risk or progression came from the earlier randomized clinical trials of the Physicians’ Health Study with five-year treatment and the Women’s Health Study with 10-year treatment. However, neither result in these two studies were significant, despite the larger sample sizes and longer aspirin exposure. Both were limited instead by reliance on self-reported AMD status and confirmed by medical reports. Self-reporting is inaccurate, though, especially in early AMD stages.

In the *JAMA Ophthalmology* article, the authors succinctly summarize that, “overall, these results do not support the suggestion that low-dose daily aspirin prevents the development or progression of AMD.”

**REFERENCE**


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**IN BRIEF**

Biocon Biologics recently announced that the FDA has approved Yesafili (afibercept-jbvf), an interchangeable biosimilar for its reference product, aflibercept (Eylea, Regeneron). Yesafili is a vascular endothelial growth factor inhibitor intended for the treatment of neovascular age-related macular degeneration, visual impairment due to macular edema secondary to retinal vein occlusion (branch RVO or central RVO), visual impairment due to diabetic macular edema and visual impairment due to myopic choroidal neovascularization. The company didn’t specify when the drug will be available for purchase, however.

AEYE Health received the first FDA clearance for a fully autonomous AI that diagnoses referable diabetic retinopathy from retinal images obtained by a handheld camera. Combining a fully autonomous AI with a handheld device, the company says that the portable solution can be used for point-of-care screening, whether in the clinic or at home.

Haag-Streit launched the Eyesi Indirect Ophthalmoscope ROP Simulator for training of retinal exams on premature babies and classification of retinopathy of prematurity.

Iveric Bio announced the U.S. Centers for Medicare and Medicaid Services assigned a unique, permanent Healthcare Common Procedure Coding System J-code for Izerxay (avacincapted pegol intravitreal solution) for the treatment of geographic atrophy secondary to age-related macular degeneration. The new J-code, J2782, was effective April 1.
Detect Early. Treat Early.

ForeseeHome is a remote monitoring program for at-risk wet AMD fellow eyes that helps detect conversion at 20/40 or better in 83% of patients.¹

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- Practice Workflow Implementation
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A 16-year-old female with no past medical or ocular history presented with flashes, gray dots and blurred vision in both eyes for one day.

Workup and imaging
Snellen visual acuity was 20/25 in the right eye and 20/20 in the left eye. Intraocular pressures were normal in both eyes. Anterior segment examination was normal. There were no cells in the anterior chamber or the anterior vitreous of either eye.

Funduscopic examination of both eyes demonstrated clear vitreous and normal optic discs (Figure 1). Subtle wedge-shaped gray lesions were noted in the macula of both eyes. The vessels and periphery were normal.

Optical coherence tomography of both eyes demonstrated multiple areas of outer retinal hyperreflectivity spanning the Henle fiber layer through the interdigitation zone and sparing the retinal pigment epithelium in both eyes (Figure 2).

Diagnosis
Our differential diagnosis for this patient included acute macular neuroretinopathy, acute posterior multifocal placoid pigment epitheliopathy, laser-induced maculopathy and contusion maculopathy. The absence of RPE involvement was inconsistent with APMPPE and laser-induced maculopathy, and there was no history of laser exposure or trauma. Furthermore, the patient’s visual symptoms began three days after an upper respiratory illness.

We diagnosed this patient with AMN based on the clinical history, examination and the OCT findings, particularly the striking HFL hyperreflectivity.

Discussion
AMN typically occurs in one or both eyes of young women. One review of 156 eyes from 101 cases demonstrated 54 percent were bilateral, 84 percent occurred in women and the median age was 26 years.1 Risk factors include a preceding viral illness, use of oral contraceptives, use of epinephrine or ephedrine, hypovolemia, pregnancy and excessive caffeine intake, which suggest AMN results from vascular compromise.1 Note that the association with oral contraceptive use is confounded by the fact that this condition commonly occurs in young women, therefore the decision whether to discontinue these medications should be individualized. Our patient did have a preceding febrile illness and was using oral contraceptive medications. Most patients present with one or more scotomas. Photopsia and blurred vision, as in this case, can also occur.1

Figure 1. Ultra-widefield fundus images of both eyes demonstrate subtle wedge-shaped gray lesions in the macula of both eyes.
AMN was initially described in the pre-OCT era. Since then, OCT has emerged as an invaluable tool for diagnosing, managing and understanding this condition.

This patient demonstrated striking hyperreflective changes involving multiple areas of the HFL in both eyes (Figure 2). The HFL comprises photoreceptor axons and Müller cell outer processes, and is oriented radially because the inner retinal elements migrate peripherally while the outer retinal elements migrate centrally during retinal development. This provides a less obstructed path for light and concentrates cones centrally. The radial pattern is why, for example, neuroretinitis classically demonstrates a macular star.

The HFL is typically difficult to distinguish from the outer nuclear layer on standard spectral domain-OCT because both layers are hyporeflective. The HFL can appear hyperreflective due to alterations in either: 1) the angle of incident light or 2) the structure of the HFL itself. The first can occur due to slight variations in the orientation of the patient’s eye or changes in the orientation of the retina itself, such as with subretinal or sub-RPE pathology (Figure 3). The second can occur when material, such as hemorrhage or exudate, accumulates in the HFL, or when the HFL itself is disrupted.

Features of the angular sign of HFL hyperreflectivity

New York retina specialist Prithvi Ramtohul and colleagues recently introduced the OCT terminology “angular sign of HFL hyperreflectivity” (ASHH) to describe disruption of the entire length of photoreceptors, which appears as a hyperreflective lesion extending from the Henle fiber layer to the interdigitation zone. Note that ASHH (an OCT finding) isn’t exclusive to AMN (a medical condition). The differential for ASHH includes APMPPE, acute retinal pigment epitheliitis, autoimmune retinopathy, contusion maculopathy and laser-induced maculopathy, among others. Yet ASHH can be useful in making the diagnosis—and may shed light onto the pathogenesis—of AMN.

ASHH occurs early in AMN then rapidly fades, and is followed by classic OCT features of AMN, including thinning of the ONL and disruption of the ellipsoid zone and interdigitation zone. In fact, in our patient, ASHH was present one day after symptom onset, and had already begun to fade one week later, at which point disruption of the EZ and IZ became more prominent (Figure 4).

The source of vascular compromise in AMN (insufficiency of the retinal versus the choroidal circulation), was previously debated, however work using OCT angiography as well as this sequence of events, where HFL...
INDICATION
IZERVAY™ (avacincaptad pegol intravitreal solution) is indicated for the treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD).

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS
IZERVAY is contraindicated in patients with ocular or periocular infections and in patients with active intraocular inflammation.

WARNINGS AND PRECAUTIONS

Endophthalmitis and Retinal Detachments

- Intravitreal injections, including those with IZERVAY, may be associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering IZERVAY in order to minimize the risk of endophthalmitis. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately.
A moment worth protecting

Every moment is precious for your patients with geographic atrophy. Help protect their moments from the start with IZERVAY™.

Learn more at IZERVAYecp.com

izervay™
(avacincaptad pegol intravitreal solution) 2 mg

Neovascular AMD

• In clinical trials, use of IZERVAY was associated with increased rates of neovascular (wet) AMD or choroidal neovascularization (7% when administered monthly and 4% in the sham group) by Month 12. Patients receiving IZERVAY should be monitored for signs of neovascular AMD.

Increase in Intraocular Pressure

• Transient increases in intraocular pressure (IOP) may occur after any intravitreal injection, including with IZERVAY. Perfusion of the optic nerve head should be monitored following the injection and managed appropriately.

ADVERSE REACTIONS

Most common adverse reactions (incidence ≥5%) reported in patients receiving IZERVAY were conjunctival hemorrhage, increased IOP, blurred vision, and neovascular age-related macular degeneration.

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

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IZERVAY™ (avacincaptad pegol intravitreal solution)

Rx only

Brief Summary: This information is not comprehensive. Visit IZERVAYecp.com to obtain the FDA-approved product labeling or call 609-474-6755.

1 INDICATIONS AND USAGE
IZERVAY is indicated for the treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD).

2 DOSAGE AND ADMINISTRATION
2.1 General Dosing Information
IZERVAY must be administered by a qualified physician.

2.2 Recommended Dosage
The recommended dose for IZERVAY is 2 mg (0.1 mL of 20 mg/mL solution) administered by intravitreal injection to each affected eye once monthly (approximately every 28 ± 7 days) for up to 12 months.

2.4 Injection Procedure
Only 0.1 mL (2 mg) should be administered to deliver a single dose. Any excess volume should be disposed.

Prior to the intravitreal injection, patients should be monitored for elevated intraocular pressure (IOP) using tonometry. If necessary, ocular hypotensive medication can be given to lower the IOP.

The intravitreal injection procedure must be carried out under controlled aseptic conditions, which includes the use of surgical hand disinfection, sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent). Adequate anesthesia and a broad-spectrum topical microbicide should be given prior to the injection. Inject slowly until the rubber stopper reaches the end of the syringe to deliver the volume of 0.1 mL. Confirm delivery of the full dose by checking that the rubber stopper has reached the end of the syringe barrel.

Immediately following the intravitreal injection, patients should be monitored for elevation in intraocular pressure (IOP). Appropriate monitoring may consist of a check for perfusion of the optic nerve head or tonometry.

Following intravitreal injection, patients should be instructed to report any symptoms suggestive of endophthalmitis (e.g., eye pain, redness of the eye, photophobia, blurring of vision) without delay.

Each vial and syringe should only be used for the treatment of a single eye. If the contralateral eye requires treatment, a new vial and syringe should be used and the sterile fields, syringe, gloves, eyelid speculum, filter needle, an injection needle should be changed before IZERVAY is administered to the other eye. Repeat the same procedure steps as above.

Any unused medicinal product or waste material should be disposed of in accordance with local regulations.

3 DOSAGE FORMS AND STRENGTHS
Intravitreal solution: 20 mg/mL clear to slightly opalescent, colorless to slightly yellow solution in a single-dose vial.

4 CONTRAINDICATIONS
4.1 Ocular or Periocular Infections
IZERVAY is contraindicated in patients with ocular or periocular infections.

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

5 WARNINGS AND PRECAUTIONS
5.1 Endophthalmitis and Retinal Detachments
Intravitreal injections may be associated with endophthalmitis and retinal detachments. Proper aseptic injection techniques must always be used when administering IZERVAY in order to minimize the risk of endophthalmitis. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay, to permit prompt and appropriate management.

5.2 Neovascular AMD
In clinical trials, use of IZERVAY was associated with increased rates of neovascular (vret) AMD or choroidal neovascularization (7% when administered monthly and 4% in the sham group) by Month 12. Patients receiving IZERVAY should be monitored for signs of neovascular AMD.

5.3 Increase in Intraocular Pressure
Transient increases in intraocular pressure (IOP) have been observed after an intravitreal injection, including with IZERVAY. Perfusion of the optic nerve head should be monitored following the injection and managed as needed.

6 ADVERSE REACTIONS
The following potentially serious adverse reactions are described elsewhere in the labeling:
• Ocular and periocular infections
• Active intraocular inflammation
• Endophthalmitis and retinal detachments

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

The safety of avacincaptad pegol was evaluated in 733 patients with AMD in two sham-controlled studies (GATHER1 and GATHER2). Of these patients, 292 were treated with intravitreal IZERVAY 2 mg (0.1 mL of 20 mg/mL solution). Three hundred thirty-two (332) patients were assigned to sham.

Adverse reactions reported in ≥2% of patients who received treatment with IZERVAY pooled across GATHER1 and GATHER2, are listed below in Table 1.

Table 1: Common Ocular Adverse Reactions (≥2%) and greater than Sham in Study E

<table>
<thead>
<tr>
<th>Adverse Drug Reactions</th>
<th>IZERVAY N=292</th>
<th>Sham N=332</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conjunctival hemorrhage</td>
<td>13%</td>
<td>9%</td>
</tr>
<tr>
<td>Increased IOP</td>
<td>9%</td>
<td>1%</td>
</tr>
<tr>
<td>Choroidal neovascularization</td>
<td>7%</td>
<td>4%</td>
</tr>
<tr>
<td>Blurred Vision*</td>
<td>8%</td>
<td>5%</td>
</tr>
<tr>
<td>Eye pain</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Vitreous floaters</td>
<td>2%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Blepharitis</td>
<td>2%</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

Blurred vision includes visual impairment, vision blurred, visual acuity reduced, visual acuity reduced transiently.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary

There are no adequate and well-controlled studies of IZERVAY administration in pregnant women. The use of IZERVAY may be considered following an assessment of the risks and benefits.

Administration of avacincaptad pegol to pregnant rats and rabbits throughout the period of organogenesis resulted in no evidence of adverse effects to the fetus or pregnant female at intravenous (IV) doses 5.1 times and 3.2 times the human exposure (based on AUC) at the maximum recommended human dose (MRHD) of 2 mg once monthly, respectively.

In the U.S. general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15%-20%, respectively.

Animal Data
An embryo fetal developmental toxicity study was conducted with pregnant rats. Pregnant rats received daily intravenous (IV) injections of avacincaptad pegol from day 6 to day 17 of gestation at 0.1, 0.4, 1.2 mg/kg/day. No maternal or embryofetal adverse effects were observed at any dose evaluated. An increase in the incidence of a non-adverse skeletal variation, described as short thoracolumbar (ossification site without distal cartilage) supernumerary ribs, was observed at all doses evaluated. The clinical relevance of this finding is unknown. Plasma exposures at the high dose were 5.1 times the MRHD, based on Area Under the Curve (AUC).

An embryo fetal developmental toxicity study was conducted with pregnant rabbits. Pregnant rabbits received daily IV injections of avacincaptad pegol from day 7 to day 19 of gestation at 0.12, 0.4, 1.2 mg/kg/day. No maternal or embryofetal adverse effects were observed at any dose evaluated. Plasma exposure in pregnant rabbits at the highest dose of 1.2 mg/kg/day was 3.2 times the human exposure at the MRHD, based on AUC.

8.2 Lactation

There is no information regarding the presence of avacincaptad pegol in human milk, the effects of the drug on the breastfed infant or on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for IZERVAY and any potential adverse effects on the breastfed infant from IZERVAY.

8.4 Pediatric Use

Safety and effectiveness of IZERVAY in pediatric patients have not been established.

8.5 Geriatric Use

Of the total number of patients who received IZERVAY in the two clinical trials, 90% (263/292) were ≥65 years and 61% (178/292) were ≥75 years of age. No significant differences in efficacy or safety of avacincaptad pegol were seen with increasing age in these studies. No dose adjustment is required in patients 65 years and above.

17 PATIENT COUNSELING INFORMATION

Advise patients that following IZERVAY administration, patients are at-risk of developing neovascular AMD, endophthalmitis, elevated intraocular pressure and retinal detachments. If the eye becomes red, sensitive to light, painful, or if a patient develops a change in vision, instruct the patient to seek immediate care from an ophthalmologist. Patients may experience temporary visual disturbances and blurring after an intravitreal injection with IZERVAY and the associated eye examinations. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

abnormalities precede deeper outer retinal changes without involving the RPE, implicate deep capillary plexus ischemia as the cause of AMN. This mechanism contrasts that of photic retinopathy, in which energy absorption by the RPE results in anterograde photoreceptor disruption, as well as APMPPE, in which choroidal abnormalities result in pathologic changes, including disruption of the RPE.

Paracentral acute middle maculopathy, or inner nuclear layer infarction due to ischemia of the intermediate and deep (and sometimes superficial) capillary plexuses, can also cause hyperreflectivity on OCT. However this occurs in the INL (and may extend into the outer plexiform layer) and results in INL thinning over time, whereas hyperreflectivity and disruption in AMN involves the OPL, HFL, ONL, EZ and IZ and results in ONL thinning over time (recall this is due to damage to the photoreceptors). Furthermore, PAMM differs from AMN in that PAMM is an OCT finding that should prompt a search for the underlying cause (similar to how cotton wool spots, when observed, should prompt further evaluation), whereas AMN is a retinal disease. While PAMM can coexist with AMN, the OCT in this case demonstrated the absence of inner retinal pathology.

Note that ASHH may be more common than we previously recognized, and it may be missed because 1) it fades early and 2) the HFL is radially oriented, so horizontal B-scans on OCT may not capture it. Treatment and prognosis

Treatment involves addressing underlying causes if any are found. In the review cited previously, at final follow-up, more than 80 percent of patients had a visual acuity of 20/40 or better, however 53 percent had persistent scotomas. In our experience, some patients with persistent scotomas may not notice them unless they look closely for them. AMN can recur, but this is uncommon.

Bottom line

AMN typically affects one or both eyes in young women and should be on the differential diagnosis in such patients. ASHH can be an early finding in AMN and supports the hypothesis that this disease results from ischemia to the deep capillary plexus. Most patients have good visual acuity, but many will have persistent scotomas.
Another tweak on the Yamane technique

This approach substitutes 27-ga trocar cannulas for the 30-ga needles.

By Patricia Fernández, MD, and Alex Alfaro, MD

S hin Yamane, MD, and colleagues in Japan in 2017 described a scleral intraocular lens haptic-fixation technique that didn’t use sutures or glue.1 They originally described the technique using two parallel 30-ga needles at 2 mm distance from the limbus. Since then, a number of subtle modifications of the Yamane technique have emerged. Here’s ours.

27-gauge trocar cannulas

For our modification, we’ve substituted the 30-ga needles for 27-ga trocar cannulas. After we appropriately mark the entry sites with the Thornton marker, we mark a 2-mm area away from the site. We place the 27-ga trocar cannula in opposite directions (Figure 1).

When placing the cannula, a tunneled sclerotomy is a must so that the haptic can rest without extrusion. When the forceps correctly grasp the haptic, they need to be taken out in the same direction as the trocar cannula. For this step, we favor the Grieshaber forceps (Alcon) rather than a needle because the forceps are easier to use. This cannula must be removed first followed by the forceps with the haptic grip, so they don’t get trapped inside.

Now, the flange can be prepared with cautery, as described in the original technique. Bear in mind that the flange must have an appropriate size to rest inside the tunnel. Very large flanges may erode through the conjunctiva over time.

A crucial step in this approach is to verify the optic centration and tilt before closing the sclerotomies. Expect a slight degree of conjunctival edema the day after.

In the case we present, we also did a valved scleral tunnel to remove the nucleus. Our preference is to suture this tunnel to avoid unnecessary postoperative complications. Not all surgeons choose to make a full posterior vitrectomy. In addition to ensuring no peripheral breaks or tears are left unidentified, some have proposed a full posterior pars plana vitrectomy to possibly decrease the risk of postoperative macular edema and vitreous traction.2

Bottom Line

We’ve used this technique in a large number of cases with satisfactory results. The decentration and tilt in our patient population has been slightly higher than with other techniques, but with few or almost no postoperative complications.

REFERENCES
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How OCT is improving early characterization of GA lesions

A comparison of B-scan and en face imaging techniques for diagnosis of early macular atrophy.

By Liang Wang, MD, Philip J. Rosenfeld, MD, PhD, and Omer Trivizki, MD, MBA

**Take-home points**

- Optical coherence tomography is ideal for directly detecting the early precursor lesions that develop into geographic atrophy.
- Precursor lesions are defined as incomplete retinal pigment epithelium and outer retinal atrophy (iRORA) and complete retinal pigment epithelium and outer retinal atrophy (cRORA) on OCT B-scans, and persistent choroidal hypertransmission defects (hyperTDs) on OCT en face imaging.
- Reliable detection of iRORA will require dense OCT raster scans with examination of neighboring B-scans or en face images.
- En face OCT imaging allows for rapid and reliable detection of persistent hyperTDs and cRORA in any dimension.

**OCT B-scan to identify GA precursor lesions**

The Classification of Atrophy Meeting (CAM) group has advocated for the use of OCT as the gold-standard for detecting the earliest macular changes that precede the formation of typical GA. The CAM group defined two terms when using OCT horizontal B-scans: 1,2

- incomplete retinal pigment epithelium and outer retinal atrophy (iRORA); and
- complete retinal pigment epithelium and outer retinal atrophy (cRORA).

iRORA is defined as photoreceptor degeneration, RPE attenuation, and increased choroidal signal transmission or choroidal hypertransmission that’s <250 μm on the horizontal B-scan.

OCT is proposed to be a precursor to cRORA, which includes all the features of iRORA1 but requires the photoreceptor and RPE loss or attenuation and choroidal hypertransmission defect (hyperTD) to be ≥250 μm.

On OCT, cRORA is considered to be
an early anatomical measure of GA that would be identified on color fundus imaging.\textsuperscript{5} iRORA, as a precursor to cRORA, could be useful for monitoring disease onset and progression.\textsuperscript{4}

However, the definitions of iRORA and cRORA on OCT B-scans have some limitations. The 250-µm horizontal cut-off in cRORA wasn’t based on a natural history or histopathological study, but rather because it was a measurement on OCT B-scans that could be reliably and accurately reproduced. The consensus also didn’t determine whether the early macular changes were transient or persistent.

iRORA and cRORA definitions also require highly averaged B-scans. Density of B-scans remains unspecified, which could lead to areas of outer retinal and RPE atrophy being missed if the B-scans are spaced too widely apart.

The orientation of B-scans relative to the location of atrophy and the relative size of the atrophic region may also limit the reliable identification of iRORA.\textsuperscript{6} Recent studies also indicate that intergrader reliability is lower for iRORA in comparison to cRORA on B-scans.\textsuperscript{3}

\textit{En face} OCT to identify GA precursor lesions

\textit{En face} OCT images derived from dense OCT raster scans can also be used for detecting potential precursor lesions of GA.\textsuperscript{7,13} As an alternative to highly averaged B-scans, \textit{en face} scans provide comprehensive volumetric views of the retina. Outer retinal degeneration with photoreceptor loss and RPE attenuation is detected through increased choroidal light transmission, which presents as abrupt changes in OCT reflectivity.\textsuperscript{7,11,14}

Using these \textit{en face} scans, investigators have identified precursor lesions defined as persistent hyperTDs, which are bright lesions with a greatest linear dimension of \( \geq 250 \) um.\textsuperscript{9,15} HyperTDs have been shown to serve as an OCT biomarker for predicting the formation of GA.\textsuperscript{16}

Reconciling B-scan, \textit{en face} imaging

With the introduction of iRORA/cRORA on B-scans and persistent hyperTDs on \textit{en face} imaging as features of early atrophy, these OCT definitions of early atrophy need to be reconciled. Federico Corvi, MD, and colleagues
reported significant agreement between persistent hyperTDs on en face imaging and cRORA on B-scans.¹⁷

Interestingly, 50 percent of the iRORA cases on B-scans were actually cRORA when the graders accounted for the non-horizontal greatest linear dimension seen on en face imaging.¹⁷ Grading discrepancies mainly occurred in the smaller atrophic areas.

This finding underscores the importance of correctly identifying iRORA by inspecting neighboring B-scans or by using en face imaging to be sure that iRORA isn’t really cRORA or a persistent hyperTD when viewed in a non-horizontal dimension.

Exploring the relationship between cRORA/iRORA and persistent hyperTDs

To explore the relationship and agreement between cRORA,iRORA and hyperTDs, our research has focused on comparing the grading of cRORA/iRORA on spectral-domain OCT B-scans using a dense raster scan pattern against the grading of persistent choroidal hyperTDs on en face swept-source OCT angiography imaging. Fifteen patients with nonexudative AMD were enrolled at the Tel Aviv Medical Center and completed same-day SD-OCT and SS-OCT imaging. The SD-OCT B-scans were extracted from the averaged 97 B-scans from a 20-degree scan pattern on the Heidelberg OCT instrument.

The B-scans were extracted using the review software and enhanced through contrast-limited adaptive histogram equalization. Masked graders at the Moran Eye Center identified the cRORA and iRORA lesions (Figure 1, page 19). For this study, cRORA lesions needed to be ≥250 µm when measured on horizontal B-scans or connected to another lesion that was ≥250 µm or linked to four or more lesions resulting in a greatest linear dimension ≥250 µm along the nonhorizontal slow scan direction.

Persistent choroidal hyperTDs were visualized by en face SS-OCT imaging on a sub-RPE slab with segmentation boundaries between 64 to 400 µm beneath Bruch’s membrane and confirmed on corresponding B-scans. Grading was completed through a collaboration between the University of Washington and Bascom Palmer Eye Institute with a previously developed machine learning algorithm, excluding lesions on en face imaging with a greatest linear dimension <250 µm (Figure 1, page 19).¹⁸,¹⁹ Two independent graders then reviewed and manually graded the en face hyperTDs and the corresponding B-scans.

Minimizing mismatches between systems

An SD-OCT iRORA/cRORA mask was manually registered to the SS-OCT images to minimize the mismatch of the lesions between systems and record the overlap between iRORA/cRORA and hyperTD lesions. All graders generated consensus iRORA/cRORA and hyperTD masks. Preliminary data presented at Angiogenesis 2023 indicated that the overlap between B-scan and en face gradings were significantly higher between cRORA and hyperTDs than iRORA and hyperTD.²⁰

Out of the 558 cRORA lesions identified on SD-OCT, 556 were identified as persistent hyperTDs. A strong correlation (R = 0.97) was found between the average area of cRORA and hyperTD with no statistically significant difference in area between groups.

However, out of the 142 iRORA lesions, 39 were also classified as hyperTDs. These “iRORA” labeled lesions were <250 µm when measured on the horizontal B-scans, but were also found to be part of larger lesions ≥250 µm in nonhorizontal dimensions when the entire lesion was taken into account with en face imaging (Figure 2).

These iRORA lesions would have been correctly labeled as cRORA when neighboring B-scans were taken into account. Thus, en face imaging provides an efficient
method for assessing persistent hyperTDS that represent early signs of GA formation through inspection of a single en face sub-RPE image rather than a large number of individual B-scans. En face imaging also allows for atrophic lesions to be topographically correlated with other retinal anatomic features, such as drusen and hyperreflective foci. While the detection of iRORA lesions hasn’t yet

Figure 2. Four representative cases used to grade incomplete retinal pigment epithelium and outer retinal atrophy (iRORA), complete retinal pigment epithelium and outer retinal atrophy (cRORA) and persistent choroidal hypertransmission defects (hyperTDS). iRORA is red and cRORA is blue. The yellow line represents the location of the B-scan in the top row.
been incorporated into clinical trial designs, the U.S. Food and Drug Administration has approved the detection of hyperTD formation on en face imaging as a clinical trial endpoint. This technique will be valuable in clinical practice, retinal research and clinical trials for determining disease progression and treatment management.

**Bottom Line**

GA is characterized by irreversible atrophy in the macula with a loss of the outer retina RPE and choriocapillaris. While OCT has been considered to be an optimal tool for directly detecting precise anatomical changes that precede GA, the best OCT imaging strategy to detect these lesions is evolving. iRORA and cRORA have been defined using averaged, horizontal B-scans, and persistent hyperTDs were defined using en face images.

Our research highlights the importance of evaluating persistent hyperTDs when classifying precursor lesions, such as iRORA and cRORA before the detection of GA. Detection of iRORA will require dense OCT raster scans with examination of adjacent B-scans to rule out nonhorizontal connecting lesions.

**En face imaging enables the rapid and reliable detection of persistent hyperTDs, which are analogous to cRORA, and serves as a valuable tool for determining disease progression and efficacy of treatment.**

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**REFERENCES**

Timely reports on retina research and professional news, from the editors of Review of Ophthalmology and Retina Specialist.

Medical Editor:
Philip Rosenfeld, MD, PhD.
Fibrin glue-assisted surgery for idiopathic macular holes

In our experience, fibrin glue has enabled closure of macular holes without the inconvenience of face-down positioning.

By G. Nikitha Reddy, MD, and Mudit Tyagi, MD

Surgical management of macular holes has undergone significant changes in the last few decades. The aim of surgery is to reduce the anteroposterior traction with the help of vitrectomy and eliminate tangential traction by using internal limiting membrane peeling for stage 3 and 4 macular holes.

While simple pars plana vitrectomy alone has a closure rate of around 58 percent,1 the addition of ILM peeling has resulted in closure rates of 96 to 100 percent, depending upon different sizes of MH.2-4 Over the years, several modifications to MH surgery have evolved, including the use of autologous ILM flaps, inverted ILM flap, temporal ILM flaps and autologous neurosensory retinal free flaps.5,6

The current protocol for macular hole management requires the filling of the vitreous cavity with air or gas along with postoperative prone positioning. Although no consensus exists for the duration of prone positioning, patients are usually advised to do so for one to two weeks. This can be undesirable and distressing for some patients. Also, it might become extremely inconvenient if a patient can’t lie prone due to old age or spinal problems, or if the patient is planning for air travel.

According to the GuARD study, by our group, fibrin glue, which is a biological tissue adhesive composed of thrombin and fibrinogen, can be used as a temporary tamponading agent for rhegmatogenous retinal detachments to avoid postoperative positioning.7,8 This study also found that fibrin glue is efficient and safe as an ocular tissue sealant.

In this study, we proposed a technique of ILM peeling along with application of fibrin glue over the hole. We hypothesized that this would obviate the need...
for postoperative prone positioning and also avoid use of the conventional gas tamponade.

Alternative to face-down positioning?
Gas or air acts as a scaffold over the macular hole for glial proliferation, and its surface tension tends to extrude the subretinal fluid around the hole. This often requires postoperative prone positioning for prolonged duration.

Although reports have suggested that a prone position is not often necessary for a successful closure of macular hole, they’ve been met with much controversy owing to the fact that they didn’t consider the duration of hole prior to surgery, with fresh and short-duration holes usually not requiring face-down positioning.

Nonetheless, a meta-analysis showed that prone positioning is often necessary for eyes with hole diameter >400 µm. However, several challenges are associated with postoperative prone positioning or the use of gas tamponade. First, maintaining the position depends on patient compliance. It can be especially difficult for older patients and patients with obesity and spinal problems.

Second, problems associated with gas tamponade, such as avoiding air travel and risk of raised intraocular pressure and cataract formation, also need to be considered. While air may also expand, it gets absorbed faster than intraocular gases, so its use can reduce the time for which air travel is restricted.

We don’t use intraocular gas in any of our patients. Neither do we advise postoperative prone positioning. We hypothesise that the fibrin glue over the macular hole helps prevent entry of fluid into the hole.

**Macular hole repair using fibrin glue:**
A step-by-step guide


1. The surgeon performs a standard three-port pars plana vitrectomy using the Constellation 25-ga vitrectomy system (Alcon). After a routine core vitrectomy, the status of posterior vitreous is assessed.

2. The posterior vitreous detachment is induced using the vitrectomy cutter with a suction pressure of 400 mmHg in cases where posterior vitreous detachment was absent. In cases of difficult PVD induction, triamcinolone acetonide is used to stain the posterior vitreous. Completion of the vitrectomy to the periphery and inspection of the peripheral retina for any treatable lesions follows.

3. Internal limiting membrane staining is done with 0.1 mL Brilliant Blue-G dye under fluid for 60 to 90 seconds, followed by washing away the excess dye. We initiate ILM peeling using the end-grasping forceps (Grieshaber Maxgrip, Alcon) around 1 disc diameter from the fovea, carefully completing the ILM peeling up to 2 disc diameters around the macular hole. An inverted ILM flap is then positioned over the macular hole in cases where the inverted ILM flap technique was used.

4. Subsequently, in an air-filled globe, 0.1 to 0.2 mL of fibrin glue (Tisseel, Baxter) is slowly injected over the macular hole. The thick component and the thin component have to be taken separately in a 1-mL syringe and injected one after the other.

5. We allow a wait time of a minimum of two to three minutes for a thick coagulum to form over the hole. Excess coagulum is either removed or repositioned using vitrectomy cutter or flute cannula. Air is left in situ at the end of the procedure. No postoperative positioning is advised.

**GuARD study findings**
In our study, we demonstrated the use of fibrin glue as an alternative to gas tamponade for macular hole closure.
Our results showed a favorable outcome with the technique as a majority of eyes demonstrated structural closure and visual acuity improvement without the need for postoperative prone positioning.

Eight of 10 cases had a complete type 1 closure of the macular hole. We noted the fibrin coagulum was present over the macular area at day one postoperative (Figure A) and was completely resorbed by the one-week visit (Figure B). Two failed cases underwent a repeat surgery with fluid gas exchange and a successful type 1 closure was achieved after the fluid-gas exchange.

One of the failed cases had an inverted ILM flap, which became displaced during the glue application. The ILM was repositioned and fluid-gas exchange was done during the second surgery.

**Concerns about fibrin glue**

One of the concerns about the use of fibrin glue is the possibility of intraocular inflammation. While the glue has been extensively used in anterior segment surgeries, such as pterygium, amniotic membrane and Tenon patch grafting, its intraocular use has rarely been described, although there have been reports of intravitreal fibrin glue use in the management of uncomplicated retinal detachment with good anatomical outcomes.

Our group also demonstrated its favorable long-term outcome and safety, with no eyes developing raised IOP or intraocular inflammation. This makes fibrin glue an attractive alternative for macular hole surgery.

One of the most important aspects about using intravitreal fibrin glue is the mode of application. Although the commercially available glues come with an injector, we think it’s better to avoid its use because it might block the 25-ga flute cannula. The thick component and the thin component have to be taken separately in a 1-mL syringe and injected one after the other. We advise injecting the thick component first because the thin component may spread over an area larger than intended. Any excess coagulum can be repositioned or trimmed with the help of a vitrectomy cutter.

**REFERENCES**

The 12th Annual Meeting of the VitBuckle Society, held in Miami, highlighted vigorous and animated surgical discussion among both trainees and post-training vitreoretinal surgeons from all over the world. Here, we present pearls for dealing with vitreoretinal surgical challenges from 14 of them.

These pearls include a novel approach to lensectomy, tips for surgery for myopic traction maculopathy, retinal detachment after globe rupture and intraocular foreign body removal, as well as managing a host of unique presentations—chronic detachment with macrocysts, subfoveal subretinal bands and metastatic cutaneous and ciliary body melanoma.

A separate session featured vitreoretinal surgeons from Mexico and Canada sharing their approaches to seven surgical dilemmas: internal limiting membrane flap complications; diabetic tractional retinal detachments; rhegmatogenous retinal detachments; implants for macular buckling; endoscopic visualization for anterior prolapse; addressing the anterior hyaloid in pediatric vitrectomy; and creative ways of managing macular holes.

Novel strategies for removing dense subluxed cataracts

Samir Patel, MD, from Retina Vitreous Consultants in Pittsburgh, discussed a novel approach to lensectomy. He presented a case of a monocular patient with a history of pathologic myopia and pseudoexfoliation glaucoma with a dislocated crystalline lens that was too dense to be removed with afragmatome.

After performing a vitrectomy, Dr. Patel explained how he used an intracapsular approach with the assistance of perfluoron to levitate the lens just below the iris plane. He then used a lens loop to elegantly remove the entire cataract through a scleral tunnel.

Mrinali Gupta, MD, of Retina Associates of Orange County in Southern California, shared her experience with a similar case in which she used a cryotherapy probe to remove the dense subluxed cataract.

**Take-home points**

- For fovea-sparing internal limiting membrane peel, it's important to carefully lift the posterior hyaloid, restain with triamcinolone and assess whether an iatrogenic macular hole has been created.
- Computed tomography can estimate the size of an intraocular foreign body and help approximate the size of the sclerotomy to remove it.
- Retinotomies and forceps with gentle countertraction from the light pipe can be used to remove subfoveal subretinal bands.
- A diagnostic vitrectomy using 23-ga instrumentation at a low cut rate along with other subtle maneuvers enabled the diagnosis of metastatic melanoma masquerading as uveitis.

**BIOS**

Dr. Singaravelu is a vitreoretinal surgery fellow with the Retina Group of Washington and MedStar Georgetown University Hospital, Washington, D.C.

Dr. Do is a vitreoretinal surgeon and uveits specialist at the Retina Group of Washington and is a clinical assistant professor at Georgetown University School of Medicine. He is also a member of the executive committee of the VitBuckle Society.

**DISCLOSURES:**

Dr. Singaravelu has no relevant financial relationships to disclose.

Dr. Do disclosed financial relationships with Abbott/Allergan, Alimera Sciences, Bausch + Lomb Pharmaceuticals and Bausch + Lomb Surgical.

By Janani Singaravelu, MD, and Brian Do, MD

Surgical tips and tricks from VBS

A selection of creative approaches to vitreoretinal surgical challenges from the VitBuckle Society.

Take-home points

- For fovea-sparing internal limiting membrane peel, it’s important to carefully lift the posterior hyaloid, restain with triamcinolone and assess whether an iatrogenic macular hole has been created.
- Computed tomography can estimate the size of an intraocular foreign body and help approximate the size of the sclerotomy to remove it.
- Retinotomies and forceps with gentle countertraction from the light pipe can be used to remove subfoveal subretinal bands.
- A diagnostic vitrectomy using 23-ga instrumentation at a low cut rate along with other subtle maneuvers enabled the diagnosis of metastatic melanoma masquerading as uveitis.
Fovea-sparing internal limiting membrane peeling techniques involve peeling around the parafovea and trimming it using the vitreous cutter while leaving a patch of ILM over the fovea.

**Macular surgery in myopic traction maculopathy**

Vitreoretinal surgery in myopic eyes can be challenging. Seasoned vitreoretinal surgeons shared their pearls and some words of wisdom for managing these cases.

Cassie Ludwig, MD, of the Byers Eye Institute at the Stanford University School of Medicine in Palo Alto, California, shared her expertise on surgery for myopic traction maculopathy with a fovea-sparing internal limiting membrane peel for foveoschisis retinal detachment. She underscored the importance of carefully lifting the posterior hyaloid due to its taut nature, restaining with triamcinolone to identify vitreoschisis, and assessing whether an iatrogenic macular hole has been created.

Fovea-sparing ILM peel techniques involve peeling around the parafovea and trimming it using the vitreous cutter while leaving a patch of ILM over the fovea, Dr. Ludwig said. An advantage of this technique is that it avoids macular hole formation, but a disadvantage is its potential to enable formation of an epiretinal membrane over the fovea. She used long-acting C3F8 gas with extended positioning to achieve a successful outcome.

Session comoderator Carl Regillo, MD, chief of the retina service at Wills Eye Hospital/Mid Atlantic Retina in Philadelphia, offered these additional pearls for vitreoretinal surgery in myopic eyes with long axial length: using 23-gauge instrumentation along with extra-long myopic instruments; and decreasing the infusion pressure to soften the globe and allow for greater indentation.

Yoshi Yonekawa, MD, an adult and pediatric retina specialist at Wills Eye/Mid Atlantic Retina, noted that while foveal ERM formation is always a risk, it’s typically mild and doesn’t require any further surgery.

**Tips for traumatic retinal detachments in repaired ruptured globes**

Kirk Hou, MD, PhD, of Doheny Eye Institute UCLA in Los Angeles, presented a case of traumatic retinal detachment in a patient with a history of a ruptured globe with a repaired corneal laceration, resulting in a limited view to the posterior pole.

After he removed the residual lens material and vitreous hemorrhage, he noted a total retinal detachment with a star-fold, retinal foreshortening, along with an area of choriotiretinal incarceration at the site of a posterior perforation. He used perfluoron and performed an inferior 180-degree retinectomy and focal retinectomy incorporating the area of incarceration. Silicone oil provided a tamponade agent, after which the retina remained attached.

Jayanth Sridhar, MD, an associate professor of clinical ophthalmology at Bascom Palmer Eye Institute in Miami, provided an update that demonstrated the retina remaining attached four months after surgery, and indicated the patient is currently awaiting a corneal transplant.

**Removing a metallic intraocular foreign body from the inferior retina**

Ediana Goduni, MD, of Retina Associates of Cleveland, shared pearls for removing a metallic intraocular foreign body from the inferior retina. After a thorough vitrectomy, she applied endolaser pulses around the IOFB impact site. Next, she removed the superotemporal cannula and enlarged the sclerotomy. She then removed the IOFB using Maxgrip forceps. C3F8 gas provided an endotamponade and the patient had intravitreal antibiotics.

Dr. Goduni offered this tip: Use computed tomography to estimate the size of the IOFB, which will help to approximate the size of the sclerotomy needed to remove the IOFB during surgery.
Dr. Regillo emphasized the importance of a circumferential pars plana scleral incision for IOFB removal when the wound requires extension. Shilpa Desai, MD, the session’s co-moderator and assistant professor at Tufts University School of Medicine in Boston, said an intraocular magnet could be an alternative method for IOFB removal.

Managing a chronic traumatic retinal detachment with macrocysts

Phoebe L. Mellen, MD, of Retina Vitreous Consultants in Pittsburgh, presented the case of a young patient with a chronic traumatic retinal detachment with two macrocysts. The initial repair with primary buckle and gas failed, so Dr. Mellen pursued a vitrectomy, which she completed with the assistance of triamcinolone.

Next, Dr. Mellen used diathermy to drain the posterior macrocyst and create a drainage retinotomy to flatten the retina. After air-fluid exchange and endolaser, one large cyst remained, but she was concerned it would tent the retina, preventing adequate closure of the associated breaks. So, she drained the cyst and instilled silicone oil. The retina remained attached two months after surgery without cyst recurrence.

Dr. Regillo and Harry Flynn, MD, professor of ophthalmology at Bascom Palmer Eye Institute, noted that traditional teaching holds that macrocysts in the setting of chronic retinal detachments resolve over time and can be observed without drainage, but external draining at the time of scleral buckle is also an option.

Managing recurrent RD with subretinal bands

Joshua H. Uhr, MD, of Retina and Ophthalmic Consultants in New Jersey, discussed a case of recurrent retinal detachment with extensive submacular PVR in the form of subretinal bands. Because of concern that the subretinal bands

Surgical pearls from north and south of the border

By Jovi Wong, MD, MSc, PhD; Aditya Rali, MD, Luke Oh, MD, and Brian K. Do, MD

In Mexico and Canada they do things a little differently from the United States, especially when it comes to retinal surgery. Vitreoretinal surgeons from across both borders shared their approaches to a host of challenging surgical scenarios, providing a study in contrasts in techniques.

Avoiding and dealing with ILM flap complications

Virgilio Morales-Canton, MD, of the Association to Prevent Blindness Mexico, demonstrated how he dealt with a displaced internal limiting membrane free flap during repair of a large macular hole in a myopic adult patient. He discussed a case in which the flap became displaced during air-fluid exchange. The patient had a postoperative retinal detachment secondary to the large macular hole.

In a subsequent operation, Dr. Morales-Canton performed the air-fluid exchange through the macular hole, then lasered the macular hole edges to secure the retina and repair the detachment. The patient ended up with 20/50 visual acuity.

In cases of lost ILM flaps, Dr. Morales-Canton offered these options for macular hole closure: hinged ILM flaps; ILM free flaps; amniotic membrane grafts; and autologous retinal transplant.

Parnian Arjmand, MD, of the Toronto Retina Institute, reviewed a variety of ILM flap complications and tips on how to avoid them. They included avoiding flap amputation, ensuring appropriate—that is, not undersized—ILM flaps, and avoiding flap movement under air. Perioperative solutions she suggested included cutting on zero suction, slowing
would impede foveal reattachment, he created retinotomies and used Maxgrip forceps with gentle countertraction from the light pipe to remove the subretinal bands.

Dr. Desai recommended a “spaghetti” technique, using a twirling motion with the forceps while removing long segments of subretinal bands. Hong-Uyen Hua, MD, a pediatric retina and vitreous disease specialist at Bascom Palmer, cautioned that subretinal bands have a branching pattern, which can cause the formation of peripheral traction and breaks when removing them through a posterior retinotomy.

**Metastatic disease masquerading as uveitis**

Jordan D. Deaner, MD, of Wills Eye/Mid Atlantic Retina, presented a case of a patient with metastatic cutaneous and ciliary body melanoma previously treated with excision of the cutaneous lesion, plaque brachytherapy and adjuvant immunotherapy, and who had worsening floaters.

He described atypical vitritis with “large clumps of vitreous cells and debris.” Ancillary imaging studies weren’t consistent with ocular inflammatory disease, so he performed a diagnostic vitrectomy.

The technique involved a thorough vitrectomy using a 23-ga instrumentation at a low cut-rate, collection of undiluted and diluted samples, partial air-fluid exchange with suturing of sclerotomies, and double-freeze thaw cryotherapy to prevent seeding.

Pathology revealed isolated vitreous metastases of cutaneous melanoma. The patient was treated with a series of five monthly intravitreal melphalan injections. The tumor burden resolved and the visual outcome was excellent.

Basil K. Williams Jr., MD, associate professor at Bascom Palmer, offered a diagnostic clue to differentiate metastatic cutaneous melanoma vitreous seeding from uveitis: the pigmented appearance of vitreous cells.

**Surgical tips and tricks from VBS**

Hand movements with forceps, and leaving multiple flaps available as backups.

For her ILM flaps, Dr. Arjmand said she likes to create multiple flaps, alternating clockwise and counterclockwise and creating progressively larger concentric circles. She also demonstrated and advocated for the use of a Tano scraper with viscoelastic to mobilize the ILM flap into position. She noted that patient selection is important. In these cases, she said, Brilliant Blue dye might be preferred over indocyanine green given the higher likelihood of toxicity from the latter.

**Managing diabetic tractional RDs**

Gerardo Garcia-Aguirre, MD, of the Institute of Technology in Monterrey, focused on maneuvers for successful diabetic tractional retinal detachment repair. Among 11 suggested plays, his tips included: using a chandelier for every case; pulling up on the tractional membrane at the nerve to look for a plane if one isn’t obviously present (space-maker); reducing the cut rate to help cut through spongy membranes (slow cutter); and using forceps along with the cutter to help hold up a membrane and simultaneously cut through (forceps dissection).

The 27-ga cutters are useful in approaching TRDs, Dr. Garcia-Aguirre said, because the shorter length between the end of the vitrectomy probe and cutter opening vs. the 25-ga instruments enables entrance into tighter spaces between the membranes and retina.

Dr. Garcia-Aguirre also suggested these two techniques for trimming the isolated fronds of fibrovascular proliferation as closely as possible:

- **The retro-shave**, which involves placing the cutter facing toward the free edge of the membrane and aspirating/cutting.
- **The Berrocal**, which involves placing the cutter over the membrane and cutting it with full aspiration/cut rate.

He also emphasized the importance of promptly controlling bleeding by applying diathermy.

**A novel approach to RRD repair**

In-office suprachoroidal viscoexy is a novel technique for rhegmatogenous retinal detachment. Rajeev Muni, MD, of St. Michael’s Hospital in Toronto recommended this technique to reduce unwanted retinal displacement and distortion following conventional RD repair with vitrectomy or scleral buckle.

He noted that anatomic reattachment doesn’t necessarily equal success. That’s because commonly used surgical repair techniques involve rapid
A slow, natural reattachment of the retina ideally shouldn’t require patient positioning or invasive surgery, Dr. Muni said. In the initial case series he presented, injecting viscoelastic into the suprachoroidal space under the retinal break achieved retinal reattachment without complications.

Patients with relatively shallow detachments, with breaks outside of the 12 and 6 o’clock positions, are good candidates for this procedure, Dr. Muni said. Using a guarded 30-ga needle with 1 mm exposed, he injects an entire syringe of Healon 5 viscoelastic into the suprachoroidal space in the area of the break, under visualization with indirect ophthalmoscopy. The viscoelastic lasts typically for about two weeks.

An anterior ring of proliferation along the ciliary body was noted and removed. Dr. Rezende said these membranes were thought to have contributed to the patient’s preoperative hypotony and likely would not have been addressed using traditional “top-down” visualization.

Notably, although iatrogenic retinal breaks were sustained, Dr. Rezende didn’t use endolaser in a move to avoid further retinal contraction. Ultimately, oil was put back into the eye, postoperative methotrexate injections were employed, and the patient’s retina was ultimately noted to have successfully reattached, with a final visual acuity of 20/300 under silicone oil.

The importance of addressing the anterior hyaloid

When performing pediatric vitrectomy, leave the posterior hyaloid alone, Maria Martinez-Castellanos, MD, of the Association to Prevent Blindness in Mexico, advised attendees. Doing so will avoid inadvertent iatrogenic breaks, proinflammatory bleeding, and the need for retinal laser, she said.

The anterior hyaloid, on the other hand, is the most important part of the eye to address in familial exudative retinopathy, retinopathy of prematurity or after retina or congenital cataract surgery. Dr. Martinez-Castellanos noted that these membranes must be removed meticulously to reduce abnormal traction, inflammation and development of fibrovascular tissue. In cases in which the anterior hyaloid is adherent to the posterior lens capsule, removal of the crystalline lens might be necessary, she said.

Endoscopic visualization for anterior proliferation

An accompanying video showed how her technique for placing the implant. She folded a 6 x 12-mm piece of PTFE felt in half, then passed a Mersilene suture through the halves to avoid losing it in the orbit. Dr. Lopez-Carasa used a Snellen loop to push the implant through the sub-Tenon’s space until an indentation appeared under the macula. A postoperative B-scan showed the axial length was shortened from 36 to 32 mm and successful treatment of a macular detachment due to staphyloma. The patient’s visual acuity improved and subretinal fluid resolved after the operation.

Leaving the posterior hyaloid alone during pediatric vitrectomy will avoid iatrogenic breaks, proinflammatory bleeding and the need for retinal laser.
The retinal pigment epithelium is a critical layer of the retina that supports healthy vision and is often thought of as the caretaker of the outer retina. Its dysfunction or malfunction is linked to several eye diseases, including age-related macular degeneration, Stargardt disease and retinitis pigmentosa. The ability to monitor changes in the molecular composition and function of the RPE will be highly significant for clinicians seeking early diagnosis and monitoring of treatment efficacy. Here, we’ll discuss an emerging imaging modality, fluorescence lifetime imaging ophthalmoscopy, or FLIO, which has the potential to help us detect diseases earlier than is currently possible.

**Fundus autofluorescence and FLIO**

Fundus autofluorescence is a widely used clinical tool that images naturally occurring fluorescent molecules (high-energy light is absorbed and then emitted with lower energy at a longer wavelength) within the RPE to visualize changes in the fluorescence intensity. Bisretinoid lipofuscin, a byproduct of molecules involved in the eye’s visual cycle, accumulates in the RPE with age, while melanin granules decrease over time. Lipofuscin builds up even faster in Stargardt disease and clumps together in AMD. FAF uses these molecules (lipofuscin and melanin) to observe intensity variations across the retina with age and disease.2

Beyond imaging fluorescence intensity, measurement of the time delay between fluorescence excitation and emission detection can provide insight into relative fluorescence contributions and the cellular environment. FLIO is a promising tool that compliments FAF.3 It’s a functional readout that’s independent of the intensity of the fluorophore. Each fluorescent molecule (and states of molecules) has a unique decay time (“lifetime”) that depends on many factors and can vary with the wavelength of light used for excitation. When there are multiple molecules present, the overall measured lifetime reflects a relative combination of their individual lifetimes.

**FLIO, with blue light excitation, used in clinical research has already shown differences in fluorescence lifetime between healthy eyes and those with various diseases.**4 Studies have also found changes in lifetime with retinal eccentricity and age.5 As mentioned earlier, the main po-
potential advantage for FLIO is the early detection of disease which might not be possible with conventional FAF. For example, researchers at the Moran Eye Center have detected FLIO variations in people with macular telangiectasia at early stages of disease before retinal damage has occurred. FLIO has also shown a characteristic ring-shaped pattern in people with AMD even in early stages. The possibility of earlier identification of patients at risk may be critical in the implementation of proposed preventative measures for disease such as vitamin and mineral supplementation or red light therapy.

Although the current clinical-scale FLIO shows promise as a functional imaging modality that might detect changes at early stages, one of its current limitations is the lack of a simplified metric analogous to RNFL thickness used in OCT for tracking disease progression. A simplified metric or analysis methodology not only makes it easy to use but will generate interest for wide usage in clinical settings.

Clinical-scale FLIO captures fluorescence originating throughout the entire thickness of the retina. It also picks up fluorescence from other parts of the eye like the lens. This makes it difficult to isolate signals specifically from individual retinal layers. To better understand the mechanisms of retinal diseases and their progression, imaging with cellular resolution and isolation to specific retinal layers of interest in living eyes is needed.

**Using adaptive optics for *in vivo* cellular-scale imaging of the RPE mosaic**

Thanks to adaptive optics technology, we can non-invasively image the cellular RPE mosaic in people. This technique corrects for the eye’s natural blurring (aberrations), allowing for incredibly sharp pictures of individual retinal cells and targeting of specific cell layers within the retina. AO combined with fluorescence lifetime imaging (AOFLIO) could provide detailed information about the composition and function of cell layers. This approach has been successfully demonstrated in mice, monkeys and even humans using a variety of fluorescence excitation and emission combinations.

For every single pixel in the clinical FLIO image, AOFLIO captures 2,742 pixels of information, allowing finer details to be appreciated. AOFLIO has the potential to provide insight into *in vivo* cellular-scale changes with age and eccentricity. Additionally, comparing the lifetime data from two or more wavelengths of excitation, we can probe into various types of molecules present and how much each contributes. In the eye, lipofuscin, melanin and melanolipofuscin are all naturally occurring and can be distinguished based on the colors of light they emit. An example of fluorescence lifetime using near-infrared (NIR) excitation light can be seen in Figure 2.

Such pictures can be difficult to interpret so analyzing the lifetime data in a different coordinate space can be sometimes useful in detecting variation. Phasor analysis

![Image](image_url)
A 30-year-old healthy eye.

(a 2D representation of the fluorescence timing in frequency space) is a graphical approach to visualize changes in fluorescence lifetime. Each pixel in the image has a corresponding data point in the phasor plot. Phosphor analysis in AOFLOI has been successful in differentiating S, M/L, and rod photoreceptors in monkeys and was sensitive enough to capture the functional changes with S cone photodamage. Metrics based on phosphor analysis have the potential to provide a rapid assessment for comparison between healthy and diseased eyes that will be easily interpreted by clinicians.

Future directions

AOFLOI and FLIO hold promise as a new, non-invasive potential method for better understanding the molecular changes behind cellular variations in retinal diseases. With AOFLOI, we can now compare fluorescence lifetime of the RPE mosaic in living humans at the cellular level and across multiple wavelengths of light, which paves the way for future longitudinal studies. The improved axial resolution afforded by AOFLOI will enable insight into the sources of fluorescence lifetime variations observed with clinical-scale FLIO. FLIO is an easy-to-use imaging method that provides novel information about the sources of retinal fluorescence that are altered in disease. Upcoming investigations using AOFLOI will investigate the cellular mechanisms underlying disease, evaluate the effectiveness of treatments, and ultimately translate these findings into improved patient care.

References

Ocular inflammatory diseases present several challenges to the clinician. These patients often have complicated histories, can be difficult to examine and the underlying diseases may rapidly become vision- or even life-threatening. However, with an organized and methodical approach, even the most complex or mysterious cases can be successfully diagnosed and managed. Here, I’ll discuss five pieces of data that can be obtained from the history and physical and can be used to generate a focused differential that can streamline your work-up and management. They can also help avoid pitfalls such as ordering an excessive number of tests or starting patients on inappropriate treatment.

1. What are the patient’s demographics?

As medical students, we all learn that the best doctors are the ones who can diagnose the patient as soon as he or she walks in. This is sometimes achievable in uveitis, as the patient’s demographics may narrow down the differential before the eye exam.

- **Age.** The majority of patients with uveitis are between 20 and 60 years old. However, certain types of uveitis are far more likely in particular age groups (Figure 1). For instance, one would not be tempted to include intraocular lymphoma high on the differential in a 23-year-old immunocompetent patient. Similarly, it would be unlikely for a 62-year-old patient to develop an acute onset of toxocariasis-related uveitis.

- **Sex.** While most ocular inflammatory diseases affect males and females equally, there are several that have a predilection for females such as multiple sclerosis, lupus, Susac syndrome and most of the white dot syndromes.

- **Race/ethnicity/geography.** The patient’s race or ethnic background may predispose him or her to certain types of uveitis. For instance, birdshot chorioretinitis is seen almost exclusively in Caucasians. Sarcoidosis is more prevalent in African Americans and patients of Northern European descent, but less common in Asians. Additionally, a patient’s presence within certain geographic regions may suggest a certain differential diagnosis.

### Figure 1. Uveitis and Age

- < 16 years
  - Retinoblastoma
  - Toxocariasis
  - TORCH infections
  - Juvenile Idiopathic Arthritis
  - Juvenile Xanthogranuloma
  - Pars planitis
- 20-50 years
  - HLA-B27
  - Tubulointerstitial nephritis and uveitis (TINU)
  - Pars planitis
  - Multiple Sclerosis
  - Systemic Lupus Erythematosus (SLE)
  - Susac Syndrome
- 30-60 years
  - Birdshot retinochoroidopathy
  - Serpiginous choroiditis
  - Polyarteritis nodosa
- > 50 years
  - Intraocular lymphoma
  - Acute retinal necrosis (ARN)

### Figure 2. Racial/Ethnic/Geographic Considerations in Uveitis

- Caucasian
  - Birdshot retinochoroidopathy
  - Multiple Sclerosis
- African American
  - Sarcoidosis (in the USA)
  - SLE
  - Asian
  - Vogt-Koyanagi Harada (VKH)
- Hispanic
  - SLE
  - VKH
- Mediterranean
  - Behcet Disease
- Ohio and Mississipi River Valley
  - Presumed Ocular Histoplasmosis Syndrome
- San Joaquin Valley
  - Coccidioidomycosis
- Central/South America
  - Cysticercosis
- Africa
  - Oncocerciasis
  - South East Asia
  - Tuberculosis
  - Wli

By Ananth Sastry, MD

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An attending surgeon and faculty member of the Vitreoretinal Service at the Cleveland Clinic Cole Eye Institute.

Disclosures

Dr. Sastry is a consultant to Allergan, Bausch + Lomb, and Genentech/Roche.

Bios

Ananth Sastry, MD
graphic locations may make him or her more vulnerable to certain endemic infectious diseases (Figure 2).

2. What is the timing/chronicity of the inflammation?

The standardization of uveitis nomenclature (SUN) working group helped to sort uveitis into various categories, one of which involved the temporal aspects of the disease in terms of onset, duration and course (Table 1). These temporal distinctions are useful when narrowing the differential, as different diseases operate at various speeds (Table 2).

3. Is the pathology unilateral or bilateral?

Most forms of uveitis are ultimately bilateral even if they're very asymmetric or take an extended period of time for the fellow eye to become involved. Thus, knowledge of the handful of uveitis conditions that are predominantly unilateral (Figure 3) may help arrive at the diagnosis.

4. What are the associated systemic symptoms or findings?

While it can be time-consuming, performing a detailed review of systems is absolutely critical when evaluating uveitis patients. Because uveitis often involves conditions that affect multiple organ systems, this is important not only for reaching a diagnosis, but also to identify conditions that may be life-threatening and need to be addressed immediately.

In my experience, it's not adequate to simply ask the patient in an open-ended manner if they have any other symptoms outside of the eye. Patients frequently leave out important associated findings because they forget, don't think they're important, or are embarrassed to talk about them. They may initially deny having any other symptoms, but later when asked about specific symptoms such as a rash (Figure 4) or joint pain, they will reveal findings that they had previously omitted. Figure 5 demonstrates a list of symptoms that can be associated with specific diagnoses.

5. Where is the inflammation located?

To say that a patient has “uveitis” is as descriptive as saying that a patient has a “retina problem.” For this reason, the SUN classification system is useful in categorizing uveitis based on the location of the inflammation (Table 3). This method of precisely describing uveitis based on localization can greatly focus down the differential. When evaluating patients, I find that many ophthalmologists aren’t sufficiently familiar with the classification and end up labeling cases of intermediate uveitis or retinal vasculitis as “posterior uveitis” or

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Table 1. SUN Classification of Uveitis Chronicity

<table>
<thead>
<tr>
<th>Category</th>
<th>Descriptor</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Sudden</td>
<td>Sudden onset and limited duration</td>
</tr>
<tr>
<td>Duration</td>
<td>Limited</td>
<td>≤ 3 months’ duration</td>
</tr>
<tr>
<td></td>
<td>Persistent</td>
<td>&gt;3 months’ duration</td>
</tr>
<tr>
<td>Course</td>
<td>Acute</td>
<td>Sudden onset and limited duration</td>
</tr>
<tr>
<td></td>
<td>Recurrent</td>
<td>Repeated episodes separated by periods of inactivity without treatment ≥ 3 months’ duration</td>
</tr>
<tr>
<td></td>
<td>Chronic</td>
<td>Persistent uveitis with relapse in &lt;3 months after discontinuing treatment</td>
</tr>
</tbody>
</table>


Table 2. Acute vs. Chronic Uveitis

<table>
<thead>
<tr>
<th>Chronicity</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute</td>
<td>Viral iridocyclitis/retinitis</td>
</tr>
<tr>
<td></td>
<td>Bacterial endophthalmitis</td>
</tr>
<tr>
<td></td>
<td>Toxoplasmia</td>
</tr>
<tr>
<td></td>
<td>HLA-B27 uveitis</td>
</tr>
<tr>
<td>Chronic</td>
<td>Tuberculosis</td>
</tr>
<tr>
<td></td>
<td>P. Acnes endophthalmitis</td>
</tr>
<tr>
<td></td>
<td>Pars planitis</td>
</tr>
<tr>
<td></td>
<td>Sarcoidosis</td>
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</tbody>
</table>

describing posterior uveitis as “panuveitis.”

Performing a thorough ophthalmic exam including the ocular surface and adnexa is critical to correctly localize inflammation. For instance, it’s important to always check under the lids, which can reveal clues such as salmon patches secondary to lymphoma or an inflamed lacrimal gland from sarcoidosis. The anterior vitreous should be examined with a 1 x 1 slit beam to check for cell, not just the anterior chamber. Additionally, the far inferior retinal periphery should be checked to evaluate for snowbanking. Sometimes scleral depression is required to visualize this.

Putting it all together

Imagine you have three patients who have been referred to you. You’re told one has anterior uveitis, the second has vitritis, and the third has panuveitis. Do you have a good sense of your diagnosis and plan for these patients with the information provided? What if we were to add each of the pieces of data described above to these scenarios?

- Now the first patient is a 28-year-old Caucasian male who presents with an acute, unilateral iridocyclitis with concurrent lower back pain.
- The second patient is a 37-year-old African female presenting with chronic, unilateral intermediate uveitis. Review of systems is positive for circular skin lesions on her shins.
- The third patient is a 43-year-old female from India presenting with acute, bilateral panuveitis. She notes that several weeks prior to her vision changes, she suffered from fever, neck stiffness and hearing loss.

With the addition of just five pieces of data for each of these cases, the clinician is guided almost directly to the diagnoses.

Bottom Line

When working up uveitis, assess the patient’s demographics, take a detailed history with emphasis on chronicity and laterality, perform a detailed review of systems, determine the location of the inflammation and use the SUN classification. This organized approach may help improve efficiency and diagnostic accuracy.

References


Table 3. SUN Classification of Uveitis

<table>
<thead>
<tr>
<th>Type</th>
<th>Subtypes</th>
<th>Clinical Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior Uveitis</td>
<td>Iris iridocyclitis</td>
<td>Anterior chamber cell/flare</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fibrin, hypopyon</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Keratic precipitates, band keratopathy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Posterior synechiae Iris nodules</td>
</tr>
<tr>
<td>Intermediate Uveitis</td>
<td>N/A</td>
<td>Anterior vitreous cell/flare</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Snowballs/snowbanking</td>
</tr>
<tr>
<td>Posterior Uveitis</td>
<td>Retinitis</td>
<td>Retinal/choroidal Infiltrates</td>
</tr>
<tr>
<td></td>
<td>Chorioretinitis</td>
<td>Optic nerve head edema</td>
</tr>
<tr>
<td></td>
<td>Neuroretinitis</td>
<td>Exudative or traction retinal detachment</td>
</tr>
<tr>
<td>Panuveitis</td>
<td>N/A</td>
<td>All of the above</td>
</tr>
<tr>
<td>Retinal Vasculitis</td>
<td>Angiitis</td>
<td>Vascular sheathing</td>
</tr>
<tr>
<td></td>
<td>Phlebitis</td>
<td>Perivascular infiltrates</td>
</tr>
</tbody>
</table>

April 8, 2024 has come and passed. Totality: A total solar eclipse, the last one visible to most of North America until 2045. For ophthalmologists and retinal specialists, it was of special importance given the risk of solar retinopathy with observing eclipses with incomplete or no ultraviolet light protection. As a result, physicians flocked to social media channels to educate the public and emphasize the importance of verifying eclipse glasses as being ISO 12312-2 and meeting the International Safety Standard for solar viewing. For example, Will Flanary, MD, better known as Dr. Glaucomflecken on social media channels including X (formerly Twitter), YouTube and TikTok, posted a video podcast on his channel Knock Knock Eye titled “A Solar Eclipse Can Melt Your Eyes: How To Watch Safely.”

We’ve written previously on the responsibility and power physicians possess to teach proper medicine and help prevent health problems. The mass disinformation spreading to unsuspecting consumers is one of the major reasons Dr. Glaucomflecken and ophthalmology influencers like him are so critical. While it may seem obvious to this retinal specialist audience that staring at an eclipse is a terrible idea for foveal health, we take our knowledge base for granted. For example, the popular social media forum, Reddit, featured questions in the week leading up to the eclipse such as the following: “Why can’t you just wear sunglasses to look at an eclipse? I look at the sun with no sunglasses on, and I haven’t gone blind yet, so why do I have to wear eclipse glasses to look at the eclipse?” This is why intelligent and knowledgeable social media participants are irreplaceable.

For retina, what are the likely areas we can add to the conversation in a meaningful way? We should consider unmet needs or areas of frustration for our patients. One well-described cohort are patients with end-stage macular degeneration (wet or dry) looking for solutions and vulnerable to predatory stem cell “clinics” trying to sell dangerous snake oil type interventions in exchange for large monetary reward. Retina social media influencers would be well-served illustrating the risks of unapproved therapies and direct patients to actual reputable clinical trial sites that may have options. Another group that needs our input are patients with typical symptoms concerning for retinal detachment; how often do we see patients finally referred to surgical retina clinics who are already mac-off for a week or more? Good social media descriptions on the importance of recognizing flashes and floaters and seeking appropriate eye exams exist and yet, we need to do more work to get these posts and videos pushed up by application algorithms to the public.

The next total solar eclipse will be in August 2026 and will be best viewed from the Northern Hemisphere (think Greenland, Iceland and parts of Spain). This gives us ample time and opportunity to continue our eclipse-viewing education. A PubMed search of “eclipse solar retinopathy” yields 73 publications as of April 12, 2024. Our goal as a field should be to keep this number as static as possible through 2026 and beyond, and social media is likely our most powerful tool to achieve this goal.
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