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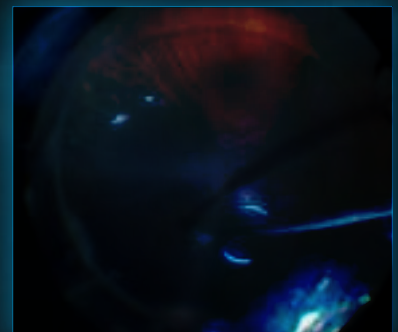
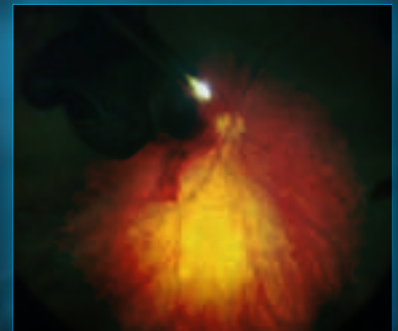
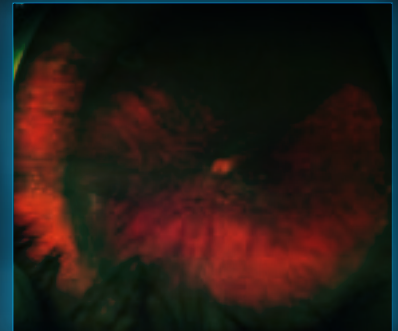
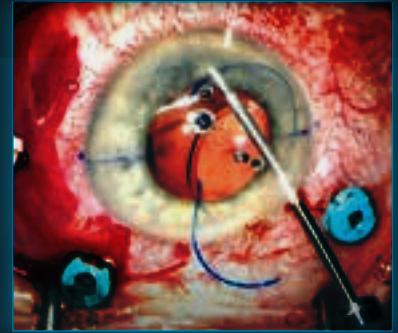
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Retina Today

JANUARY/FEBRUARY 2024 VOL. 19, NO. 1
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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 $\geq 5\%$) 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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US-AP-2300207 09/23

**IVERIC
BIO**
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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 field, syringe, gloves, drapes, eyelid speculum, filter needle, and 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 (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.

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
- Neovascular AMD
- Increase in intraocular pressure

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in 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 Eye

Adverse Drug Reactions	IZERVAY N=292	Sham N=332
Conjunctival hemorrhage	13%	9%
Increased IOP	9%	1%
Choroidal neovascularization	7%	4%
Blurred Vision*	8%	5%
Eye pain	4%	3%
Vitreous floaters	2%	<1%
Blepharitis	2%	<1%

* 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.

Manufactured by:
IVERIC bio, Inc., An Astellas Company. Parsippany, NJ 07054

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THE FUTURE IS HERE



We are well into a new year, and changing the date on our forms always seems to prompt a sense of nostalgia, along with the drive to

start fresh with our resolutions. As we worked on this issue focused on surgical tools and techniques, we were reminded just how far we have come in our field. Our retina clinics and ORs are a far cry from what they were when *Retina Today* first launched in 2006. Back then, authors were debating the value of 25-gauge versus 20-gauge vitrectomy,¹ combined vitrectomy/scleral buckling was still the norm for retinal detachments,² and the utility of peeling the internal limiting membrane (ILM) for the treatment of macular holes was still up for debate.³ There was nary a peep about AI, robotics, ultra-widefield anything, 3D visualization, or gene therapy. We barely had drugs to deliver, let alone various surgical delivery approaches.

But those tools, so far in the future they weren't even mentioned nearly 20 years ago, are a reality in today's ORs. Within these pages, experts discuss new intraoperative visualization tools, advanced IOLs and implantation techniques, novel approaches to macular holes and diabetic vitrectomy, and innovative surgical drug delivery methods.

The latest advances in the OR have allowed us to treat patients who once had very few, if any, treatment options, and they have certainly improved anatomic and functional outcomes. Take those macular holes, for example. No one is debating the utility of ILM peeling anymore, considering the closure rate can be as low as 58% with vitrectomy alone but jumps to a whopping 92% with ILM peeling.⁴ Marcelo Zas, MD, PhD, and colleagues provide a robust look at the latest surgical approaches in *Macular Surgery: Current and Innovative Techniques*.

And not only do we have 3D visualization in the OR, but we are also adding to that technology with intraoperative imaging, whether it's OCT (see *3D Heads-Up Display: Pearls for New Users* in the April 2023 issue) or fluorescein angiography, discussed here in *The Ins and Outs of Intraoperative FA* by Alan J. Franklin, MD, PhD, and his team.

The 2006 research suggesting 25-gauge instruments added too much time to the surgery is long forgotten with the advent of 27-gauge tools.¹ The smaller-gauge instruments have made early vitrectomy for diabetic retinopathy not only possible, but also potentially the best treatment approach for certain patients, according to Andreas Pollreis, MD, and colleagues in this issue's article, *Vitrectomy for Diabetic Retinopathy: Think Early, Not Late*.

Each of the innovations discussed in this issue is a product of intense collaboration—with colleagues, patients, researchers, industry partners, and regulators. We couldn't care for our patients to the best of our ability without it. So, we thank everyone who has helped create the OR we step into every day and is working toward a better one for the future. ■

— Lejla Vajzovic, MD, FASRS, and M. Ali Khan, MD

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Want to learn more about visualization in the OR? Check out **3D Heads-Up Display: Pearls for New Users** in the April 2023 issue



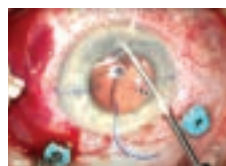
ON THE COVER

MAIN IMAGE



Intraoperative fluorescein angiography. From *The Ins and Outs of Intraoperative FA*, by Lukan Mishev, MD; Nassim Abreu-Arbaje, MD; Joaquin Sosa-Lockward, MD; Lauren Gibson, MD; Aly Nguyen, BS; and Alan J. Franklin, MD, PhD.

INSETS



Off-label sutureless flanged intrascleral haptic fixation of an IOL. From *IOL Options for Sutureless Fixation*, by Murtaza Adam, MD.



One month after silicone oil removal for rhegmatogenous retinal detachment repair. From *How to Choose the Right Tamponade*, by Lucy V. Cobbs, MD, and Vaidehi S. Dedania, MD.



Proliferative diabetic retinopathy in a 26-year-old woman with type 1 diabetes. From *Vitrectomy for Diabetic Retinopathy: Think Early, Not Late*, by Andreas Pollreis, MD; Peter Szurman, MD, PhD; and Boris V. Stanzel, MD.



Autologous retinal transplant for refractory macular holes. From *Macular Surgery: Current and Innovative Techniques*, by Marcelo Zas, MD, PhD; Mariano Cotic, MD; and Marcos Mendaro, MD.

WET AMD EYE

ANTI-VEGF

Therapy yields better long-term VA results when wet AMD detected with good VA¹

FELLOW EYE

20/79 VA

Mean VA of fellow eyes at wet AMD diagnosis according to real-world data¹

**Over 60% of wet AMD “fellow eyes” lose too much vision¹—
even with frequent treatment visits**

Detect Early. Treat Early.

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

✓ FDA Cleared ✓ Medicare Covered

ForeseeHOME™
AMD Monitoring Program



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

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

The Key to Successful Home Monitoring

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& Education

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Verification &
Authorization

Continuous
Monitoring



Practice Workflow
Implementation

Remote Patient
Management

Vision Alert
Management



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

See website for FDA Indication for Use.

SM-125.3



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SURGICAL TECHNIQUES and TECHNOLOGIES

Image courtesy of Alan J. Franklin, MD, PhD

- 28 The Ins and Outs of Intraoperative FA**
By Lukan Mishev, MD; Nassim Abreu-Arbaje, MD;
Joaquín Sosa-Lockward, MD; Lauren Gibson, MD; Aly Nguyen, BS; and
Alan J. Franklin, MD, PhD
- 31 IOL Options for Sutureless Fixation**
By Murtaza Adam, MD
- 33 Vitrectomy for Diabetic Retinopathy: Think Early, Not Late**
By Andreas Pollreis, MD; Peter Szurman, MD, PhD; and Boris V. Stanzel, MD

- 36 Macular Surgery: Current and Innovative Techniques**
By Marcelo Zas, MD, PhD; Mariano Cotic, MD; and Marcos Mendaro, MD
- 40 How to Choose the Right Tamponade**
By Lucy V. Cobbs, MD, and Vaidehi S. Dedania, MD
- 44 Surgical Drug Delivery Roundup**
By Nikhil K. Bommakanti, MD; Michael A. Klufas, MD; and David Xu, MD

UP FRONT

- 6 Guest Medical Editors' Page**

- 10 Retina News**

MEETING MINUTES

- 12 Tackling Diabetes at ARDS 2023**
By Mohammad Ali Sadiq, MD
- 14 Hot Topics From AVTT 2023**
By Frank Ma, MD, and Hesham Gabr, MD

ONE TO WATCH

- 16 Sruthi Arepalli, MD**

MEDICAL RETINA

- 17 Workup and Management of Choroidal Folds**
By Sayena Jabbehdari, MD, MPH, and Sami H. Uwaydat, MD

GLOBAL PERSPECTIVES

- 23 Managing The Ocular Effects of Steroid Overdose**
By Fernando Godin, MD; Nimesh A. Patel, MD; Eduardo
Cadena, MD; Diana Concha, MD; Maria Adelaida Piedrahita, MD;
and Carolina Parra, MD

SURGICAL PEARLS

- 46 Myopic Traction Maculopathy in a Surgical Setting**
By Elham Sadeghi, MD, and Jay Chhablani, MD



ONLINE EXCLUSIVE:
Pediatric Retina Cases and Conclusions
By Mariam Al-Feky, MD, FRCSC

OCULAR ONCOLOGY

- 48 Ocular Toxicity of New-Age Cancer Therapies**
By Ronak Shah, BS; Robin Vora, MD; Amar Patel, MD; and
Ying Qian, MD

CODING ADVISOR

- 52 Five Retina Coding Updates for 2024**
By Joy Woodke, COE, OCS, OCSR

RISING STARS IN RETINA

- 54 Leanne M. Clevenger, MD**

FELLOWS' FOCUS

- 55 AI in Medicine for the Retina Fellow**
By Nikhil K. Bommakanti, MD

IN THE BACK

- 57 Ad Index**

VISUALLY SPEAKING

- 58 Bietti Crystalline Dystrophy With Choroidal Caverns**
By Mustafa Kayabasi, MD, and Ali Osman Saatci, MD



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RESEARCHERS IDENTIFY BEST OCT PREDICTORS OF AMD PROGRESSION

After evaluating which OCT biomarkers best predict the risk of progression from early or intermediate to late-stage AMD, researchers narrowed down the six most relevant OCT prognostic biomarkers and found that they have greater predictive ability than the presence of large drusen alone.¹

The review pooled studies that followed the Grade of Recommendations, Assessment, Development, and Evaluation (GRADE) approach and identified a total of 114 OCT prognostic biomarkers.¹ With high GRADE certainty of evidence, the best predictors of progression to late AMD were external limiting membrane abnormality (odds ratio [OR] = 15.42), ellipsoid zone abnormality (OR = 10.80), interdigitation zone abnormality (OR = 7.68), concurrent large

drusen and reticular pseudodrusen (hazard ratio = 6.73), hyporeflective drusen cores (OR = 1.85), intraretinal hyperreflective foci (OR = 5.08), and large drusen (OR = 1.98).¹

There was a greater risk of progression to geographic atrophy (GA) for intraretinal hyperreflective foci and hyporeflective drusen cores ($P < .05$) and neovascularization for ellipsoid zone abnormality ($P < .05$). Other OCT biomarkers, such as drusenoid pigment epithelium detachment, shallow irregular retinal pigment epithelium elevation, and nascent GA, exhibited large magnitudes of risk but require further study for validation, the team concluded in their paper.¹

1. Trinh M, Cheung R, Duong A, Nivison-Smith L, Ly A. OCT prognostic biomarkers for progression to late age-related macular degeneration: a systematic review and meta-analysis [published online ahead of print December 26, 2023]. *Ophthalmol Retina*.

3D TECHNOLOGY HELPS MAP HUMAN RETINA FORMATION

Using lab-grown retina models, researchers at the National Eye Institute have mapped the 3D organization of genetic material of five crucial developmental stages of human retina formation. The team used deep Hi-C sequencing to create a high-resolution map of chromatin—long strands of DNA that are packaged together, spooled around histone proteins, and repeatedly looped to form chromosomes—in a human retinal organoid at five key points of development. The chromatin loops create millions of contact points where genes encounter non-coding DNA sequences, known as *junk DNA*.¹

The researchers sequenced and analyzed billions of these chromatin contact point pairs and discovered that contact between genes and junk DNA plays a crucial role in gene expression. They noted that when immature cells start developing retinal cell characteristics, the chromatin contact points shift away from a proximal-enriched state to more distal interactions.

These findings open the door to further investigations into how non-coding sequences affect divergent phenotypes in single-gene mutations, paving the way for a deeper understanding of complex retinal diseases.

1. NEI study shows how genes in retina get regulated during development. Eyewire News. December 15, 2023. Accessed January 3, 2024. eyewire.news/news/nei-study-shows-how-genes-in-retina-get-regulated-during-development

RESEARCHERS LINK PAMM AND RETINAL VASCULAR DISEASE

In a recent study, researchers found that patients with paracentral acute middle maculopathy (PAMM) and retinal artery occlusion (RAO) were more likely to have a history of cardiovascular events and worse presenting visual acuity compared with patients with no retinal vascular disease and those with retinal vein occlusion (RVO).

The retrospective cohort study ($n = 78$) was designed to evaluate the sociodemographic profile, association with retinal vascular disease and systemic comorbidities, and visual outcomes of patients with PAMM. Forty patients (51.3%) presented with no retinal vascular disease, 20 (25.6%) with RVO, 16 (20.5%) with RAO, and two (2.6%) with both RAO and RVO. Patients with PAMM and RAO had a greater likelihood of a history of major adverse cardiovascular events than those with RVO ($P = .01$). They also had worse presenting BCVA compared with those with RVO ($P = .02$) and those with no retinal vascular disease ($P < .001$). Patients with isolated PAMM had a higher prevalence of previous major adverse cardiovascular events, as well as sickle cell disease.

Given these findings, the authors concluded that a diagnosis of PAMM should prompt an immediate referral for a comprehensive systemic workup; however, visual outcomes were good across the cohort, with 64 patients (85.3%) having

a BCVA of 20/32 or better at the last follow-up. They noted that the association of PAMM with retinal vascular disease may point to an ischemic etiology.

1. Limoli C, Raja LD, Wagner SK, et al. Exploring patient demographics and presence of retinal vascular disease in paracentral acute middle maculopathy [published online ahead of print December 15, 2023]. *Am J Ophthalmol*.

BENEFITS OF AN INVERTED ILM FLAP TECHNIQUE REVEALED

A recent study evaluated the surgical outcomes associated with the use of three internal limiting membrane (ILM) peeling techniques—standard ILM peeling, fovea-sparing ILM peeling, and an inverted ILM flap—for the treatment of myopic traction maculopathy. The researchers found that patients who underwent vitrectomy with an inverted ILM flap had a significantly lower risk of postoperative full-thickness macular hole (FTMH).¹

A total of 101 eyes treated with vitrectomy with either standard ILM peeling, fovea-sparing ILM peeling, or the inverted ILM flap technique from July 2017 to August 2020 were included. After 12 months, there was no difference in BVCA between the groups; however, none of the eyes in the inverted ILM flap group had developed a FTMH versus five (15.6%) in the standard ILM peeling group and six (17.1%) in the fovea-sparing ILM peeling group ($P = .026$). Moreover, the ILM peeling technique was found to be an independent factor in the development of FTMH ($OR = .209$, $P = .014$).¹

The authors concluded that, in cases where there is a high risk for postoperative macular hole development, the inverted ILM flap technique may be an effective treatment option with the potential to mitigate this risk.¹

1. Feng J, Shao Q, Xie J, et al. Comparison of three internal limiting membrane peeling techniques for myopic traction maculopathy with high risk of postoperative macular hole development. *Retina*. 2023;43(11):1872-1880.

VISUAL IMPAIRMENT IN WORKING-AGE INDIVIDUALS ON THE RISE

Researchers recently reported in *JAMA Ophthalmology* that visual impairment in working-age individuals is a growing global health challenge.¹ Despite the mild decrease in visual impairment prevalence rates in less-developed countries, the number of cases globally has increased substantially, with discernible, unfavorable patterns in developed regions, the study findings suggest.

The cross-sectional, population-based study analyzed data from 1990 to 2019 for individuals between 15 and 64 years of age from 204 countries and territories obtained from the 2019 Global Burden of Disease study.¹

The team found that there were 437,539,484 cases of visual impairment globally (53.12% female) in 2019, an increase of 91.46% from 1990. Over 3 decades, visual

impairment-associated disability-adjusted life-years (DALYs) increased from 7,601,852 to 12,563,276. Among the five sociodemographic index groups, the lowest had the largest increase in DALYs. Regionally, the greatest increase in prevalence was observed in Eastern Europe. Among all countries and territories, Nepal had the highest national prevalence of visual impairment per 100,000 people in 2019, while South Sudan had the highest DALY rate per 100,000 people.¹

The researchers concluded that a better understanding of this global challenge may help to facilitate the development of prevention and treatment measures.¹ ■

1. Chen J, Yang C, Zheng W, et al. Global, regional, and national epidemiology of visual impairment in working-age individuals, 1990-2019 [published online ahead of print December 7, 2023]. *JAMA Ophthalmol*.

Eyewire+ Pharma Update

- **Annexon** announced that it will use the prevention of $\geq$ a 15-letter loss of BCVA as the primary outcome measure in the evaluation of ANX007 for the treatment of geographic atrophy (GA). Of note, the FDA will not require Annexon to study whether the drug slows GA lesion growth.
- **Johnson & Johnson** acquired the rights to the investigational gene therapy botaretigene sparaparvovec (bota-vec; formerly AAV-RPGR) for the treatment of X-linked retinitis pigmentosa from MeiraGTx.
- The FDA granted regenerative medicine advanced therapy designation for **OCU400 (Ocugen)**, an investigational product for the treatment of retinitis pigmentosa associated with *RHO* mutations.
- **Oculus** began the second stage of its phase 3 DIAMOND-1 trial of the OSC-01 drop for the treatment of diabetic macular edema. The company will enroll 350 to 400 patients who will be randomly assigned to receive OCS-01 or a vehicle six times daily.
- **Regeneron** received marketing authorization in the European Union from the European Commission for 8 mg aflibercept (Eylea HD).
- **Carl Zeiss Meditec** entered into an agreement to purchase 100% of the shares of the Dutch Ophthalmic Research Center, International, from Eurazeo SE for approximately \$1.07 billion.
- **Clearside Biomedical** completed randomization in the phase 2b ODYSSEY clinical trial evaluating axitinib (CLS-AX) for the treatment of wet AMD. The trial is designed to evaluate at least 60 patients treated with either 1 mg CLS-AX or aflibercept (Eylea, Regeneron). Topline data are expected in the third quarter of 2024.
- **Apellis** anticipates receiving a negative opinion from the Committee for Medicinal Products for Human Use of the European Medicines Agency on intravitreal pegcetacoplan (Syfovre), its targeted C3 therapy for GA. The vote is expected to take place during the organization's next meeting from January 22-25.
- The first patient has been dosed with **AAV-RORA (OCU410, Ocugen)**, a modifier gene therapy candidate for the treatment of GA, in a phase 1/2 safety and efficacy trial.

Want more retina news from **Eyewire+**?



TACKLING DIABETES AT ARDS 2023



Experts came together in Snowmass Village to discuss the nuances of treating diabetic eye disease.

BY MOHAMMAD ALI SADIQ, MD

The Aspen Retinal Detachment Society (ARDS) meeting in Snowmass, Colorado, is always a haven of learning—a place where clinicians come together to discuss new data, therapeutics, and surgical approaches. During the 2023 meeting, held March 4-8, Charles C. Wykoff, MD, PhD; Susan B. Bressler, MD; and Zofia A. Nawrocka, MD, PhD, shared recent findings that have shifted the way we treat patients with diabetic retinopathy (DR) and diabetic macular edema (DME). Here, you can find a summary of their excellent lectures (Figure).

ARDS 2024 is just a few weeks away, set for March 2-6. Visit aspenretina.com to register, find lodging, and prep for another year of top-notch education!

- Timothy G. Murray, MD, MBA

RETINAL NONPERFUSION IN DR

Dr. Wykoff began his lecture by outlining the evidence for retinal nonperfusion as a biomarker of DR progression. First, a RISE and RIDE post-hoc analysis showed that, over 3 years, the risk of progression to proliferative DR (PDR) was substantially lower in patients treated with monthly ranibizumab (Lucentis, Genentech/Roche) compared with sham.¹ However, despite monthly injections, close to one in five patients still developed PDR. The only baseline factor that helped to predict progression was retinal nonperfusion. Second, the DRCR Protocol AA trial showed that greater baseline nonperfusion on fluorescein angiography was associated with a higher risk of disease worsening.² Finally, a post-hoc analysis of the PANORAMA study found that retinal nonperfusion once again played a critical role in progression.³

The phase 2 RECOVERY trial studied nonperfusion changes in patients with PDR without DME, Dr. Wykoff said. Patients were treated with aflibercept (Eylea, Regeneron) either monthly or every 3 months, and the 1-year results showed relatively stable nonperfusion with monthly dosing and a 29% worsening with the extended dosing schedule.⁴

Dr. Wykoff then discussed reports of retinal reperfusion in the literature.⁵⁻⁷ In the RISE, RIDE, and VISTA studies, there was a steady increase of nonperfusion over time in eyes in the sham arm. In the group that received anti-VEGF therapy, the increase in nonperfusion appeared to be blunted.^{8,9}

Dr. Wykoff explained that the best evidence we have of reperfusion is the concept of a leukostatic plug. According

ABOUT THE SPEAKERS



Charles C. Wykoff, MD, PhD

- Director of Research, Retina Consultants of Texas/Retina Consultants of America, Houston; Deputy Chair for Ophthalmology, Blanton Eye Institute, Houston Methodist Hospital, Houston
- Editorial Advisory Board Member, *Retina Today*



Susan B. Bressler, MD

- Julia G. Levy, PhD, Professor of Ophthalmology, Wilmer Eye Institute, Johns Hopkins University, Baltimore



Zofia A. Nawrocka, MD, PhD

- Vitreoretinal Specialist, Ophthalmic Clinic, "Jasne Blonia," Lodz, Poland

to the concept, in any hypoxic state, there is an upregulation of VEGF and other cytokines. A downstream effect is the upregulation of the ICAM-1 molecule, a receptor that endothelial cells express to attract white blood cells. White blood cell clumping can then block the blood vessel. Through VEGF inhibition, downstream expression of these molecules is modified, causing a reversal of the breakdown of this plug and improving flow.

Dr. Wykoff concluded his talk with a brief look at therapies in the pipeline working to address retinal reperfusion.

DME MANAGEMENT: STEP THERAPY

Dr. Bressler provided an update on first-line therapy for patients with DME. In DRCR Protocol T, aflibercept, bevacizumab (Avastin, Genentech/Roche), and ranibizumab were all effective in achieving visual improvement through 2 years in patients with center-involving DME (CI-DME).¹⁰ However, a subgroup analysis found that, at 1 year, aflibercept showed superiority for patients with a VA of 20/50 or worse and remained superior to bevacizumab but was statistically similar to ranibizumab at 2 years, Dr. Bressler explained.¹¹ An area-under-the-curve analysis found that aflibercept

Images courtesy of Kevin Caldwell Photography



Figure. During ARDS 2023, Drs. Wykoff (left), Bressler (middle), and Nawrocka (right) share the latest data and treatment approaches for DME.

remained superior to ranibizumab for patients with a presenting VA of 20/50 or worse. It's reasonable to consider aflibercept as the first-line therapy for patients with CI-DME and a VA of 20/50 or worse, she said.

She then moved on to discuss Protocol AC, in which patients with CI-DME with a VA of 20/50 or worse were randomly assigned to either aflibercept monotherapy or bevacizumab and switched if necessary.¹² Within 2 years, 70% of patients who started with bevacizumab had switched to aflibercept, Dr. Bressler noted. Although the net number of injections was similar between the two groups over 2 years, there is a cost savings when starting with bevacizumab, she said, adding that step therapy did not compromise long-term visual outcomes when using the Protocol AC criteria.

She then discussed Protocol V, in which patients with CI-DME with a VA of 20/25 or better were randomly assigned to either anti-VEGF treatment, focal grid laser, or observation until vision loss occurred. Regardless of the strategy, 15% to 19% lost 1 or more lines of vision, Dr. Bressler explained. Within each treatment arm, about half of patients who lost vision lost between 5 and 9 letters. There was no difference between the treatment strategies, she emphasized. At the end of 2 years, 85% maintained a VA of 20/25 or better, regardless of treatment approach.

VITRECTOMY FOR DME

Finally, Dr. Nawrocka discussed vitrectomy as a treatment option for patients with DME. She highlighted her study in which 44 eyes with treatment-naïve DME underwent vitrectomy and experienced an improvement in DME and visual acuity.¹³

She then discussed another study that reported that a subretinal injection of balanced salt solution (BSS) in DME led to a decrease in osmotic pressure and the viscosity of subretinal fluid.¹⁴ This can promote water transport from the subretinal space into the choroid and wash out cytokines and migratory cells. To further test this hypothesis, Nawrocki et al designed a study in which each patient's better-seeing eye (n = 14) was treated with aflibercept

and the worse-seeing eye underwent vitrectomy with ILM peeling and a subretinal injection of BSS. The team found that the central subfield thickness decreased similarly in each group, Dr. Nawrocka explained. The delta in visual acuity was similar in each group. A mean of 3 injections were performed over the course of 6 years in half of the vitrectomized eyes, suggesting that these eyes responded well to anti-VEGF treatment, Dr. Nawrocka added.

She concluded by emphasizing that the rate of visual acuity improvement is similar in eyes treated with anti-VEGF injection and those treated with vitrectomy. Performing vitrectomy decreases the possible number of required future anti-VEGF injections, may reduce the density of the superficial foveal avascular zone, and may have a protective effect on future DR complications. ■

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- Financial disclosure: None

HOT TOPICS FROM AVTT 2023



Experts discussed the latest advances, debated controversial topics, and led a wet lab.

BY FRANK MA, MD, AND HESHAM GABR, MD

The 24th annual Advanced Vitreoretinal Techniques and Technology (AVTT) Symposium, held August 18-20, 2023, provided a comprehensive summary of the latest advances and best practices in the field of retina. Although the course was designed for second-year fellows, it was also open to residents, first-year fellows, and community ophthalmologists to connect and hear from the leaders in the field.

DAY 1: SETTING THE STAGE

The AVTT Symposium kicked off with an early breakfast, during which attendees had the opportunity to explore exhibits showcasing cutting-edge technologies. Meeting organizer William F. Mieler, MD, provided a warm welcome, setting the tone for a day packed with insightful discussions and a hands-on wet lab.

The morning session focused on career development and the state of ophthalmology. Dr. Mieler began by delving into current practice patterns and demographics in ophthalmology—the good news is that female representation has increased to 40% of incoming residents, but there is still work to be done. To that end, R.V. Paul Chan, MD, MSc, MBA, spoke about the AAO's Leadership Development Program, various international alliances, and global ophthalmology.

Other speakers included Sunil Srivastava, MD, who shared his thoughts on the transition from fellow to mentor; Jennifer I. Lim, MD, who discussed the pros and cons of participating in clinical trials and scientific advisory

boards; and Anita Agarwal, MD, who provided a framework for early career development. Mary Elizabeth Harnett, MD, gave an interesting talk on how fellows can incorporate clinical research into their long-term career goals, and Yannek Leiderman, MD, PhD, provided a glimpse into the medical device development process.

Wrapping up the first session of the meeting was Srinivas R. Sadda, MD, who shared tips for remaining active in academics, and George A. Williams, MD, past AAO president, who gave a talk that highlighted issues with prior authorization and the lack of inflation adjustment for physician fee schedules.

A highlight of the day, and the entire meeting, was the wet lab. The afternoon started with lectures by Peter K. Kaiser, MD, and Dr. Leiderman on vitrectomy dynamics and how to prepare for surgical success. Residents and fellows were then able to practice vitrectomy techniques on the latest systems, including Alcon's Ngenuity, Bausch + Lomb's Stellaris Elite, and DORC's Eva Nexus, with one-on-one instruction from faculty (Figure).

Other stations were set up to give attendees an opportunity to experiment with various medication injections, including intravitreal dexamethasone (Ozurdex, Abbvie) and fluocinolone acetonide intravitreal implants (Iluvien and Yutiq, Alimera Sciences). While the other half of the group waited for their chance in the wet lab, Dr. Agarwal, Dr. Sadda, and Amani A. Fawzi, MD, led a discussion of medical and surgical cases.

(Continued on page 25)

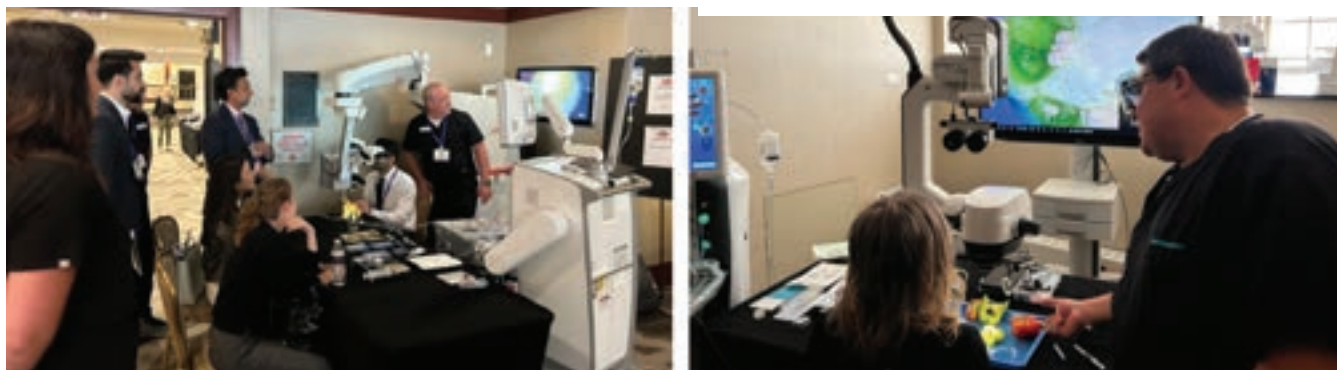


Figure. During the AVTT wet lab, residents and fellows tested out various microscopes and had the chance to operate on practice eyes and peppers.

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REGENXBIO



SRUTHI AREPALLI, MD

WHERE IT ALL BEGAN

My parents immigrated from India to Maryland and did an incredible job navigating a new country. Their stories and struggles shaped my childhood. My sister and I heard how my father used to study outside by streetlight because he did not have electricity growing up, and we watched our mother work odd jobs before going back to school. Their resilience instilled within me a strong work ethic and motivation to care for the underserved. I decided to become a doctor in high school and was admitted to a combined BA/MD program at the George Washington University.

MY PATH TO RETINA

I discovered ophthalmology late in medical school and completed a research year with Carol L. Shields, MD, at Wills Eye Hospital to explore the field. I was awestruck by the complexity of her clinic and her thoughtful, tailored care for each patient. I realized I wanted to emulate this in my own career and was particularly interested in posterior diseases. Dr. Shields has provided a phenomenal amount of support during my journey, and she was the first to suggest I consider vitreoretinal surgery because of my interests.

I attended the Cole Eye Institute for residency, where I worked with a dynamic retina and uveitis department. I developed a particular interest in uveitic retinal conditions and found their connections to systemic disease intriguing. Seeing the department provide end-of-the-line surgical care solidified my desire to train in both vitreoretinal surgery and uveitis. I completed my uveitis fellowship at the Casey Eye Institute in Portland, after which I returned to the Cole Eye Institute for my vitreoretinal fellowship.

SUPPORT ALONG THE WAY

In addition to Dr. Shields, I've had other invested and caring mentors throughout my training. At Cole Eye, I worked with many specialists who helped me build a foundation in retina and uveitis. A few include Peter K. Kaiser, MD, a phenomenal surgeon and teacher who treated me like family and has provided unwavering support; Justis P. Ehlers, MD, who helped me develop my imaging research interests; and Alex Yuan, MD, PhD, who walked

Dr. Arepalli's Advice: Your journey after fellowship will be immensely rewarding but will also contain challenges. Treat these difficulties as an opportunity to learn. These experiences can enhance your clinical knowledge, help determine the career you want, and can make a future patient's situation better.



me through my first surgeries. At Casey Eye, I watched Phoebe Lin, MD, PhD, and Eric B. Suhler, MD, MPH, approach complicated patients with grace and diligence, and they are still a sounding board for my diagnostic dilemmas.

I've also been struck by the willingness of many who have provided mentorship without directly training me. Gaurav K. Shah, MD; Christina Y. Weng, MD, MBA; Sophie J. Bakri, MD; Purnima S. Patel, MD; Steven Yeh, MD; Baker Hubbard, MD; and Jiong Yan, MD, have helped guide my early career, and I am indebted to them for their time and support.

AN EXPERIENCE TO REMEMBER

Being trusted to work with pediatric and young adult patients with difficult pathology has been an honor, and it has been immensely satisfying to preserve their vision so they can maintain independence. Recently, I took care of a young man without insurance with acute retinal necrosis, who later developed a detachment. To help pay for his care, our team applied for Emory charity funds. We successfully reattached his retina and improved his vision. At the last visit, his mother cried, hugged me, and told me how grateful she was to our team. Seeing the effect of our team's work and enabling others to live full, productive lives regardless of their financial situation has been incredibly rewarding. ■

Sruthi Arepalli, MD, is an assistant professor at the Emory Eye Center in Atlanta, where she practices vitreoretinal surgery and uveitis with an exceptional retina service. She works with retina fellows and ophthalmology residents in the OR and clinic.

WORKUP AND MANAGEMENT OF CHOROIDAL FOLDS



Diagnostic imaging and a thorough systemic workup are warranted if you encounter this finding on routine examination.

BY SAYENA JABBEHDARI, MD, MPH, AND SAMI H. UWAYDAT, MD

Choroidal folds are clinical entities in which subretinal striae are seen in the posterior pole or periphery of the retina. Choroidal folds rarely extend beyond the equator,¹ and they present with undulations of the inner choroid, Bruch membrane, overlying retinal pigment epithelium (RPE), and neurosensory retina.^{2,3}

This clinical finding is usually detected during routine ophthalmic examination of patients who are asymptomatic. It has been suggested that choroidal folds form when the Bruch membrane is forced to fold with choroidal expansion or swelling.^{1,2} Strain between the sclera and the choroid has also been proposed as a mechanism of choroidal fold development.⁴

Regardless of the cause, long-lasting choroidal folds can lead to RPE atrophy, Bruch membrane breaks/damage, and, eventually, choroidal neovascularization (CNV). They are usually horizontal but can also present in an oblique, vertical, circumferential, or irregular pattern.^{1,3}

While generally idiopathic, choroidal folds can be seen in a wide variety of ophthalmic and systemic conditions, ranging from hyperopia to infectious, neoplastic, inflammatory, infiltrative, or immunologic disorders; thus, distinguishing the underlying condition is essential.^{2,3}

Herein, we present a case of choroidal folds in a middle-aged man, along with the clinical appearance, etiology, pathophysiology, differential diagnosis, and management of this condition.

CASE REPORT

A 63-year-old White man presented for his annual diabetic eye examination. His past medical history included hyperlipidemia and type 2 diabetes with a hemoglobin A1c of 7%. His past ocular history was unremarkable except for new-onset and progressive hyperopia (+1.00 OD, +1.75+0.5 x 040 OS).

On examination, his BCVA was 20/20-3 OD and 20/30-2 OS. The anterior segment of each eye was unremarkable on slit-lamp evaluation except for 1+ nuclear sclerotic cataract in each eye.

The fundus examination of the right eye revealed no vitreous cell, normal optic nerve with a cup-to-disc ratio of 0.2, normal retinal vessels, and faint choroidal folds (Figure 1A). The left eye was similar, with the addition of RPE changes located peripherally and nasally to the optic nerve (Figure 1B). B-scan ultrasonography was normal, with no choroidal thickening or fluid. Fundus autofluorescence showed linear hyperreflective streaks compatible with the pattern seen on fundus photography (Figure 2).

OCT revealed characteristic undulations of the RPE consistent with choroidal folds (Figure 3). Fluorescein angiography (FA) highlighted the choroidal folds in each eye

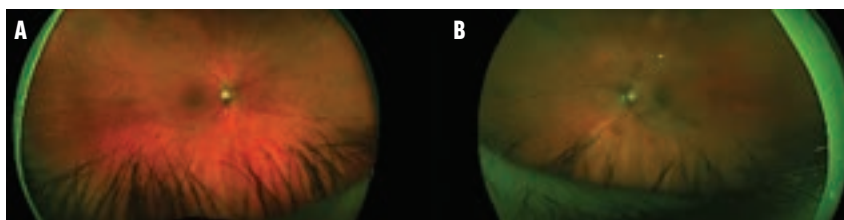


Figure 1. Color fundus photos of the right (A) and left (B) eye showed a linear pattern of pigmentary changes in the posterior pole.

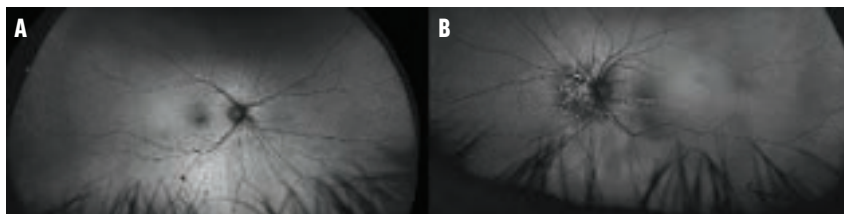


Figure 2. Fundus autofluorescence of the right (A) and left (B) eye showed linear hyperreflective streaks compatible with the pattern noted on fundus photography.

(Figure 4). ICG did not reveal any choroidal masses (Figure 5), and a CT of the orbit was within normal limits. Blood workup was unremarkable.

After ruling out all potential major causes of the choroidal folds, our patient was diagnosed with bilateral idiopathic choroidal folds. He has been followed for the past few years through annual diabetic eye examinations, with stable pathology.

POTENTIAL CAUSES

Choroidal folds can develop due to shrinkage of the inner sclera, infiltration or effusion into the choroid, or mechanical deformities. They may also occur due to various ocular conditions, such as hyperopia, hypotony, disciform scars, posterior scleritis, scleral buckling surgery, orbital tumors, uveal effusion, and AMD. Systemic conditions, including sinusitis, enlarged lacrimal gland caused by dacryoadenitis, idiopathic intracranial hypertension, thyroid eye disease (often in visually threatening forms), and complications of prolonged space flight among astronauts are other potential causes of choroidal folds.^{3,5-8}

In a case series of 59 eyes with choroidal folds, Cangemi et al reported hyperopia as the most common cause; 17% of cases were idiopathic.¹ Leahey et al likewise conducted a case series of 78 eyes with choroidal folds and revealed that AMD and hyperopia, followed by idiopathic, were the most common etiologies.⁹

Olsen et al proposed that with advances in diagnostic testing, the number of patients diagnosed with idiopathic choroidal folds will be reduced.³ They reported six cases of idiopathic choroidal folds in a series of 40 patients with choroidal folds, where five had a history of autoimmune disease. Thus, mild and undiagnosed ocular inflammatory conditions may contribute to the formation of choroidal folds.³

DIAGNOSTIC PEARLS

Multimodal imaging can help characterize the pathology and, in combination with a systemic workup, distinguish the etiology of choroidal folds.³ B-scan ultrasonography should be performed if posterior scleritis is suspected.

OCT is the most specific imaging tool to detect and distinguish idiopathic choroidal folds from other etiologies, such as epiretinal membrane.¹⁰ FA is the most sensitive imaging modality, where choroidal folds usually present as alternating hypofluorescent and hyperfluorescent

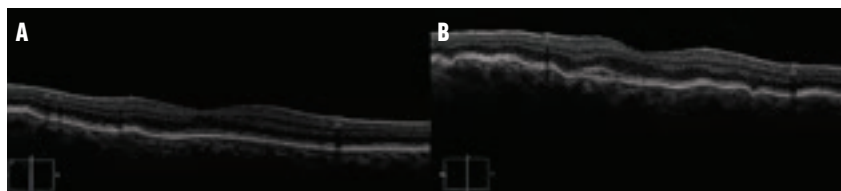


Figure 3. OCT of the right (A) and left (B) eye showed the characteristic undulations of the RPE consistent with choroidal folds with a nearly flat retinal surface and a variable retinal thickness.

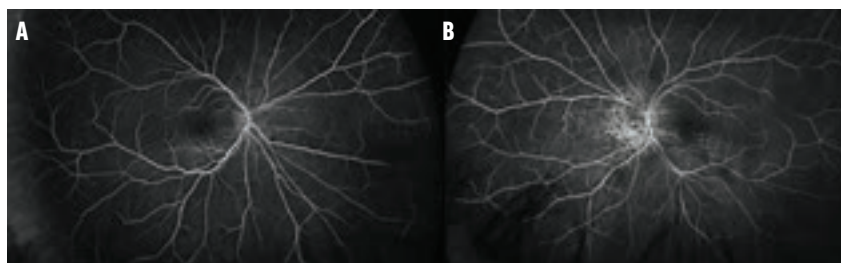


Figure 4. FA showed an increased stippled hyperfluorescence with late staining corresponding to an area of pigmentary disturbance in the right (A) and, more prominently, the left (B) eye.

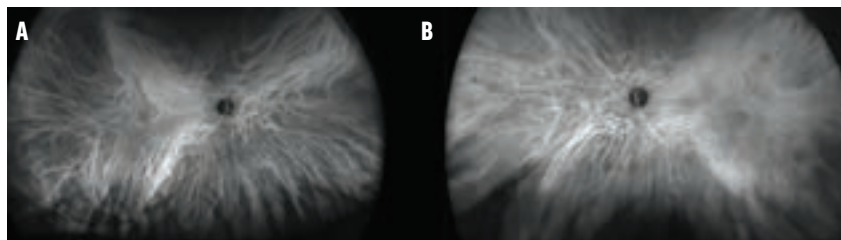


Figure 5. ICG revealed no choroidal lesions or neovascularization in either the right (A) or left (B) eye.

bands due to rarefaction and redundancy of the RPE at the folds' peaks and pits, respectively.¹⁰ On ICG, a delay in the choroidal vessel filling has been reported in cases of choroidal folds caused by orbital tumor.¹⁰

To exclude extraocular causes, neuroimaging and lumbar puncture in cases of papilledema should be considered. In aged eyes, loss of elasticity in the choroid-Bruch membrane complex can lead to thickening, fragility, and calcification of the Bruch membrane. Fracture of the Bruch membrane due to the strain created by choroidal folds in an ischemic environment may lead to CNV.¹¹ Olsen et al reported four cases of CNV related to choroidal folds; each patient received anti-VEGF therapy, but none showed visual improvement. Visual deterioration was reported in two cases post anti-VEGF injections.³

Although our patient was diagnosed with idiopathic choroidal folds, there are some reports of choroidal folds among patients with diabetes with and without diabetic retinopathy.^{12,13} We postulate that the thick choroid and alterations in the choroidal sublayers secondary to diabetes may be the cause of the choroidal folds noted in our patient.

BEWARE OF A MASQUERADER

Choroidal folds can be mislabeled as retinal folds; however, retinal folds are much finer, are not limited to the posterior pole, and can present in various alignments. They

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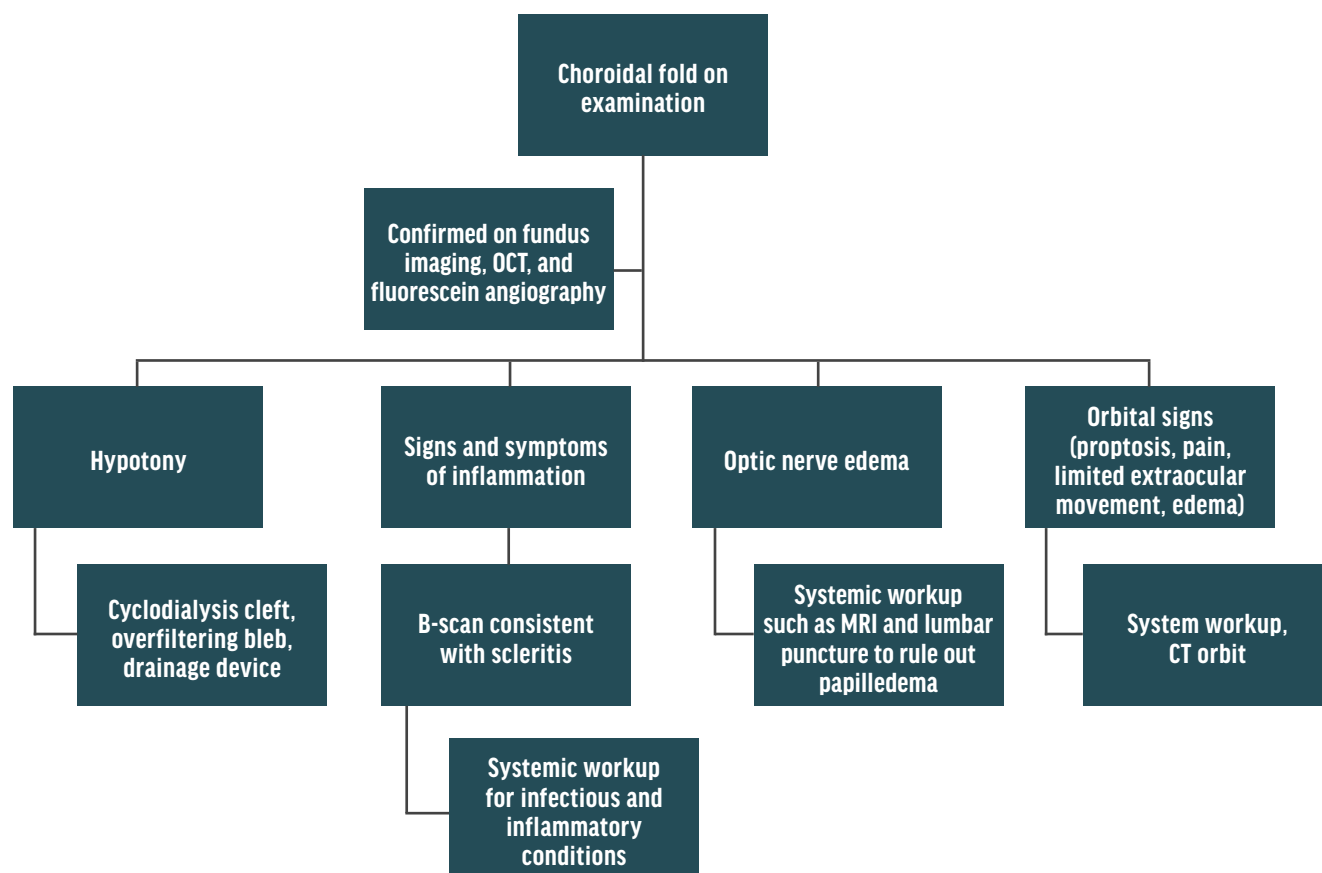


Figure 6. Our step-by-step algorithm of choroidal fold management.

are frequently seen in cases of epiretinal membranes after intraocular surgery, particularly vitreoretinal procedures. FA and ICG are helpful modalities in distinguishing retinal folds, which present as periodic surface undulations that do not involve the deep layers of the choroid.^{3,4} In addition, linear signal decreases in choriocapillaris perfusion captured on OCT angiography may be associated with choroidal folds.^{10,14}

DON'T NEGLECT APPROPRIATE TESTING

While choroidal folds require no intervention, distinguishing and managing any underlying pathology is essential. Failure to identify an association between choroidal folds and tumors or CNV can lead to severe, irreversible vision loss. In addition, chronic choroidal folds with macular involvement can lead to maculopathy; thus, long-term follow-up with multimodal imaging and appropriate treatment is recommended.³ A step-by-step algorithm of management can aid in clinical decision making when you encounter choroidal folds (Figure 6). ■

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MANAGING THE OCULAR EFFECTS OF STEROID OVERDOSE



Improper use to boost athletic performance caused this case of retinal vascular occlusion.

BY FERNANDO GODIN, MD; NIMESH A. PATEL, MD; EDUARDO CADENA, MD; DIANA CONCHA, MD; MARIA ADELAIDA PIEDRAHITA, MD; AND CAROLINA PARRA, MD

Androgenic-anabolic steroids (AAS) can be improperly used to increase muscle mass and thereby boost performance and aesthetics. Although AAS are banned by the World Anti-Doping Agency, their abuse in sports and among fitness enthusiasts remains common, especially among young men.¹⁻⁴

The goals of testosterone replacement therapy are to treat the symptoms of deficiency, such as reduced appetite in cachexia, low libido and mood, erectile dysfunction, and reduced muscle mass and bone density.⁵ The abuse of these medications by taking them in doses much higher than recommended represents a severe public health issue because of serious potential short- and long-term side effects, including cardiovascular, metabolic, psychiatric, and kidney disorders, especially in young people.^{1,4,6}

Herein, we report the first known case of retinal vascular occlusion secondary to the abuse of AAS.

A CASE OF UNILATERAL VISION LOSS

A 39-year-old man presented to the ophthalmology service complaining of sudden blurred vision and decreased visual acuity in his right eye over the past 20 days. His BCVA was light perception OD and 20/20 OS. Evaluation of the anterior segment and IOP was normal. After dilation, vitreous opacity in the right eye was noted on fundoscopy, and there was evidence of vitreous hemorrhage (++), preretinal hemorrhage involving the central subfield, and diffuse intraretinal microhemorrhages in the posterior pole and middle periphery. There was an afferent pupillary defect.

Diagnosis

Complementary laboratory tests (ie, antinuclear antibody, antineutrophil cytoplasmic antibodies, erythrocyte

sedimentation rate), as well as vertical sleeve gastrectomy and polymerase chain reaction were negative. In addition, total protein and thromboplastin testing was within normal limits, venereal disease research laboratory was nonreactive, and he had a negative carotid doppler. He had no history of associated systemic disease.

Medical history revealed he was a bodybuilder, and he reported using AAS in a supraphysiological dose of 500 mg testosterone cypionate weekly for the past 8 months. He had also increased the dosage to about double his usual amount 24 hours before he experienced the vision loss.

Fluorescein angiography of the right eye demonstrated severe vascular occlusion that was predominantly ischemic with neovascularization and vitreous hemorrhage. These findings prompted a diagnosis of retinal ischemia secondary to mixed vascular occlusion (Figure 1).

To the OR

A posterior vitrectomy was performed on the right eye with endophotocoagulation and insertion of silicone oil. At the 8-day follow-up, his BVCA had improved to 20/100 OD, and fundoscopy showed an adequate central emergence of the vessels, arteriolar attenuation over the arcades, ghost vessels, laser scars, and silicone in the vitreous cavity (Figure 2). Intravitreal antiangiogenic factor therapy was applied 1 month after the procedure.

POSSIBLE ETIOLOGY

AAS use has increased over the past decade,⁷ commonly used by professional and Olympic athletes, recreational and high school-level athletes, and noncompetitive bodybuilders. Side effects of anabolic steroids include behavioral alterations, obesity, infertility, osteoporosis, erectile

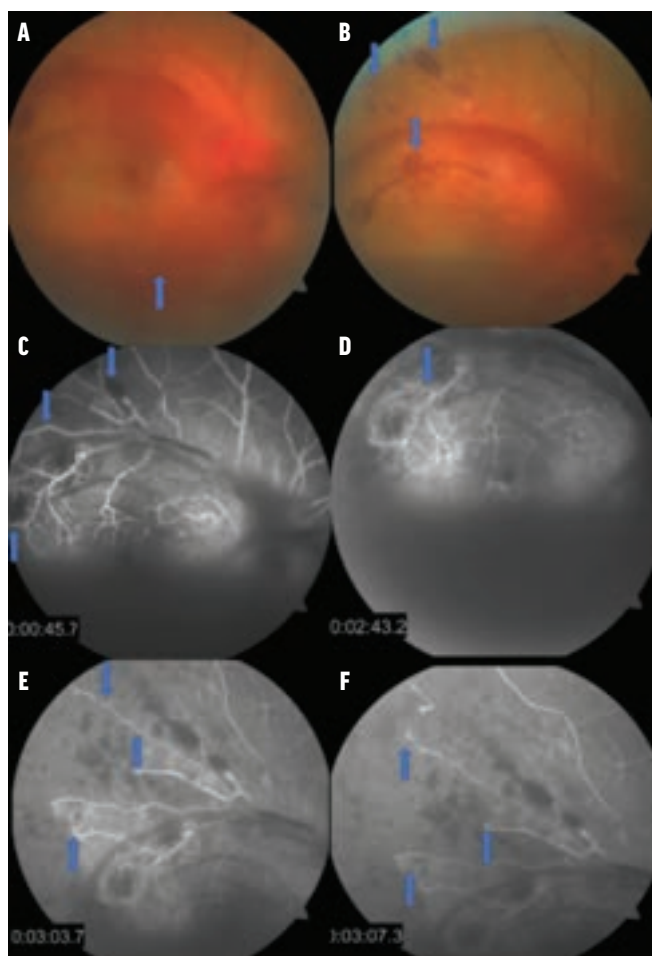


Figure 1. Color fundus photographs of the right eye showed vitreous hemorrhage and retinal and preretinal hemorrhage (A, B). Fluorescein angiography of the right eye showed hyperfluorescence due to a peripheral filling defect (C, D). Vascular changes were noted with areas of hyperfluorescence due to staining in the arterial phase and areas of hypoperfusion due to a filling defect toward the late phases of the angiographic study on arcades and in relation to the mixed vascular occlusion (E, F).

dysfunction, and even renal failure.⁸ There is also a high rate of hepatotoxicity among AAS users, leading to cirrhosis and cardiovascular disorders.^{3,6,8}

AAS abuse can also lead to a hypercoagulable state by increasing the production of thromboxane A₂ and platelet thromboxane A₂ receptor density, which causes aggregation and a decrease in the production of prostaglandins.^{9,10} Moreover, a component of endothelial dysfunction has been proposed that may contribute to abnormal vessel reactivity.⁹⁻¹²

Younger men are involved in AAS abuse twice as frequently as women; however, in the latter group, head injury, hypercholesterolemia with type IIa and type IV lipid-ethanolamine phosphoglyceride patterns, and use of estrogen-containing medication seem to be predisposing factors.¹³⁻¹⁵ Long-term steroid abuse increases cardiac debit due to increased metabolism, leading to arterial

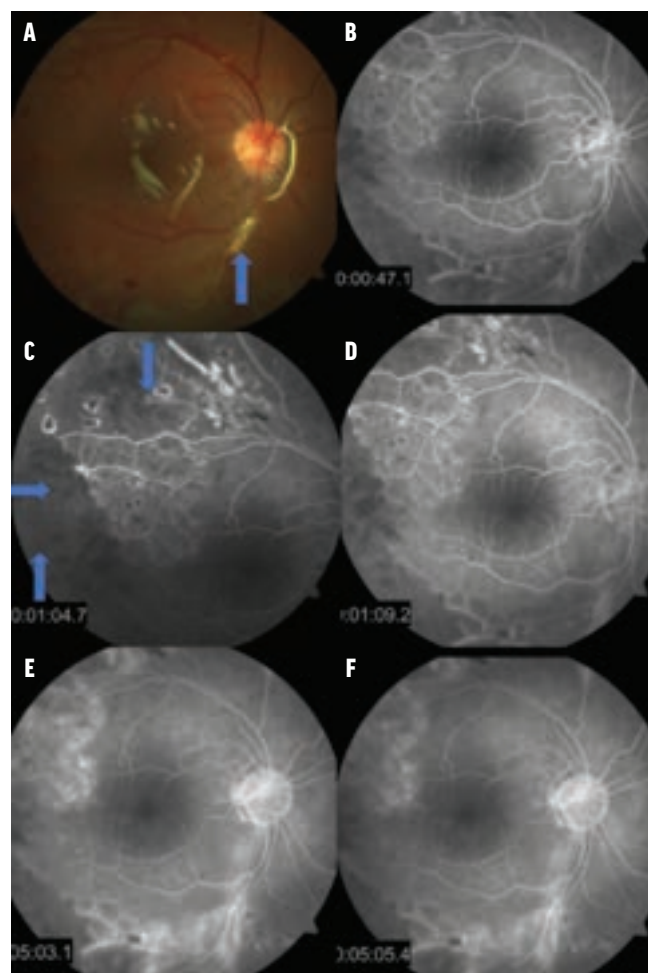


Figure 2. In the color fundus image of the right eye at the patient's follow-up visit 8 days after vitrectomy (A), the optic disc with defined edges, vascular attenuation over the arches, bloodless vessels, and intraretinal hemorrhagic changes were noted in the lower arch. Fluorescein angiography showed hypofluorescence due to a filling defect related to the mixed vascular occlusion (arrows), retinal laser photocoagulation scars on the upper arch, and changes in hyperfluorescence due to vascular staining (B, C). Note the leakage toward the late phases of the angiographic study on the upper and lower arch in relation to possible areas of retinal neovascularization. Changes in hypofluorescence are also seen due to the filling defect in the late phases of the angiographic study of mixed vascular compromise, and changes in hyperfluorescence are due to vascular staining (D-F).

hypertension.^{3,15,16} Another consequence is alteration in the metabolism of lipoproteins, giving rise to hypercholesterolemia and hypertriglyceridemia.

Our case demonstrates a vascular occlusion secondary to AAS. To our knowledge, there are no prior reports of AAS leading to retinal damage or adverse effects on vision. The etiology of the venous obstruction our patient experienced appears to include three factors: increased blood viscosity, disorder of the vascular walls of the blood vessels, and arterial hypertension (ie, Virchow triad), which compresses the common arteriovenous sheath at the site of an arteriovenous crossing. He fared well postoperatively, regaining his vision within several days after vitrectomy.

THE BOOST ISN'T WORTH THE RISKS

It is essential to maintain a high index of suspicion for AAS-related ocular adverse events and advise affected patients to discontinue the use of such substances immediately. ■

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(Continued from page 14)

DAY 2: BACK TO THE CLASSROOM

The second day took attendees through a whirlwind tour of retinal imaging, tumors, retinopathy of prematurity, and treatment algorithms for diabetic eye disease. The day ended with a surgical session that provided pearls on topics such as internal limiting membrane peeling, retinectomies, subluxated IOL management, and scleral buckling versus primary vitrectomy for rhegmatogenous retinal detachments.

Interspersed between these lectures were spirited debates on controversial topics, including the role of internal limiting membrane peeling for epiretinal membranes, use of steroids in diabetic macular edema, implementation of AI, the advent of home monitoring for the detection of choroidal neovascularization, and the value of 3D heads-up displays. The debates pitted old friends against each other, and the speakers battled for audience votes with friendly banter. Perhaps the most interesting debate—and one that received a lot of laughs—was between Dr. Mieler and Dr. Williams on the utility of vitrectomy to treat floaters; it ended with Dr. Williams recommending a vitrectomy for Dr. Mieler!

DAY 3: THE SUMMIT OF KNOWLEDGE

The last day began with updates on clinical trials and the latest treatments for AMD. This was followed by debates on the use of anti-VEGF biosimilars, the role of complement inhibition in geographic atrophy, and the need for OCT angiography when managing choroidal neovascularization.

The meeting concluded with a great session on uveitis, which covered pediatric uveitis, masquerade syndromes, white-dot syndromes, and vitreoretinal surgery for patients with uveitis.

UNTIL NEXT YEAR

The AVTT Symposium brought together experts, innovators, and trainees to share insights, discuss challenges, and envision ways to incorporate the latest advances that have improved patient care. We hope to see you all at next year's meeting! ■

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SAVE THE DATE!
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 August 9-11, 2024 • Chicago, Illinois

REFLECTIONS ON A SUCCESSFUL EVENT WITH RECORD-BREAKING ATTENDANCE

An overview of the YoungMD Connect Meeting at AAO 2023.

The YoungMD Connect (YMDC) capstone event, held annually at the AAO meeting, is a dedicated forum for medical students, residents, and fellows to receive firsthand mentorship from experts in eye care as well as to engage with innovative industry partners. This year's YMDC meeting turned out to be the best-attended in the event's history, with more than 300 participants, 20 thought leaders across subspecialties, and 31 faculty mentors.

This article reviews the key components of the event, from industry engagements to faculty mentoring to peer networking.

VISIONARY PANEL AND MENTORING SESSION

The event kicked off with an industry panel featuring YMDC Visionary Partners AbbVie/Allergan and Johnson & Johnson Vision (Figure 1). The panelists discussed how each organization focuses on making an impact on young ophthalmic leaders.

Following was a live mentoring session, during which participants had an opportunity to interact with esteemed faculty mentors across subspecialties in ask-me-anything roundtable discussions (Figure 2; see Faculty Mentors). The dynamic engagement allowed attendees to delve into a plethora of topics, ranging from industry-specific queries to career advice. The interactive nature of the session fostered a sense of camaraderie, forging meaningful connections between participants and mentors and creating a platform for ongoing mentorship and support beyond the conference.

"I'm not sure I have been to a venue that offered such an in-depth mentoring session as this with the breakout sessions. Kudos to the organizers," one attendee said.

EDUCATIONAL WORKSHOPS

Following the mentoring session, attendees were able to participate in one of six workshops supported by AbbVie/Allergan, Dompé, Johnson & Johnson Vision, Lumibird, Regeneron, and Zeiss. Attendees experienced thoughtfully designed workshops that covered a wide array of subjects relevant to their training and future careers. Workshop topics included the art of patient communication, geographic atrophy diagnosis and management, technological advancements, women in leadership, case presentation success, and physician-industry collaboration.

The Art of Patient Communication

Moderators Joe Coney, MD, and Priya Vakharia, MD, discussed essential tools, acquired skills, and personal experiences with patient communication. The subsequent discussion covered information management, technology use, approaches to delivering difficult news, and strategies for ensuring positive patient experiences. The faculty members each led a role-play scenario illustrating a patient encounter and then reflected on their approaches.

Getting Ready for GA

This workshop focused on diagnosing and managing geographic atrophy (GA) in age-related macular degeneration (AMD). Faculty members Jorge Fortun, MD, and Yasha Modi, MD, focused on the clinical assessment, imaging methods, progression risks, and potential treatments. Dr. Modi invested the time to teach attendees how to identify pathology on an OCT image, and the workshop concluded with a detailed equipment demo from workshop supporter Zeiss.

EDUCATIONAL ASSOCIATIONS

FACULTY MENTORS

- Chris Alabiad, MD
- Sarah Avila, MD
- Jesse Berry, MD
- Robert Chang, MD
- Kim Cockerham, MD
- Joe Coney, MD
- Jorge Fortun, MD
- Reena Garg, MD
- Himani Goyal, MD
- Michael Greenwood, MD
- Eric D. Hansen, MD
- Sumitra Khandelwal, MD
- Zaiba Malik, MD
- Morgan Micheletti, MD
- Yasha Modi, MD
- Julius Oatts, MD
- Joe Panarelli, MD
- Brian Shafer, MD
- Deepika Shah, MD
- Neda Shamie, MD
- Shameema Sikder, MD
- Rachel Simpson, MD
- Priyanka Sood, MD
- Stuart Stoll, MD
- Geoff Tabin, MD
- Audrey Talley Rostov, MD
- Priya Vakharia, MD
- George O. Waring IV, MD
- Mitch Weikert, MD
- Basil Williams, MD
- Rupa Wong, MD
- Julie Woodward, MD

Technological Advancements: Elevating Techniques and Approaches

Morgan Micheletti, MD, shared the story of how he developed the modified twist-and-out technique for IOL exchange and other techniques for cataract surgery. Dr. Micheletti emphasized key aspects of evolving surgical



Figure 1. Neda Shamie, MD, led a panel discussion with Tara Capalbo (AbbVie/Allergan) and Allie Holmes (Johnson & Johnson Vision).



Figure 2. YMDC members engaged in thought-provoking discussions with faculty mentors.



Figure 3. YMDC members enjoyed additional networking with other attendees and mentors during the event reception.

techniques and encouraged a proactive approach to innovation. The discussion delved into finding inspiration, embracing change, seeking mentorship, learning from setbacks, leveraging technology, and adopting the right mindset for developing and refining surgical techniques.

Women in Leadership

In this workshop, Himani Goyal, MD, and Audrey Talley Rostov, MD, shed light on the underrepresentation of women in ophthalmology leadership roles. They discussed strategies for female ophthalmologists to pursue such positions, emphasizing the role of mentoring and sharing key experiences. Dr. Goyal offered insights into achieving leadership positions in academia, while Dr. Talley Rostov discussed becoming a key opinion leader, getting involved in research, and attaining positions within professional organizations. The workshop concluded with a discussion of work-life balance challenges, addressing lifestyle decisions, time demands, and family realities for women ophthalmologists.

Nailing Your Case Presentation

Led by Sumitra Khandelwal, MD, and Deepika Shah, MD, this workshop kicked off with the speakers sharing their most memorable case presentations. Dr. Khandelwal

YMDC EVENT: BY THE NUMBERS

300+ attendees

6 educational workshops

20 thought leaders

31 faculty mentors

guided attendees through the structuring of clinical case presentations, emphasizing key elements such as chief complaints, summarizing exam findings, and reviewing diagnostics. Dr. Shah advised on podium presentations, stressing the importance of engaging storytelling, detailed discussions, and voice projection. Attendees learned how to captivate audiences, from case selection to delivery techniques, with ample opportunity for questioning.

Working With Industry

This workshop, led by George O. Waring IV, MD, and Reena Garg, MD, explored the benefits and evolving landscape of physician-industry collaborations. The

panelists discussed how working with industry shapes patient care, fosters education on treatments and technology, and serves as an opportunity to contribute to innovation. Both mentors shared practical steps to collaborate with industry partners and initiate these connections. Dr. Garg pointed out that it is important to engage with industry representatives early in one's career and noted that industry partners are eager to discuss data and/or set up wet labs to introduce technologies. In addition, the panelists expanded on the importance of accepting speaking opportunities and leveraging networks for industry engagement.

CONCLUSION

Following the visionary industry panel, mentorship roundtable discussions, and educational workshops, attendees convened for a networking reception to continue their professional and personal conversations with colleagues old and new (Figure 3).

YMDC is passionate about shaping and empowering the next generation of eye care leaders by providing world-class education, mentoring, and opportunities to broaden skills and knowledge. Consider joining the next YMDC AAO event in 2024 as a participant or mentor faculty. To learn more visit <https://youngmdconnect.com/>. ■

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THE INS AND OUTS OF INTRAOPERATIVE FA

Bringing this imaging tool to the OR has changed our approach to vitrectomy for diabetic retinopathy.

By Lukan Mishev, MD; Nassim Abreu-Arbaje, MD; Joaquín Sosa-Lockward, MD; Lauren Gibson, MD; Aly Nguyen, BS; and Alan J. Franklin, MD, PhD



Intraoperative fluorescein angiography (IOFA) has transformed the way our team approaches vitrectomy. We have found that real-time 3D high-definition (3DHD) angiography accurately detects many fluorescein biomarkers observed in

the clinic and provides important information for surgical decision making, which we believe improves surgical results.

IOFA has been used successfully by many researchers since its development by Steve Charles in the 1980s.^{1,2} However, imaging through the optical microscope without widefield viewing was limited by both resolution and two dimensionality, hindering adoption.³⁻⁶ With the advent of 3DHD visualization, Imai et al developed IOFA during digitally assisted vitreoretinal surgery and reported on the treatment of proliferative diabetic retinopathy (PDR) and retinal vein occlusion.^{7,8} I (L. M.) first reported on the use of a digital barrier filter; subsequently, Cardamone et al modified the method by placing the exciter filter directly into the vitrectomy system to avoid switching to an alternative light source. This type of digital barrier filter made IOFA more seamless and efficient during vitrectomy.⁹

Using IOFA, surgeons can observe many FA biomarkers during vitrectomy, including vascular filling times, microvascular blockage, areas of nonperfusion, microvascular leakage, inflammatory-based leakage, and retinal and choroidal neovascularization (Video).¹⁰⁻¹⁴

THE SETUP

An optical filter with a dedicated wavelength (475 nm – 490 nm) needs to be used in the illumination light source to achieve optimal fluorescein excitation. The optical

exciter filter can be placed in a number of different light sources, and many different optical filters are available.¹⁵⁻¹⁷

Contrast enhancement is key to successful IOFA, and we determined the optimal excitation source to maximum fluorescein signal intensity. To create the best digital barrier filter recipe in the presence of a 532 laser notch filter (which can reduce the fluorescence intensity), it is important to have a high dynamic range and sensitivity camera (Figure 1).¹⁸ The digital barrier filter reduces red and blue emissions to enhance the green signal. The saturation and hue are modified to diminish the blue-green color, and the signal is enhanced with brightness and contrast to produce a grayscale image similar to that observed in office-based FA.¹⁹

Initiating IOFA simply involves switching to the light source with the optical exciter filters and changing the digital surgical channel or filter. The switch back to standard visualization once IOFA is complete is equally efficient.²⁰ We have found that dual light output with a chandelier light source and a light pipe endoilluminator produces the best signal.

AT A GLANCE

- ▶ With the advent of 3D visualization, researchers have improved the utility of intraoperative fluorescein angiography during vitreoretinal surgery.
- ▶ An optical filter with a dedicated wavelength (475 nm – 490 nm) needs to be used in the illumination light source to achieve optimal fluorescein excitation.
- ▶ Early data demonstrates both improved vision and reduced rates of postoperative vitreous hemorrhage with intraoperative fluorescein angiography-guided surgery compared with standard vitrectomy.

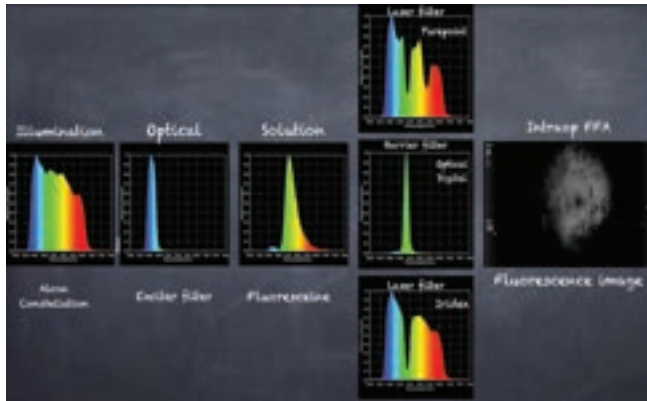


Figure 1. As demonstrated by the schematic order of achieving the digital IOFA shown here, the 532 laser notch filter can reduce the fluorescence intensity because it coincides with the wavelength emission of the fluorescein, 510 nm to 540 nm.

SURGICAL DECISION MAKING

IOFA provides additional helpful information to guide and enhance many surgical decisions.⁹ A delay in vascular filling time can be observed if blood pressure is low, IOP is high, or a combination of both.²¹ Vascular epiretinal membranes are well visualized, and the contrast between the vascularized fluorescent vessels and a dark background is helpful to visualize the correct surgical plane to delaminate (Figure 2).²² Once delamination is complete, both areas of residual abnormal vascularities and retinal ischemia can be visualized.

We are currently treating these residual areas of abnormal vascular leakage with confluent laser and placing more confluent laser in the areas of peripheral ischemia, while sparing the better-perfused retina. Doing so can reduce the rate of postoperative vitreous hemorrhage, while maximizing peripheral and night vision.²³ Often, media opacities such as vitreous hemorrhage or inflammation preclude sufficient visualization of fluorescein biomarkers preoperatively. In these scenarios, IOFA is helpful with diagnosis and postoperative management, in addition to guiding surgical decision making.

LACK OF TOXICITY

FA is a well-accepted and safe diagnostic aid in the clinic. In the OR, all current surgical light sources and bandpass exciter filters are above the wavelength noted to be toxic (440 nm). However, light toxicity has been reported from the straight light pipe if it is held close to the retina for longer than 15 minutes.²⁴ The fluorescein signal significantly fades after 5 to 10 minutes, limiting the risk of phototoxicity. Although some suggest that fluorescein may enhance laser burn intensity, there are no reports of excessive laser burning with macular laser after in-clinic FA. In the OR, it is rare to place any photocoagulation burn near the macular center. Nevertheless, we recommend using a chandelier light source combined with a light pipe endoilluminator held relatively far from the retinal surface to minimize any potential light toxicity.²⁵

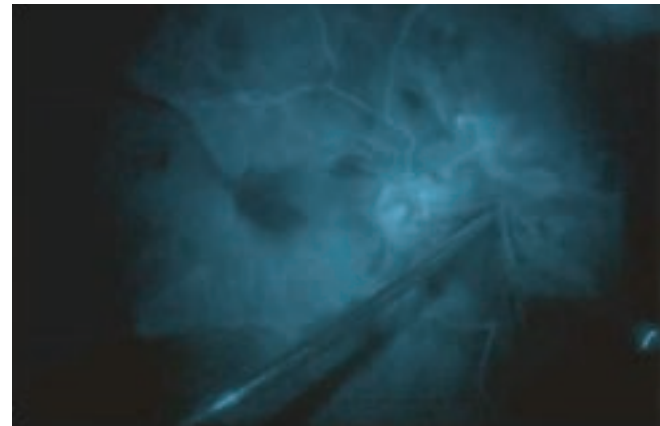


Figure 2. The patient depicted here is undergoing vitrectomy for the treatment of PDR. This image illustrates the typical IOFA view the surgeon has while delaminating the vascular epiretinal membranes using a bimanual technique.

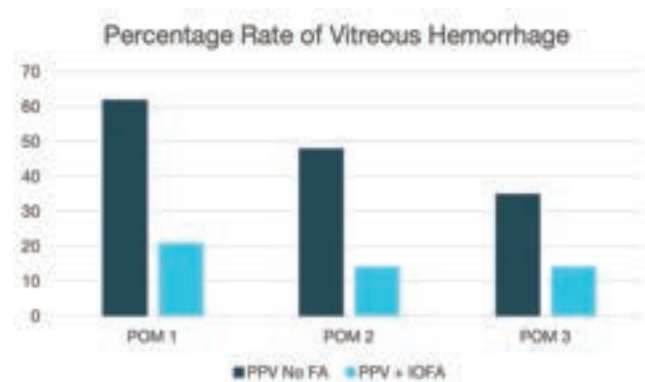
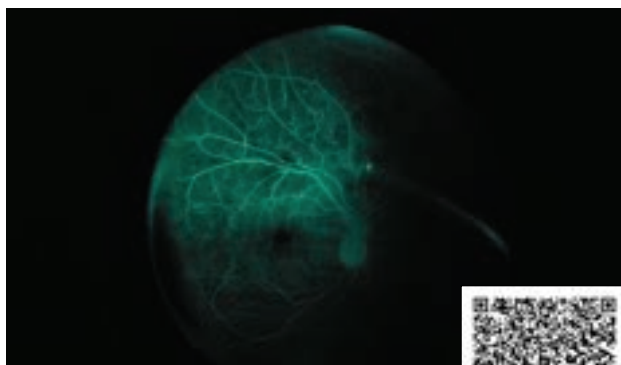


Figure 3. Our research shows that IOFA guidance during vitrectomy for patients with PDR reduces the rate of postoperative vitreous hemorrhage throughout the first 3 months of follow-up. As noted in this chart, at postoperative months 1, 2, and 3, the rate of vitreous hemorrhage was demonstrably lower in patients who underwent IOFA-guided vitrectomy versus those who didn't ($P < .05$ at all points measured).

EFFICACY AND POSTOPERATIVE RESULTS

We are in the process of analyzing visual acuity and rates of postoperative vitreous hemorrhage after vitrectomy with and without IOFA for PDR. Preliminary results indicate a relatively low rate of postoperative vitreous hemorrhage 1 month following vitrectomy in 21% of patients who underwent IOFA, which is in the low range of historically reported rates of 13% to 40% and is significantly lower than our group of patients who underwent vitrectomy without IOFA, more than 50% (Figure 3).²⁶⁻²⁸ This trend continued through postoperative month 2, where vitreous hemorrhage was observed in 14% of patients who underwent IOFA versus 48% without IOFA, and month 3, where vitreous hemorrhage was observed in 14% of those who underwent IOFA versus 35% of those without IOFA. In addition, postoperative visual acuity in patients when IOFA was performed was, on average, at least 3 lines better than those for whom IOFA was not performed.

WATCH IT NOW



Video. The Utility of Intraoperative Fluorescein Angiography.

FUTURE DEVELOPMENTS

IOFA can provide important diagnostic information when preoperative media opacities limit visualization of fluorescein biomarkers and can guide surgical decision making. There have been no reports of light toxicity in more than 200 cases where IOFA was employed. However, clinicians should continue to measure postoperative safety parameters, such as vision, spectral-domain OCT, multifocal ERG, and visual fields, to objectively show that IOFA does not lead to toxicity.

Early data demonstrate both improved vision and reduced rates of postoperative vitreous hemorrhage with IOFA-guided surgery compared with standard vitrectomy. This provides significant credibility to the potential benefits of adding IOFA to the surgical armamentarium during vitrectomy. Further optimization of the optical exciter filter has been accomplished, and the improvement of the digital barrier filters will lead to improved and more useful information. Thus, we believe that IOFA is an important developing technology that can assist surgical decision making during vitrectomy and will ultimately enhance outcomes for our patients. ■

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IOL OPTIONS FOR SUTURELESS FIXATION

With many three-piece lens options available, being thoughtful in your selection will help to maximize your patients' outcomes.

By Murtaza Adam, MD



After graduating from fellowship, I felt well prepared to handle any IOL complication that came through the door. With anterior chamber IOLs and the Bausch + Lomb AO60 and MX60 with polytetrafluoroethylene (Gore-Tex, W.L.

Gore) suture fixation on hand, what else could a vitreoretinal surgeon need to manage eyes without capsular support?

In my first few months of practice, however, I met Bill Richheimer, MD, a talented and thoughtful cornea surgeon who walked me through his approach to off-label sutureless flanged intrascleral haptic fixation (ISHF) of three-piece IOLs—an approach based on the Yamane technique.¹ It doesn't require a large incision to accommodate an anterior-chamber IOL, and I don't have to suture the conjunctiva or worry about the tension on my Gore-Tex sutures. Since adopting this technique, I haven't looked back and now perform three to six ISHF cases each week.

When it comes to ISHF, most retina specialists prefer a 27-gauge trocar-assisted technique to capture and externalize their IOL haptics. I prefer a needle-assisted technique with thin-walled 30-gauge needles (TSK) because it costs significantly less, and the reduced diameter of the 30-gauge scleral tunnels may lend to improved long-term IOL stability (Figure 1).²

In addition, recent advancements in ISHF have led to many new lens options. Depending on availability, refractive goals, surgical history, and axial length, certain lens choices may be better than others. In this article, I review some of the IOL options available for aphakic eyes without capsular support and provide my personal experience with these IOLs while working along their expected learning curves.

APHAKIC PATIENTS

The adage that nobody ever went blind from aphakia can be a very reasonable option for patients with high axial length and biometry results within approximately 1.00 D to 3.00 D of plano. In limited cases of aphakic patients without a dislocated IOL, a referral for aphakic correction with PRK or LASIK is a reasonable option for patients who

have the means and desire to avoid intraocular surgery while minimizing the need for spectacle correction.

REUSE AND RECYCLE

Implanting a subluxed three-piece polymethylmethacrylate (PMMA) IOL requires a 6 mm scleral tunnel or corneal incision and increases the risk of wound leakage and postoperative astigmatism. As such, rescue of a previously placed IOL may be prudent. My recently published series of 25 eyes highlights the technique and outcomes of rescuing three-piece PMMA IOLs for ISHF.³ This technique works quite well and lends to a rapid postoperative recovery, but centration and tilt must be optimized to reduce the risk of significant optical aberrations in these IOLs with spheric optics.

PLACING A NEW IOL

When the clinical scenario calls for a new IOL (eg, if rescue is not an option due to IOL type or damaged/weak haptics), the following are the currently available options for ISHF, and my personal thoughts on each.

AT A GLANCE

- ▶ Off-label sutureless flanged intrascleral haptic fixation (ISHF) of three-piece IOLs doesn't require a large corneal incision or suturing of the conjunctiva.
- ▶ Rescuing existing three-piece polymethylmethacrylate IOLs for ISHF lends to a rapid postoperative recovery, but centration and tilt must be optimized.
- ▶ A recently available option, the RxSight Light Adjustable Lens can be treated with a UV laser approximately 3 weeks postoperatively to correct any residual astigmatism and sphere.



Figure 1. This surgical image depicts the docking of the leading haptic of a CT Lucia 602 into a 30-gauge thin-walled TSK needle.

In my limited experience with **Alcon's MA60AC** (6 mm acrylic optic; +6.00 D to +30.00 D; A-constant, 118.4), ISHF has been difficult. The PMMA haptics are quite brittle and are more curved than other three-piece IOLs, lending to an increased risk of haptic kinking or breakage during ISHF.² It is a reasonable option in a pinch but is not my first choice for scleral fixation.

The **Carl Zeiss Meditec CT Lucia 602** (6 mm acrylic optic; +4.00 D to +34.00 D; A-constant, 118.4) has been a staple for many surgeons employing ISHF. The polyvinylidene fluoride haptics are well suited for scleral fixation because they have a unique combination of mechanical resilience and flexibility that minimizes the risk of haptic kinking and breakage. Additionally, the aspheric optics of this monofocal IOL minimizes aberrations even with mild to moderate IOL tilt or decentration. Unfortunately, I and others have noticed unexpected and visually significant postoperative IOL tilt in several cases over the past 2 years. A multicenter, retrospective series of 45 cases from 20 surgeons suggests that this tilt issue relates to instability at the haptic-optic junction.⁴ Although the exact rate of severe IOL tilt following ISHF with the CT Lucia is unknown, authors have recommended use of the "laser lock" technique—in which laser retinopexy is applied to the haptic-optic junction to minimize rotation of the haptic—to reorient a tilted IOL and avoid a lens exchange.⁵ The unpredictability and visual impact of this complication has led me to avoid using the Lucia.

Bausch + Lomb's LI61AO (6 mm silicone optic; +0.00 D to +34.00 D; A-constant, 118.7) has pliable PMMA haptics that resist kinking and breakage; however, the silicone optic is potentially problematic in patients with a history of vitreo-retinal disease who may require oil tamponade in the future. This lens comes with a decent range of IOL powers for eyes with both short and long axial length, and I've found it to work well in both these axial length situations.

The **AMO Tecnis ZA9003** (6 mm acrylic optic; +10.00 D to +30.00 D; A-constant, 119.1) for ISHF is an excellent option that I use often. The PMMA haptics are less pliable and more resistant to kinking than polyvinylidene fluoride haptics; however, the difference is not great enough to lend to significant haptic-related issues. Some surgeons advocate

for heating the haptics in warm water to make them more pliable, but I have not found this necessary. The haptic-optic junction appears to be well constructed, and I have not seen any delayed cases of IOL tilt. Although this lens has been easy to obtain, the company discontinued it at the end of 2023.

The **AMO AR40** (6 mm acrylic optic; -5.00 D to +30.00 D; A-constant, 119.1) is a three-piece IOL suitable for scleral fixation with a rare trait of providing minus powers. I found this lens when treating a monocular patient with a 32 mm eye and a biometry that called for a -5.00 D IOL. The patient did not want to undergo hyperopic LASIK as an alternative to an IOL exchange. With some luck, the lens centered well and has remained stable with excellent uncorrected vision. I have found this IOL to behave similarly to the AMO ZA9003, and it has now become my most-used IOL for ISHF. In addition, the aspheric optic of the AR40 is quite forgiving when it comes to mild postoperative tilt and centration issues.

There is a small caveat, however: The diameter of the haptics does not appear to be as uniform as other IOLs, in my experience. If you are using a double-needle technique with 30-gauge TSK needles, test the fit of the haptics into the needle before loading the IOL. I have occasionally cut the end of the trailing haptic at an angle to allow for intraocular needle docking. This issue should not cause a problem for surgeons using a modified 27-gauge trocar approach.

A LIGHT ADJUSTABLE IOL

Adjustable IOLs offer the opportunity to change refractive outcomes after surgery, which is a welcome addition to refractive technology for surgeons performing secondary IOL surgery. Now available on the market, the **RxSight Light Adjustable Lens** (6 mm silicone optic; +10.00 D to +30.00 D; A-constant, 118.7) is an option for ISHF. With this IOL, a UV laser can be applied to the IOL optic approximately 3 weeks postoperatively. The laser effectively changes the lens shape to correct any residual astigmatism (-2.00 D to -0.50 D) and sphere (-2.00 D to +2.00 D) after the IOL has settled within the capsular bag or scleral tunnels.

There are myriad issues that surgeons must consider with the light adjustable lens, including adequate dilation (7 mm minimum), potential weakness at the haptic-optic junction,⁶ centration, tilt (Figure 2), and the need for UV protective glasses in the immediate postoperative period. As with the LI61AO, this silicone lens can be problematic in patients who may require oil tamponade in the future. In addition, an appropriate financial model should be considered for out-of-pocket billing of this premium IOL. Of the many patients who are candidates for this IOL in my retina practice, most find that the out-of-pocket costs of a premium IOL are a barrier to adoption. However, this IOL may be a game changer for the right patient looking for an option that could achieve the most desired refractive outcomes.

(Continued on page 43)

VITRECTOMY FOR DIABETIC RETINOPATHY: THINK EARLY, NOT LATE

Preemptive surgery may preserve vision long-term for these patients.

By Andreas Pollreisz, MD; Peter Szurman, MD, PhD; and Boris V. Stanzel, MD



Proliferative diabetic retinopathy (PDR) continues to be a major contributor to global blindness, as it may lead to tractional

retinal detachment (TRD) and vitreous hemorrhage. While advanced treatment approaches, such as panretinal photocoagulation (PRP) and anti-VEGF therapy, decrease the likelihood of vision loss, a significant portion of eyes—approximately one-third—may still experience long-term complications related to PDR.¹ Therefore, standard treatment with PRP or anti-VEGF therapy appears insufficient to prevent vision loss in specific high-risk eyes. Here, we discuss the value of early vitrectomy for the treatment of PDR before vision-threatening complications occur (Figures 1-3).

ANGIOFIBROTIC SWITCH

Vision loss from PDR stems from the growth of new blood vessels and the formation of scar tissue in the vitreous cavity. In PDR, there is a response, similar to wound healing, that involves neovascularization with infiltration of inflammatory cells and the formation of myofibroblasts. This advances to fibrovascular contraction, leading to complications such as hemorrhage, TRD, and subsequent vision loss. Various growth factors are involved, including VEGF-A, transforming growth factor- β , hepatocyte growth factor, platelet-derived growth factor, and the profibrotic connective tissue growth factor (CTGF).

VEGF is recognized as the principal factor driving angiogenesis and, among other elements, increases the expression of CTGF in different cell types within the newly developed neovascular membranes. Kuiper et al suggested that elevated CTGF levels, which have been found in the vitreous of PDR patients with active neovascularization, inactivate VEGF by diminishing production. When the balance between these two factors reaches a specific threshold ratio, the transition to angiofibrotic conditions, or an *angiofibrotic switch*, occurs with excessive CTGF levels driving fibrosis, which results in scarring and eventual blindness.²

TREATMENT CONCERNS

Parikh et al showed that when eyes presented with PDR and vitreous hemorrhage, there was a 34% probability of needing vitrectomy within 2 years.³ As demonstrated in the DRCR Retina Network Protocol S study, which compared PRP with ranibizumab (Lucentis, Genentech/Roche) in patients with PDR, just one-third of eyes treated with either PRP or ranibizumab exhibited a regression of new vessels and an improvement in the DR grading from PDR to nonproliferative DR. Among these eyes, half presented with vitreous hemorrhage at some stage during the 5-year follow-up period, 6% to 15% showed a TRD, and 11% to 20% required vitrectomy.⁴

In addition, anti-VEGF agents lack long-term effectiveness with vascular growth potentially recurring, which may result in patients presenting with pronounced retinal neovascularization, particularly when follow-up appointments are missed. Despite the substantial resources of the DRCR Retina Network to engage with patients, the 5-year results indicated a high rate of loss to follow-up of 39%.⁴

AT A GLANCE

- In proliferative diabetic retinopathy (PDR), when the balance between VEGF and the profibrotic connective tissue growth factor reaches a specific threshold ratio, an angiofibrotic switch occurs, which results in scarring and eventual blindness.
- The traditional indication for vitrectomy in the setting of PDR is waiting until relevant vision loss has occurred.
- Early vitrectomy, performed before the angiofibrotic switch occurs, is an important and viable treatment option to prevent vision-threatening complications in eyes with PDR.

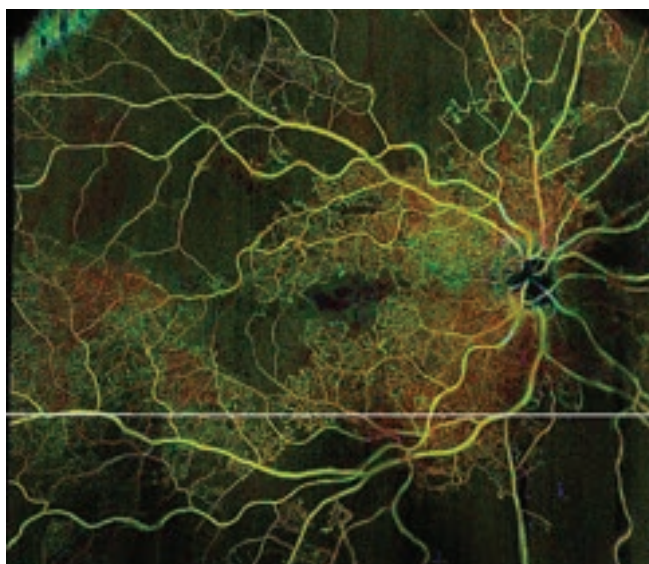


Figure 1. Widefield swept-source OCT angiography of a 56-year-old PDR patient with an indication for early vitrectomy.

THE CASE FOR EARLY VITRECTOMY

The DRCR Retina Network's Protocol AB was a prospective surgical study ($n = 205$ eyes) that compared the efficacy of immediate vitrectomy with anti-VEGF therapy with aflibercept (Eylea, Regeneron) for vitreous hemorrhage due to PDR.⁵ In the 2-year follow-up period, 33% of eyes in the aflibercept group required vitrectomy compared with 8% of eyes in the initial vitrectomy group, which also experienced a significantly lower recurrence rate of vitreous hemorrhage or active neovascularization (3%) compared with the aflibercept group (49%). About a tenth of eyes treated initially with aflibercept presented with TRD over the course of the observational period.

Patients who have experienced permanent vision loss in one eye due to diabetic TRDs are at an elevated risk of facing visual loss due to similar causes in the fellow eye. A recent series published by Schreur et al reported a 5-year cumulative incidence of up to 25% in such cases.⁶

The traditional indication for vitrectomy in PDR is waiting (a reactive approach) until a relevant vision loss has occurred due to non-clearing vitreous hemorrhage, TRD, macular traction, or dense premacular subhyaloid hemorrhage. One of the concerns with diabetic vitrectomy has been the high rate of complications shown in the Diabetic Retinopathy Vitrectomy Study, reporting a risk of significant vision loss of up to 40%.⁷

Over the past few decades, advancements in small-gauge vitreoretinal surgery—including enhanced fluidics and highly efficient vitreous cutters—have significantly enhanced the safety of the procedure with notable success rates in achieving retinal reattachment and fewer occurrences of severe vision loss in these eyes.⁸

The need for vitrectomy in the fellow eye rises to up to 36% within 5 years following the first vitrectomy.⁹ Moreover, a suboptimal visual outcome after vitrectomy in the first

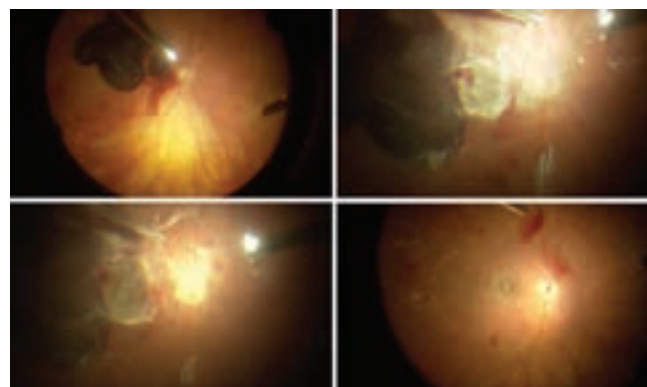


Figure 2. A 26-year-old woman with type 1 diabetes and PDR. With triamcinolone staining, note the facile separation of the vitreous cortex, despite several vascular pegs/bleeding points. Such stage of vitreoretinal interface changes from PDR is ideally suited for early vitrectomy with a likely good long-term visual prognosis.

eye serves as a predictor for a less favorable outcome in the fellow eye, particularly when the indication for vitrectomy is still considered reactive.¹⁰

Although it is feasible to enhance retinal structure and function reactively using current surgical techniques, restoring good vision is a rare outcome once traction has been established.¹¹ In TRD cases, vitrectomy combined with delamination or segmentation of the preretinal fibrovascular membranes showed an intraoperative complication rate of 30%, with 58% of eyes requiring an intravitreal tamponade and 15% needing a second vitrectomy.¹² Although there was an overall visual improvement after surgery, fewer than one-third of eyes analyzed in the Royal College of Ophthalmologists' National Ophthalmology Database maintained the standard visual requirement for driving.¹²

IS EARLY VITRECTOMY CLINICALLY JUSTIFIED?

Tan et al investigated the safety and efficacy of preemptive diabetic vitrectomy in patients with severe, non-fibrotic retinal neovascularization (before the angiofibrotic switch).¹³ They reported that the overall intraoperative complications were less frequent compared with those reported in the UK National Ophthalmological Database (UKNOD) study for diabetic vitrectomy (10% vs 23%).^{12,13} The primary intraoperative complication noted was iatrogenic breaks, occurring at a rate of 10%, which was similar to that reported in the UKNOD series when delamination was not necessary but lower when delamination was performed (28%).^{12,13} Tan et al reported the need for gas tamponade in 10% of eyes and no case of silicone oil, while 60% to 100% of eyes required a tamponade in reactive diabetic vitrectomy with silicone oil rates reaching up to 20%.^{13,14}

The reduced complication rate may be attributed to the relatively normal vitreoretinal interface allowing a less traumatic surgical separation of the vitreous from the retina, which also contributes to long-term stabilization.¹⁵ This contrasts with eyes that had already undergone an

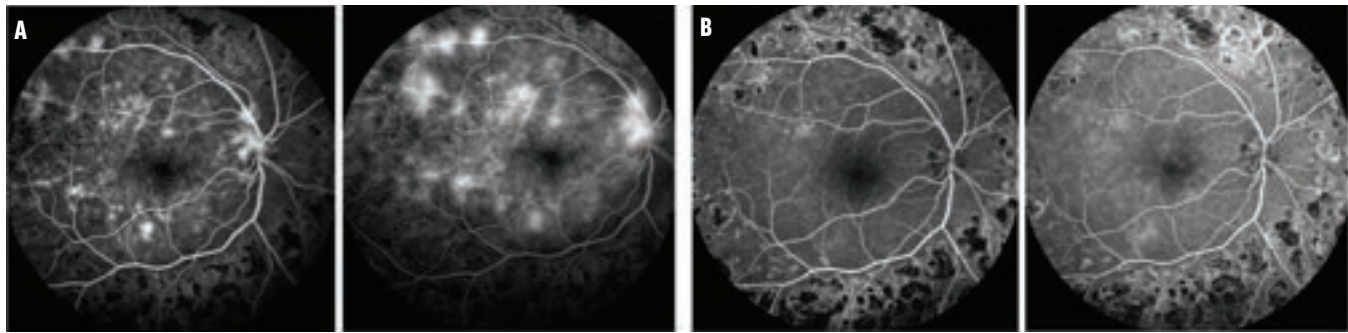


Figure 3. Long-term course of early vitrectomy in PDR (patient used in dataset for Tan et al. *Eye (Lond)*.¹³). Preoperatively (A), the patient's VA was 0.6 (0.2 logMAR). Four years after surgery (B), the patient's VA was 0.8 (0.1 logMAR).

angiofibrotic switch, where fibrovascular complexes with traction are present.

Postoperative vitreous hemorrhage is a common complication following diabetic vitrectomy; its reported incidence ranges from 20% to 75%.^{13,16} The administration of anti-VEGF agents before surgery has been linked to a decrease in this risk, bringing it down to 10% to 20%.¹⁷ In the Preemptive Diabetic Vitrectomy study, the incidence of postoperative vitreous hemorrhage was 40%, occurring mainly within 4 weeks after surgery; the authors hypothesized that the elevated occurrence was a result of cutting or avulsion of numerous pegs connecting the retinal and neovascular circulations upon posterior vitreous detachment.¹³

Thus, it is crucial to inform patients about the potential risk for a temporary decrease in vision in the initial postoperative period and the likelihood of intravitreal injection or second surgery before achieving long-term stabilization of vision.

THE CLINICAL PEARL

We have excellent treatment options available for patients with PDR to preserve vision. While PRP and anti-VEGF therapy continue to play an important role, early vitrectomy, performed before the angiofibrotic switch and before silicone oil filling is necessary, is another important and viable treatment to prevent vision-threatening complications. ■

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MACULAR SURGERY: CURRENT AND INNOVATIVE TECHNIQUES

Novel surgical approaches are changing the way surgeons address macular traction and macular holes.

By Marcelo Zas, MD, PhD; Mariano Cotic, MD; and Marcos Mendaro, MD



The assessment of the vitreomacular interface has evolved significantly, and we can now accurately determine its histological

architecture like never before. OCT and OCT angiography are the most relevant tools available to help clinicians image and evaluate changes in the posterior pole. These imaging capabilities have given rise to improved macular surgery performance and better communication with the patient about their condition, both of which have improved care.

CONDITIONS WE TREAT

Epiretinal membranes (ERMs), vitreomacular traction, and full-thickness macular holes (FTMHs) are the most common disorders that can arise due to vitreoretinal interface changes. Currently, these conditions are treated with surgery.

ERMs and Vitreomacular Traction

In the past, ERMs were considered an epiretinal phenomenon caused by two vectors of traction: anteroposterior and tangential. This is now known as *vitreomacular traction syndrome* (VMTS), where 20% of the population is asymptomatic; some patients may experience spontaneous resolution, while others progress to a FTMH.¹⁻³

In 2016, the PACORES group published a retrospective multicenter study of 168 eyes, of which 21.4% (36 eyes) showed spontaneous resolution of VMTS after a mean follow-up of 11.4 ± 12.6 months. An unfavorable anatomic outcome occurred in 7.7% (13 eyes). In addition, the study found that the baseline spectral-domain OCT grade may predict the progression to FTMH.⁴

In 2017, Govetto et al published a new OCT staging scheme for ERMs, in which ERMs were classified based on foveal thickness measures and the identification of specific biomarkers, such as the presence of ectopic inner foveal layers. The ability to properly classify ERMs is crucial to

achieve optimal results in our everyday practice.⁵

The OCT-based staging scheme uses morphologic and functional characteristics to classify ERMs into four stages: presence of the foveal pit and well-defined retinal layers (stage 1); absence of the foveal pit and well-defined retinal layers (stage 2); absence of the foveal pit, well-defined retinal layers, and presence of ectopic inner foveal layers (stage 3); and absence of the foveal pit, disrupted retinal layers, and presence of ectopic inner foveal layers (stage 4).⁵

This classification is clinically relevant and has prognostic implications because higher stages correlate with worse visual acuity outcomes.

Macular Holes

To determine the appropriate treatment approach for FTMHs, we first measure the hole size and the baseline visual acuity. Based on these criteria, clinicians can decide to monitor, treat medically, or proceed to the OR. A surgical approach to FTMHs has three main objectives: lower the resistance to facilitate the closure with the maculorexis; decrease the size by drying with fluid-air exchange; and provide a gas tamponade (SF₆).⁶

AT A GLANCE

- Peeling the internal limiting membrane and epiretinal membranes has become the standard technique to address vitreomacular interface diseases.
- Human amniotic membrane transplant and autologous retinal transplant are recent approaches to the treatment of refractory macular holes.
- Retinal expansion is a valuable technique for macular holes, in which subretinal injection of balanced salt solution creates a macular detachment.

One of the most disruptive innovations in the field was made in 1997 by C. Eckardt, who published the results of macular holes that were treated with vitrectomy plus internal limiting membrane (ILM) peeling (Figure 1A).⁷ The procedure—novel at the time—led to an unprecedented 92% success rate, ushering in an era of ILM peeling as the standard for FTMHs.⁷

A few years later, Michalewska et al described the inverted ILM flap technique, which improved both functional and anatomic outcomes of vitrectomy for FTMHs with a diameter greater than 400 μm .⁸

More recently, Wiedemann provided insight into the mechanisms of ILM peeling, including improved retinal flexibility, better oxygen supply to the inner retina, and, potentially, retinal glial cell proliferation. These mechanisms lead to reduced foveal thickness and improved visual acuity, closure rates, and macular function.⁹

Despite this growing body of work, we have yet to find a definitive solution for macular holes. Many FTMHs that are refractory to conventional management may be less than 400 μm , requiring a revised classification scheme and novel treatment options.¹⁰ At the 2019 Retina World Congress, Tamer H. Mahmoud, MD, PhD, presented on autologous retinal transplantation (ART) for macular holes, adding to our growing armamentarium. Human amniotic membrane transplant (hAM) is yet another recent technique that has made the treatment of recurrent and refractory FTMHs possible.^{11,12} Both are equally valid and widely accepted.

With the capability to enhance epithelial cell growth, hAM is a well-known adjuvant used for the treatment of corneal and conjunctival defects. The initial technique, described by Rizzo et al, used bimanual manipulation to insert the graft into the subretinal space under perfluorocarbon liquid.¹¹ The restoration of the retinal layers observed in the postoperative period resembles a healthy eye, suggesting that the amniotic cells are inducing tissue remodeling.¹¹

A large retrospective case series of 130 patients undergoing ART for the repair of primary and refractory macular holes showed good anatomic and functional outcomes (Figure 1B). In the study, 89% of macular holes closed (78.5% complete; 10% small eccentric defect), visual acuity improved by at least 3 lines in 43% of eyes and at least 5 lines in 29% of eyes, and there were low complication rates.¹²

Several alternative surgical options may prove useful for certain refractory macular holes, such as various ILM flap techniques, retinal expansion, lens capsule transplantation, blood products, and macular buckling.

The CLOSE study group examined a total of 1,135 eyes and proposed a surgical classification for large FTMHs

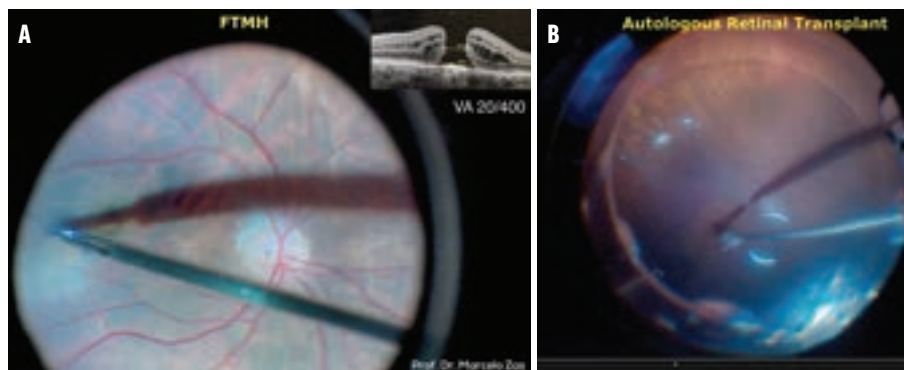


Figure 1. ILM peeling (A) became a standard surgical approach to FTMHs after C. Eckardt published on the technique in 1997. ART (B) may be a useful technique for refractory macular holes, leading to good anatomic and functional outcomes.

based on surgical techniques. The study found that large (400 μm – 550 μm) and X-large (550 μm – 800 μm) holes can be successfully treated with ILM peeling and ILM flap techniques, respectively. The team noted that further studies are necessary for XX-large ($\geq 800 \mu\text{m}$ – $< 1,000 \mu\text{m}$) and giant macular holes ($\geq 1,000 \mu\text{m}$) to determine which technique is best based on hole size and characteristics.¹³

Parolini et al published a classification and management system for patients with myopic traction maculopathy (MTM), which suggests that surgeons should observe early stages of MTM but address schisis and detachments with macular buckling. FTMHs should be treated with vitrectomy and ILM peeling to alleviate the tangential forces.¹⁴

The retinal expansion technique is another valuable alternative to macular hole closure. Subretinal injection of balanced salt solution creates a macular detachment, which may lead to hole closure. Our team recently published a retrospective interventional case series of two patients with chronic FTMHs who were treated with retinal expansion; one patient achieved complete hole closure.¹⁵

Alezzandrini et al published a study to compare the functional and anatomic outcomes at 24 months of eyes with a primary FTMH that failed to close after surgery and were treated with either an ART of ILM (ART-ILM) or the retinal expansion technique (Figure 2). Patients in the ART-ILM group ($n = 14$) experienced a statistically significantly improved BCVA (median 49.5, range 20–66 letters) compared with preoperative BCVA (median 39 letters). In contrast, patients in the retinal expansion group ($n = 14$) did not achieve a statistically significant improvement. At 24 months, 85.7% of patients in the ART-ILM group achieved closure compared with 57.1% in the retinal expansion group (Tables 1 and 2). The baseline macular hole size was not a significant preoperative factor that influenced closure rates.¹⁶

NOVEL TECHNIQUES ON THE RISE

Macular surgery has been a hot topic in retina for years, fostering the growth of many novel techniques. With advanced diagnostics and imaging, we now embrace the fact

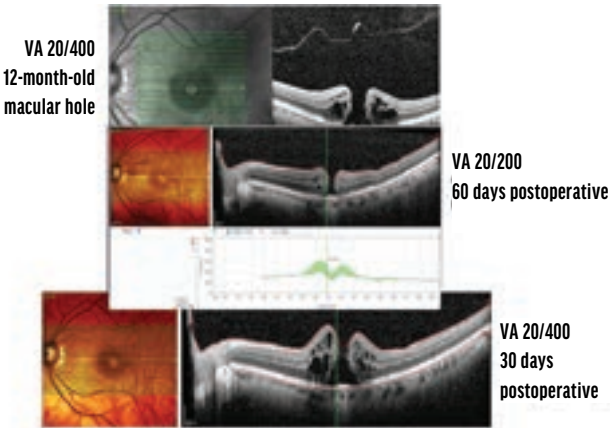


Figure 2. Although retinal expansion may help to close refractory FTMHs, recent research suggests patients may not experience significantly improved vision postoperatively.

that functional results are as equally relevant as anatomic outcomes. Thus, we must begin assessing the visual function of our patients using BCVA, microperimetry, mERG, and multimodal images. These postoperative evaluations could provide surgeons with significant insight into the true nature of our surgical results. ■

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TABLE 1. BASELINE CHARACTERISTICS OF PATIENTS			
Variable	Treatment		P Value
	ART-ILM (n = 14)	Retinal Expansion (n = 14)	
Male gender	50%	50%	.703
Hole size (µm)	640.79 ± 94.75	646.43 ± 99.15	.879
BCVA (ETDRS)	0.703	0.703	.563
Time between first and second surgery (months)	11.3 ± 3.2	11.3 ± 3.2	NA

Abbreviation: ART-ILM, autologous retinal transplant of internal limiting membrane

TABLE 2. LINEAR REGRESSION MODEL WITH ANATOMIC STATUS OF MACULAR HOLE AND POSTOPERATIVE VISUAL ACUITY AS THE DEPENDENT VARIABLE								
Variable	Univariate Model				Multivariate Backward Model			
	Estimate (SE)		P value		Estimate (SE)		P value	
	Anatomic Status	Visual Acuity	Anatomic Status	Visual Acuity	Anatomic Status	Visual Acuity	Anatomic Status	Visual Acuity
Sex (male vs female)	- 0.511 (0.966)	9.188 (5.917)	.597	.133	NA	NA	NA	NA
Macular hole size (µm)	0.023 (0.009)	- 0.139 (0.018)	.009	< .001	0.023 (0.009)	- 0.087 (0.016)	.009	< .001
Baseline VA (ETDRS)	- 0.065 (0.043)	1.262 (0.163)	.136	< .001	NA	0.779 (0.140)	NA	< .001
Time between first and second vitrectomy (months)	0.704 (0.290)	- 3.217 (0.901)	.015	.001	NA	NA	NA	NA

Tables adapted from Alezzandrini A et al. *Int J Retina Vitreous*. 2021;7(1):57.¹⁶

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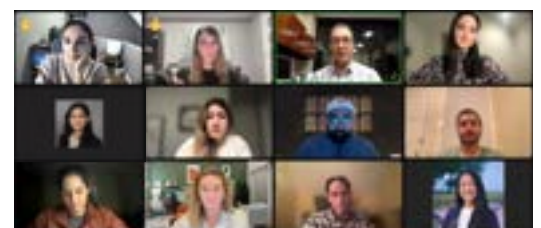
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HOW TO CHOOSE THE RIGHT TAMPONADE

Surgeons have several options, and knowing which one will serve the patient best is the key to a successful surgery.

By Lucy V. Cobbs, MD, and Vaidehi S. Dedania, MD



Intraocular tamponades play an essential role in vitreoretinal surgery, acting as a force to displace fluid away from retinal breaks and plug them to allow the retina to reattach

to the underlying retinal pigment epithelium (RPE).¹ Tamponade agents have evolved over the years, and new innovations are on the horizon. Although choosing the right tamponade is nuanced and case-dependent, this article outlines some general evidence-based guidelines for common clinical scenarios.

THE CHOICES

The most common tamponades in the United States include gas (air, SF₆, C₃F₈), silicone oil, and perfluoro-n-octane (PFO), a heavier-than-water tamponade.

Both SF₆ and C₃F₈ are fluorocarbon gases that are inert, odorless, clear, and low density (Table 1).² The duration of a gas is important to consider when choosing a tamponade because it needs to support retinal breaks until the retinopexy has taken effect. Laser retinopexy requires approximately 24 hours to create an adherent chorioretinal scar and 2 to 3 weeks to develop maximum adhesive force.² Cryotherapy may initially weaken the retina-RPE adhesive forces over the first week due to edema before effectively sealing the retina to the RPE.² The disadvantages of using a gas with a longer duration include increased risk of cataracts and elevated IOP, as well as the inability to travel by plane.²

To simplify the process of preparing intraoperative gas tamponades, Alcon created syringes that can be connected to its vitrectomy machine to auto-purge and auto-fill with pure expansile gas.³ This enables a member of the sterile surgical team to prepare the gas without relying on a non-sterile team member.

Silicone oil is available at two different viscosities, 1,000 centistokes (cSt) and 5,000 cSt (Table 2). Although

patients may see through silicone oil more clearly compared with a gas bubble, silicone oil requires surgical removal from the eye. In addition, it induces a hyperopic shift in phakic patients and, to a lesser degree, in pseudo-phakic patients, and a myopic shift in aphakic patients.

Heavier-than-water tamponades include PFO and heavy silicone oils, the latter of which are not currently approved for use in the United States.

SELECTING THE BEST TAMPONADE

For rhegmatogenous retinal detachments (RRDs), expansile gas at an iso-expansile concentration is typically used if there is no high-grade proliferative vitreoretinopathy (PVR), prior failed reattachment surgery, or inflammatory/infectious processes. Silicone oil may be considered in cases with any of these complicating factors. For combined tractional RDs and RRDs, silicone oil or gas tamponade is typically used. Short-acting gases are increasingly used for macular hole repairs. Using air or no tamponade is acceptable for epiretinal membrane peels.

AT A GLANCE

- For rhegmatogenous retinal detachments, expansile gas is typically used if there is no high-grade proliferative vitreoretinopathy, prior failed reattachment surgery, or inflammatory/infectious processes. In those cases, consider silicone oil.
- Because gas and silicone oil tamponades are buoyant, materials heavier than silicone oil have been used when treating inferior pathology.
- IOP aberrations are among the most common complications of intraocular tamponades.

TABLE 1. TYPE OF GAS TAMPONADES FOR VITREORETINAL SURGERY IN THE UNITED STATES

	Expansile Characteristics	Iso-expansile Percentage	Duration	Precautions
Air	Not expansile		1 week	- Counsel patient that vision will be blurry for the duration of the bubble (be mindful of monocular patients) - Avoid very high altitudes (air travel) or low altitudes (scuba diving) - Avoid nitrous gas anesthesia (risk of rapid expansion of bubble and increased IOP)
SF ₆ (sulfur hexafluoride)	Expands 2x in 2 days	20%	2-3 weeks	
C ₃ F ₈ (perfluoropropane)	Expands 4x in 4 days	14%	6-8 weeks	

For RRDs without PVR, gas tamponade with or without vitrectomy is frequently favored over silicone oil tamponade. Pneumatic retinopexy typically employs 100% expansile gas to treat tears in the superior two-thirds of the retina because the partial fill of the buoyant gas is a less effective plug for inferior pathology.

For RRDs without PVR that undergo vitrectomy, a retrospective study of almost 100 eyes showed that there was no significant difference in rates of recurrent detachment between C₃F₈ and silicone oil fill.⁴ Another retrospective study of more than 500 eyes with RRD found no difference between air and 20% SF₆ tamponade overall, but for eyes with inferior RRDs, tamponade with 20% SF₆ gas had a higher success rate than air.⁵

For RRDs with PVR, two large studies, the Silicone Oil Study and the European Vitreoretinal Society Retinal Detachment Study,^{6,7} investigated the use of gas versus silicone oil tamponade. The Silicone Oil Study, a prospective, randomized multicenter study, showed that patients with RRDs with PVR experienced no significant difference in anatomic or visual outcomes with C₃F₈ versus silicone oil 1,000 cSt at 1 year postoperatively, but patients with SF₆ tamponade had inferior outcomes.^{6,8}

Similarly, the European Vitreoretinal Society Retinal Detachment Study showed that rates of anatomic failure in complex RRD eyes were not significantly different between gas and silicone oil groups.⁷

Smaller retrospective studies of RRD subpopulations have identified significant benefits of one tamponade type over others for specific clinical scenarios. For example, in eyes with pathologic myopia and a staphyloma undergoing vitrectomy for RRD due to a macular hole, C₃F₈ tamponade resulted in better visual outcomes and initial success compared with silicone oil.⁹ This may be because oil does not tamponade the irregular contours of a staphyloma as well as gas. A retrospective study of more than 50 eyes with RRD and PVR that underwent vitrectomy and retinectomy showed that eyes with silicone oil did significantly better than eyes with gas.¹⁰

Several studies have compared 1,000 cSt versus 5,000 cSt tamponade. A study of more than 300 eyes with complex RRDs found no significant difference in

TABLE 2. SILICONE OIL TAMPONADES

	Viscosity (cSt)	Specific Gravity	Approved in the United States
Silicone Oil	1,000	0.97	Yes
Silicone Oil	5,000	0.97	Yes
Perfluoro-n-octane (PFO)	438	1.76	Yes
Densiron 68	3,300	1.06	No
Oxane HD	1,400	1.02	No

outcomes between 1,000 cSt and 5,000 cSt silicone oil.¹¹ In a smaller retrospective study of 82 eyes with complex RRDs, eyes with 5,000 cSt had higher rates of redetachment after silicone oil removal.¹² For diabetic tractional RDs, a retrospective study of 62 eyes found that eyes with silicone oil had significantly lower rates of postoperative vitreous hemorrhage than eyes with gas or no tamponade.¹³

Because gas and silicone oil tamponades are buoyant, materials heavier than silicone oil may be necessary when treating inferior pathology. Two heavy silicone oils are approved for use in Europe, but not in the United States: Densiron 68 and Oxane HD. The Heavy Silicone Oil Study, a randomized control trial that compared Densiron 68 with silicone oil tamponade in eyes with inferior RRDs and PVR, did not find a significant difference in anatomic or functional outcomes.¹⁴ Of note, face-down positioning with gas and silicone oil tamponades for inferior retinal pathology is the current standard to provide tamponade to these areas.

PFO is a heavier-than-water tamponade typically used intraoperatively as a “third hand” to flatten the retina. It has also been proposed as an effective temporary postoperative tamponade in RRDs with giant retinal tears (GRTs) or multiple scattered breaks. However, its use is controversial because prolonged exposure to PFO greater than even 60 minutes can be toxic to the retina.¹⁵

For other retinal pathology, such as macular holes, short-acting gases such as SF₆ are increasingly favored, although current literature lacks consensus on which gas is most effective for hole closure.¹⁶

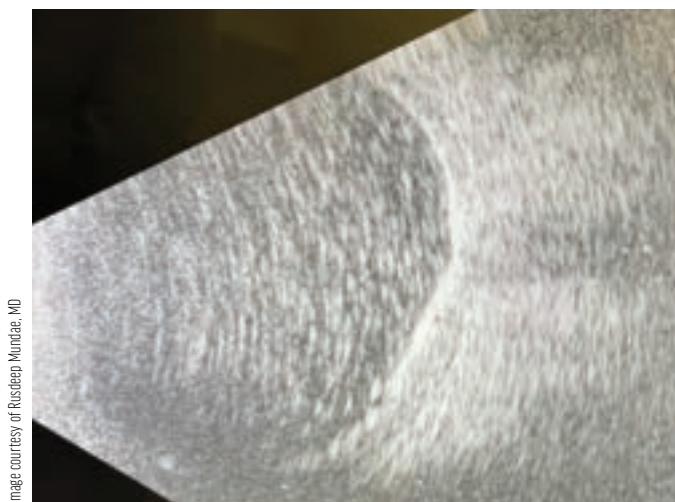


Image courtesy of Ruseep Mordae, MD

Figure. B-scan ultrasound of a patient's eye after silicone removal surgery demonstrates numerous oil droplets remaining in the vitreous cavity, which evaded removal.

TAMPONADE RISKS

IOP aberrations are among the most common complications of intraocular tamponades. Gas is more frequently associated with hypotony and silicone oil with ocular hypertension. Development of cataract is common, regardless of the tamponade.⁶

Retinal slippage occurs more frequently with gas tamponade than silicone oil.¹⁷ Preoperative counseling about activity restrictions with gas tamponade is crucial. Specifically, patients with gas bubbles are advised to avoid air travel, scuba diving, and use of nitrous anesthesia (commonly used during dental procedures) due to the risk of rapid gas expansion. A unique, rare complication of gas tamponade is migration of gas into the optic nerve and intracranial spaces.¹⁸

Complications unique to silicone oil include emulsification with migration into the subconjunctival

AN ILLUSTRATIVE CASE

A 50-year-old man with a fovea-involving rhegmatogenous retinal detachment (RRD) with a temporal giant retinal tear (GRT) with grade C proliferative vitreoretinopathy (PVR) presented with a VA of 20/100 (Figure 1). He underwent a combined scleral buckle and 25-gauge vitrectomy with silicone oil 1,000 cSt tamponade. Five months after his initial surgery, he underwent silicone oil

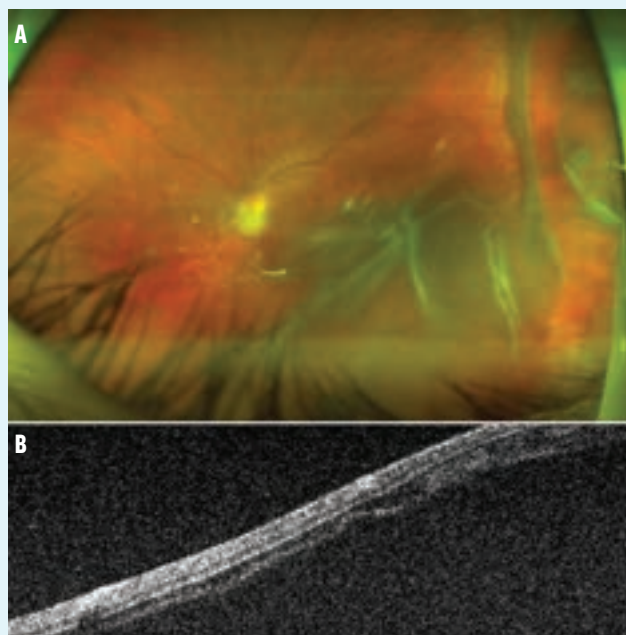


Figure 1. Widefield fundus imaging of the left eye of our patient demonstrates a temporal GRT spanning from the 12 to 5 clock hours with an associated fovea-involving RRD and a temporal star fold (A). The horizontal raster of a macular OCT showed subretinal fluid involving the macula (B).

removal for mild emulsification. One month later, his retina remained flat, and his VA was 20/150 (Figure 2).

GRTs have typically been managed using silicone oil tamponade.¹ One report estimated that more than 80% of GRTs in England were managed with silicone oil tamponade after vitrectomy.² However, a recent retrospective study of 88 eyes with fresh GRT detachments found that eyes with C_3F_8 tamponade had significantly better post-operative vision and similar rates of redetachment compared with eyes with oil.³ Notably, this study excluded eyes with trauma or high-grade PVR.

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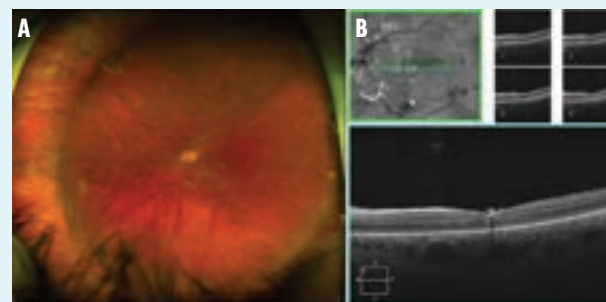


Figure 2. The widefield fundus image of the left eye 6 months after the initial RRD repair surgery and 1 month after silicone oil removal demonstrates a flat retina, laser barricade surrounding the GRT temporally, and an encircling scleral buckle (A). The horizontal raster of a macular OCT shows resolution of subretinal fluid (B).

space, suprachoroidal space, or anterior chamber. Emulsified oil droplets in the anterior chamber increase the risk of glaucoma, and residual droplets may remain even after attempted surgical removal of silicone oil (Figure). In addition, after oil removal, there is a risk of redetachment or vision loss likely related to silicone oil toxicity.¹⁹ Rarely, silicone oil is toxic to retinal ganglion cells either by intraretinal migration of oil or direct contact with cells, causing vision loss and thinning of inner retinal layers.²⁰ ■

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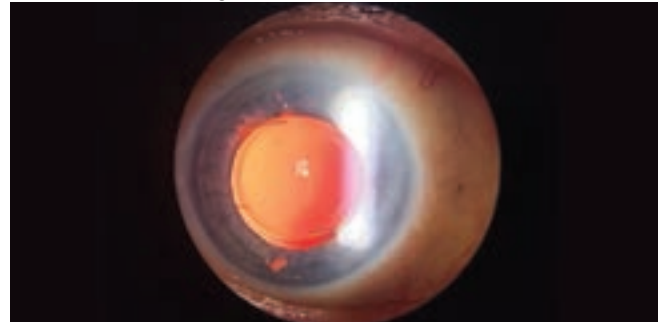


Figure 2. The key to success with scleral fixation of the light adjustable lens is maximizing centration and minimizing tilt.

Early Experience

I first used this lens for ISHF in October of 2022 in a patient with a dislocated multifocal toric IOL. I performed the surgery, and Matthew Kruger, MD, a cornea colleague, applied the postoperative laser treatment. We were able to correct residual -1.00 D sphere and +2.00 D astigmatism after ISHF, and the patient's manifest refraction was plano at 1 month postoperative. Since then, I have performed three more scleral fixation cases using the light adjustable lens, with a plan to publish a case series in 2024. Currently, there is a single case report of using the light adjustable lens for ISHF, which reported excellent results.⁷

CONCLUSIONS

Many lens options exist for ISHF of a secondary IOL. Personal preference, experience, and refractive goals all factor into the decision making regarding IOL choice. Integrity of the haptics within scleral tunnels and within the haptic-optic junction remains a critical consideration for this technique. With new technology, including light adjustable IOLs and more anticipated in the future, vitreoretinal surgeons will continue to evolve with improved IOL options and techniques to treat patients with dislocated IOLs and aphakia. ■

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SURGICAL DRUG DELIVERY ROUNDUP

These novel innovations have helped clinicians improve therapeutic access to the posterior pole.

By Nikhil K. Bommakanti, MD; Michael A. Klufas, MD; and David Xu, MD



Ophthalmic drugs can be delivered by multiple pathways, including systemic, topical, periocular, subconjunctival,

sub-Tenon's, suprachoroidal, intracameral, intravitreal, and subretinal. Intravitreal injections—commonly of anti-VEGF agents but also corticosteroids, antibiotics, antivirals, antifungals, complement inhibitors, and chemotherapy—were the most performed ophthalmic procedure among the Medicare Fee-For-Service population in 2020, based on the authors' analysis of the publicly available Part B National Summary Data File. In-clinic suprachoroidal injections may become more common with the development of the suprachoroidal microinjector (SCS Microinjector, Clearside Biomedical) and the FDA approval of suprachoroidal triamcinolone acetonide (Xipere, Bausch + Lomb and Clearside Biomedical).^{1,2}

Certain treatments, however, are best administered surgically, including intravitreal devices for sustained release, subretinal tissue plasminogen activator injection for submacular hemorrhage displacement, and subretinal gene therapy. More generally, options for surgical drug delivery include intravitreal implants and subretinal access by vitrectomy and retinotomy or a suprachoroidal approach.

IMPLANTED INTRAVITREAL DEVICES

Intravitreal implants elute small concentrations of medication over long periods and are an attractive option to reduce treatment burden associated with neovascular retinal diseases such as wet AMD and diabetic macular edema. Examples of this technique include the fluocinolone acetonide intravitreal implant (Retisert, Bausch + Lomb),³ the NT-501 encapsulated cell therapy implant (Neurotech Pharmaceuticals),⁴ and the port delivery system (PDS) with ranibizumab (Susvimo, Genentech/Roche).⁵

The PDS is implanted in the OR, and refill-exchanges are performed in the clinic. Although the company voluntarily recalled the PDS,⁶ the surgical technique is described here

because a similar approach may be used in the future. To implant this device, place an infusion line in the inferotemporal quadrant, followed by a superotemporal corneal traction suture. Perform a conjunctival peritomy in the superotemporal quadrant to expose bare sclera, followed by a 3.5 mm scleral cutdown incision that is parallel and 4 mm posterior to the limbus. Next, ablate the choroidal pars plana vasculature using a 532 nm laser endoprobe. Incise the pars plana using a 3.2 mm blade, and achieve hemostasis using fine-tip diathermy. Insert the implant, close the conjunctiva and Tenon's capsule, and remove the infusion line.⁷

The voluntary recall did not include the refill-exchange solution or needle. Thus, patients who received the implant can continue receiving in-office refill-exchange procedures.

SUBRETINAL ACCESS BY VITRECTOMY

Subretinal drug delivery offers the advantage of placing the medication in direct contact with the target (eg, placing tissue plasminogen activator in contact with blood for a subretinal hemorrhage or placing a viral vector in contact with the photoreceptors and retinal pigment epithelium [RPE] for gene therapy).⁸ In the case of viral vectors for gene therapy, subretinal administration also results in reduced inflammation compared with intravitreal injection due to the immune-privileged nature of the subretinal space.⁹ Voretigene neparvovec-rzyl (Luxturna, Spark Therapeutics)

AT A GLANCE

- ▶ Intravitreal implants elute small concentrations of medication and may reduce treatment burden.
- ▶ Subretinal drug delivery places the medication in direct contact with the target.
- ▶ The subretinal space can be accessed suprachoroidally, which avoids a vitrectomy and retinotomy.

is the first FDA-approved therapy using this technique; however, many trials are underway for other gene therapies delivered via subretinal surgery.¹⁰

Begin subretinal delivery with a core vitrectomy, induce a posterior vitreous detachment, and create a retinotomy. Either directly inject the vector into the subretinal space, creating a bleb via a subretinal cannula and pneumatic injector (Figure), or administer the vector after creating a saline pre-bleb, which may minimize drug reflux. Intraoperative OCT can help to confirm subretinal administration. Adjunctive techniques such as subretinal air or fluid-air exchange can be considered, although these are not always necessary. In some protocols, the patient is placed in a supine position postoperatively to ensure the bleb remains in the posterior pole.

Disadvantages of this technique include the need for a vitrectomy (due to its associated risks) and a retinotomy, with the resulting possibility of medication reflux leading to dose reduction or epiretinal membrane formation, damage from transient neurosensory retinal detachment, and macular hole formation. Inadvertently inserting the subretinal cannula too deep can lead to RPE damage or suprachoroidal infusion, whereas shallow insertion can lead to retinoschisis.

SUBRETINAL ACCESS VIA SUPRACHOROIDAL CATHETER

The subretinal space can also be accessed surgically via a suprachoroidal approach using a tunneled catheter with a microneedle that penetrates the choroid and RPE. This surgical modality has entered human clinical trials for suprachoroidal-to-subretinal delivery of gene and cell therapies.

The general surgical technique involves first accessing the suprachoroidal space by a localized conjunctival peritomy and scleral cutdown, then introducing and tunneling a catheter under direct visualization and chandelier illumination. Once in the desired location, the needle is deployed to the subretinal space and the medication is delivered.¹¹

This approach has been used to treat geographic atrophy with GT005 (Novartis) using the Orbit Subretinal Delivery System (Gyroscope Therapeutics), palucorcel (Janssen Pharmaceuticals),¹² and OpRegen (Lineage Cell Therapeutics).¹³ The scientific programs for GT005 and palucorcel have since been discontinued.

An advantage of this approach is the avoidance of vitrectomy and its associated complications. This can be especially helpful for gene therapies that may be given to younger patients with a more adherent hyaloid. Furthermore, this technique obviates the need for a retinotomy, preserving retinal tissue and avoiding reflux of medication into the vitreous chamber via the retinotomy site.

THE FUTURE

We have made significant advances in surgical drug delivery to the posterior segment, typically in tandem with new drug

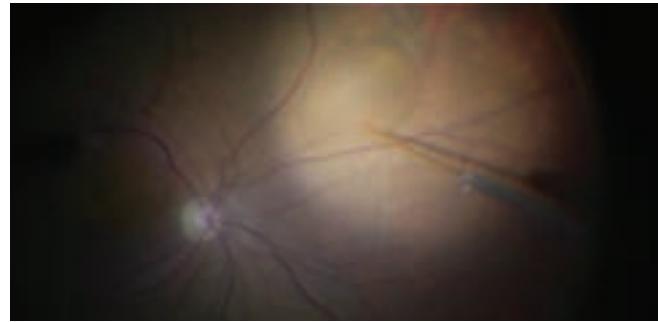


Figure. Subretinal bleb creation for the administration of RGX-314 (Regenxbio) gene therapy.

developments. Our toolkit continues to expand, and these exciting developments may provide new options for patients, ultimately changing the field for the better. ■

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MYOPIC TRACTION MACULOPATHY IN A SURGICAL SETTING



Here's why technique selection and instrumentation are key.

BY ELHAM SADEGHI, MD, AND JAY CHHABLANI, MD

Myopia, a multifactorial ocular disorder, is the most common refractive error, and it's only becoming more prevalent.¹ Up to 33% of myopic eyes may progress to high myopia, defined as a refractive error greater than -6.00 D to -8.00 D and an axial length greater than 26 mm to 26.5 mm.^{2,3} Further, eyes with pathologic myopia experience both posterior staphyloma and axial length progression.^{2,3}

Myopic traction maculopathy (MTM) occurs in 30% of eyes with high myopia and presents with decreased visual acuity, metamorphopsia, and central scotoma.^{4,5} It is caused by increased retinal stretching tangentially and posteriorly due to preretinal factors, including incomplete posterior vitreous detachment, vitreomacular traction, epiretinal membrane (ERM), and internal limiting membrane (ILM), as well as posterior factors, such as posterior staphyloma, leading to macular hole, myopic retinoschisis, and retinal detachment.^{2,3} Risk factors for MTM progression include longer axial length, more severe posterior staphyloma, and the absence of a dome-shaped macula.³

SURGICAL CONSIDERATIONS

As most MTM patients have a stable natural course, a follow-up approach is usually recommended.⁵ Nevertheless, decreased vision due to macular hole or retinal detachment, progression of macular schisis, and VA less than 20/50 are indications for surgery.⁶ Surgery follows the ab-externo method, including macular buckling, to serve as an iatrogenic dome-shaped maculopathy, and the ab-interno method, including pars plana vitrectomy (PPV) with membrane peeling.⁵ However, ILM peeling with intravitreal gas tamponade is controversial, and although macular buckling is reversible and without risk of cataract progression, it is associated with a high risk of complications, including muscle slippage and misalignment, esotropia, scleral perforation, buckle exposure, altered choroidal perfusion, and retinal pigment epithelium damage.^{7,8}

The most widely used classification system for MTM based on OCT is the MTM Staging System, which consists

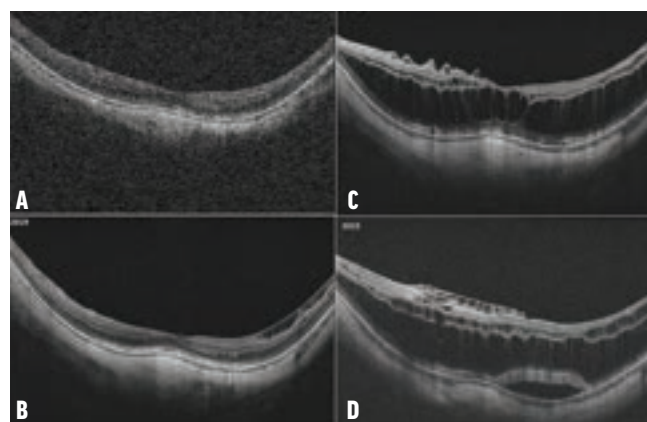


Figure 1. The OCT scan of the left eye in 2015 shows a staphyloma and a normal retinal contour (A). In 2019, the OCT shows inner retinal traction by ERM and inner retinal schisis (B). The OCT scan in 2022 shows a staphyloma, fine ERM, and outer retinal schisis (C). In 2023, the OCT shows no change in the staphyloma curvature, more traction from a thickened ERM, increased outer retinal schisis, and neurosensory detachment (D).

of foveal morphology classification (normal foveal architecture, lamellar macular hole, full-thickness macular hole [FTMH]) and MTM staging (stage 1: inner/outer maculoschisis; stage 2: predominantly outer maculoschisis; stage 3: maculoschisis/macular detachment; stage 4: macular detachment).⁹ PPV with ILM peeling or ILM flap and gas tamponade has a high success rate in cases of mild maculoschisis with lamellar macular holes or FTMHs. In stages 2, 3, and 4 without a FTMH, macular buckling is typically the primary choice of surgery.¹⁰ In stages 2, 3, and 4 with a FTMH, combined macular buckling and PPV may be necessary.¹⁰

One of the biggest challenges associated with membrane peeling in these cases is the limited utility of conventional forceps. Removing the cannula and reducing IOP are common surgical tricks to grasp the membranes using conventional forceps. The case report of MTM progression described here involves successful removal of the ERM and ILM using myopic forceps and recovery of the foveal contour without a tamponade.

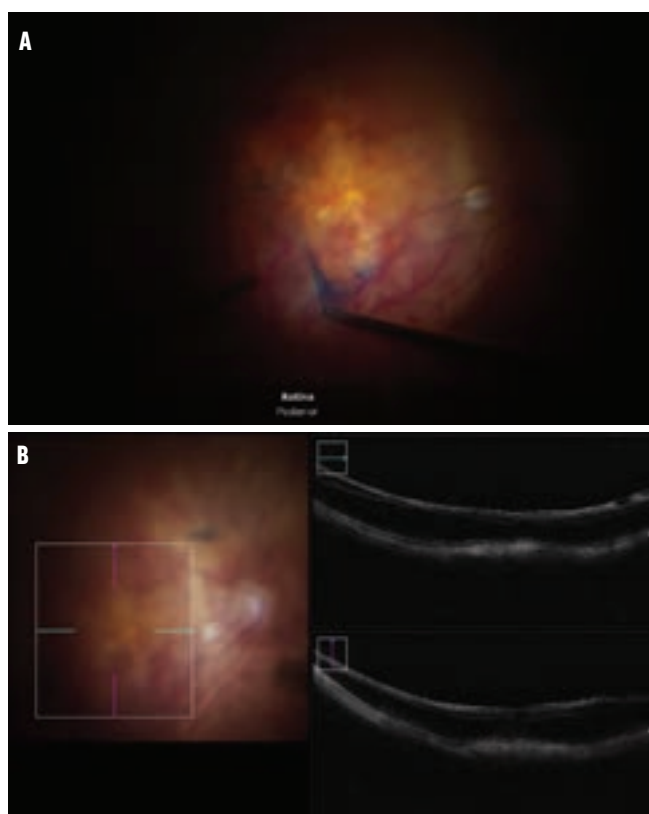


Figure 2. The patient underwent ILM peeling with brilliant blue G dye staining (A). Intraoperative OCT immediately after membrane peeling showed decreased retinal thickness (B).

THE CASE

A 72-year-old man was under routine follow-up for glaucoma and high myopia for 15 years. His regular OCT scans showed myopic changes without any schitic cavity for the first 10 years (Figure 1A). His VA was 20/20 in both eyes without symptoms. Subsequent OCT scans showed increased traction with the appearance of a schitic cavity (Figure 1B). However, his VA remained 20/20 without symptoms of distortion. Over 3 years of follow-up, the schitic cavity increased with symptoms of increased distortion over the last 6 months and decreased VA of 20/60 (Figure 1C and D).

As his visual acuity deteriorated along with worsening macular schisis, the patient underwent PPV with ILM and ERM peeling with myopic forceps after brilliant blue G dye staining (Video and Figure 2A). The post-ILM peeling intraoperative OCT showed an immediate decrease in retinal thickness (Figure 2B).

One month post-surgery, the left eye's VA had improved to 20/40, and the follow-up OCT showed complete resolution of the macular schisis and recovery of the foveal contour (Figure 3). Overall, the patient's symptoms had significantly improved, and he continued with routine follow-up as scheduled.

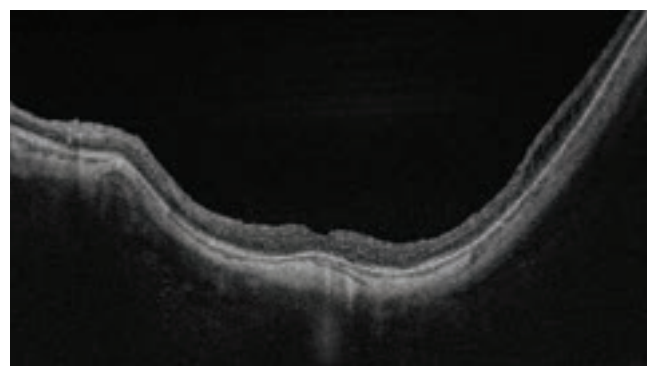


Figure 3. OCT after 1 month of follow-up shows decreased retinal thickness, significant improvement in the retinal schisis, no ERM, and complete resolution of the neurosensory detachment.

WATCH IT NOW



Video. Pars Plana Vitrectomy in Myopic Traction Maculopathy.

DISCUSSION

In this case, the patient's MTM started with mild inner retinal schisis without any deterioration of visual acuity or presence of any symptoms. A follow-up approach was considered for 4 years, at which time the patient presented with decreased vision and worsening of macular schisis with a small portion of sensory layer detachment.

Based on the MTM Staging System, this case was classified as stage 2 MTM with predominantly outer macular schisis and no sign of a lamellar macular hole or FTMH. As anteroposterior traction seemed a prominent cause for the schisis progression, an ab-interno approach was taken. Because OCT did not show a lamellar macular hole or FTMH, PPV and membrane peeling without gas tamponade was performed with overall good results.

In cases of challenging macular pathology with a thin retina, peeling the ERM and ILM with complementary intraocular instruments is critical in avoiding complications and encouraging better structural and visual outcomes. Choosing myopic forceps of a suitable length is crucial

(Continued on page 51)

OCULAR TOXICITY OF NEW-AGE CANCER THERAPIES



Because modern medications may induce immune-related ocular adverse events, a collaborative approach is important when caring for these patients.

BY RONAK SHAH, BS; ROBIN VORA, MD; AMAR PATEL, MD; AND YING QIAN, MD

The development of novel anticancer drugs has transformed the field of oncology.¹⁻³ The latest cancer therapies work in a variety of ways, many of which involve functional modification of the immune system with immune checkpoint inhibitors (CPIs), cancer vaccines, and v-Raf murine sarcoma viral oncogene homolog B1/mitogen-activated protein kinase (BRAF/MEK) inhibitors. Whether through stimulation of the body's native immune system to detect and clear cancer cells or manipulation of specific markers to decrease survival of cancer cells, such targeted therapies provide a revolutionary method of cancer clearance.

CPIs target certain proteins that act as checkpoints by allowing cancer cells to evade the immune response. The first CPI to receive FDA approval was ipilimumab (Yervoy, Bristol Meyers Squibb) in 2011 for metastatic melanoma.⁴ Since then, five other CPIs have been FDA-approved, including nivolumab (Opdivo, Bristol Meyers Squibb) and pembrolizumab (Keytruda, Merck) for non-small cell lung cancer.⁵ These advancements have broadened the number of potentially treatable cancers to include colon cancer, renal cell carcinoma, gastric cancer, head and neck squamous cell carcinoma, and Hodgkin lymphoma.⁶

Cancer vaccines are another type of immunotherapy designed to enhance the immune system's ability to recognize and destroy cancer cells. These vaccines fall into three broad categories: cell-, peptide-, and nucleic acid-based. While cancer vaccines are not typically used as monotherapy, combination therapy with conventional chemotherapy and radiation has demonstrated increased efficacy.⁷

BRAF and MEK inhibitors form another promising class of chemotherapy.⁸ They interfere with the mitogen-activated

protein kinase signaling pathway, thus limiting cell proliferation, differentiation, and survival. MEK inhibitors administered independently have been approved for use in various cancers.⁹ The combined use of BRAF and MEK inhibitors has been further shown to improve clinical efficacy and delay the development of drug resistance.¹⁰ For that reason, it has become the preferred treatment modality for melanoma containing the BRAFV600 mutation present in almost half of all melanomas.^{11,12}

WATCH FOR SIDE EFFECTS

Despite the promising efficacy of these new cancer therapies, autoimmune side effects involving numerous organs, including the eyes, have been described.^{4,13,14} The extensive vascular and neural networking within the eye increases its susceptibility to these immune adverse events. Furthermore, the high metabolic activity of the retina makes it particularly vulnerable to toxicity from cancer immunotherapies.¹³

Immune CPIs

Immune-related ophthalmic adverse events have been shown to involve intraocular, extraocular, and periorbital structures.¹⁵ Ocular adverse effects typically present within 6 months of initial exposure to immunotherapy, although in some cases, they may become apparent within weeks.¹⁵ Generally, inflammation is at the core of these events and can involve any structure of the eye and orbit, including the uvea, retina, optic nerve, and extraocular muscles. Documented immune-related adverse events of CPIs include anterior uveitis (52%), Vogt-Koyanagi Harada (VKH) syndrome/serous retinal detachment/panuveitis (23%), optic neuritis (13%), and corneal edema (3.2%).¹⁵

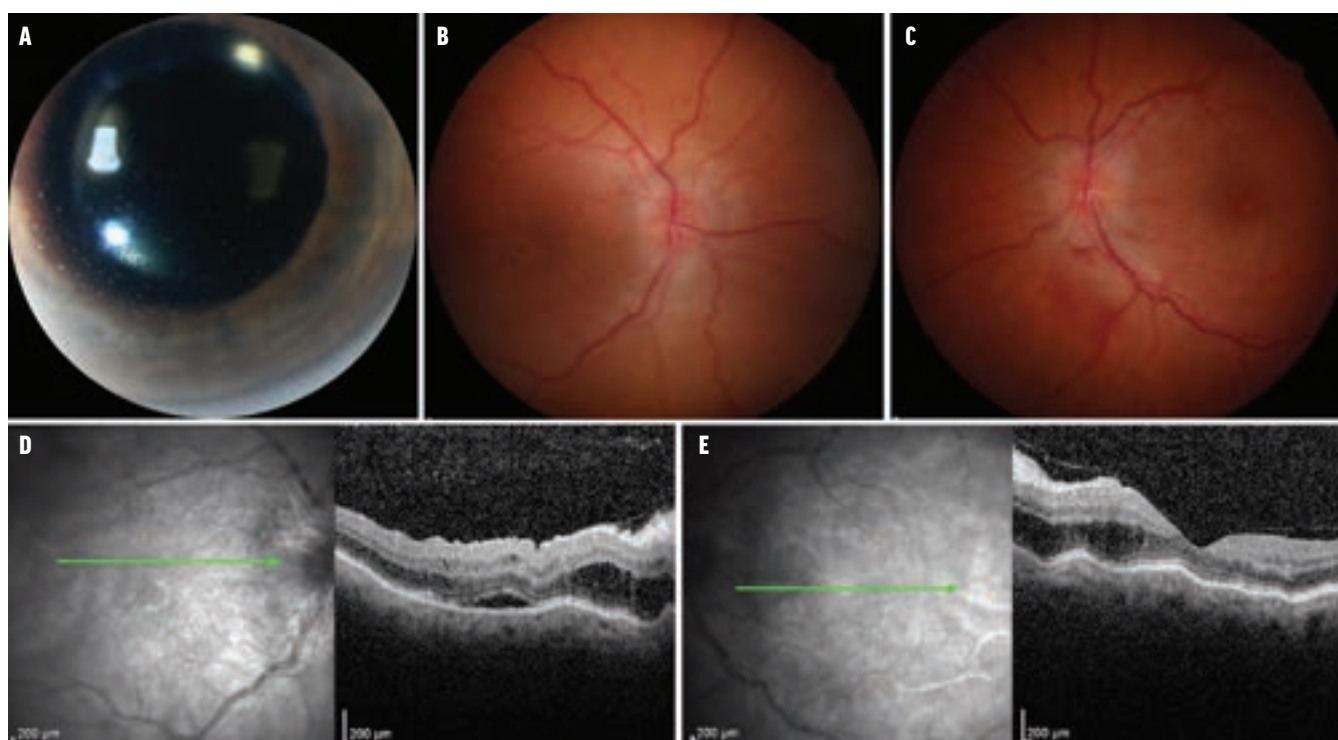


Figure 1. A 68-year-old White woman with metastatic renal cell carcinoma developed VKH-like panuveitis 6 weeks after starting nivolumab treatment (A). Keratic precipitates with panuveitis were noted on color fundus photography (B, C). Fundoscopy also demonstrated bilateral optic nerve edema, and OCT displayed VKH-like serous retinal detachments with shallow fluid accumulation and choroidal elevation and thickening in each eye (D, E).

While the relationship between such events and CPIs is not completely understood, it is believed that CPIs disrupt immune regulation within the eye. There also appears to be a relationship between ocular side effects and specific CPIs, with ipilimumab and nivolumab being the most frequently cited suspects.^{4,15} Finally, combination therapy seems to lead to more severe immune-related adverse events.⁶

BRAF/MEK Inhibitors and Cancer Vaccines

BRAF and MEK inhibitors can also induce prominent ocular side effects. BRAF inhibitors, such as dabrafenib (Tafinlar, Novartis) and vemurafenib (Zelboraf, Genentech/Roche), may lead to dry eye, conjunctivitis, uveitis, central serous-like chorioretinopathy, and syndromes mimicking VKH. MEK inhibitors, such as trametinib (Mekinist, Novartis), cobimetinib (Cotellic, Genentech/Roche), and binimetinib (Mektovi, Pfizer), are associated with similar adverse events as BRAF inhibitors and have also been linked to retinal vein occlusion, intraretinal fluid accumulation, retinal pigment epithelium toxicity, ischemic optic neuropathy, metamorphopsia, and altered color perception.¹³

There are several suggested mechanisms by which autoimmune ophthalmic side effects arise with use of these small-molecule inhibitors: 1) crossing the blood-retinal barrier and inciting an autoimmune response¹⁶; 2) apoptosis of cancer cells with subsequent stimulation of T lymphocytes, leading

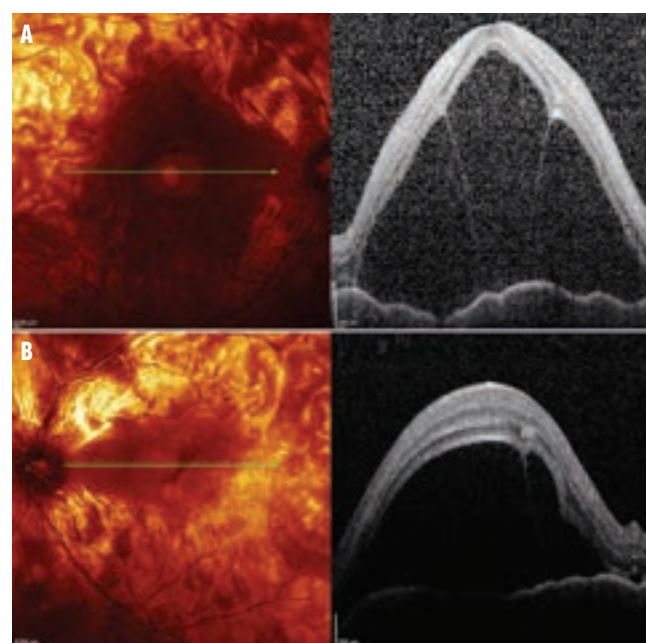
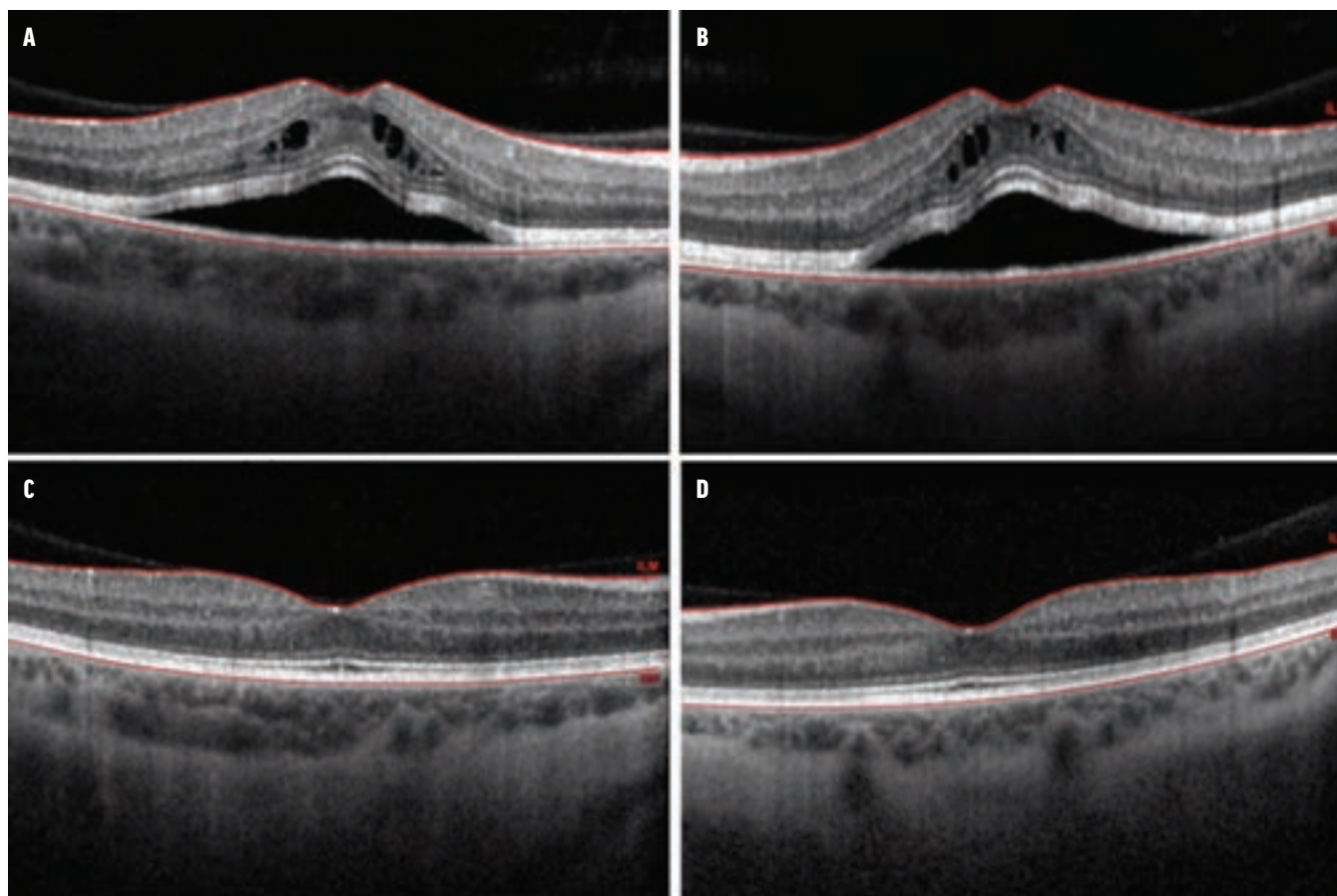


Figure 2. A 62-year-old White man with metastatic melanoma developed findings 2 weeks after starting nivolumab. Serous retinal detachment was noted in the right (A) and left (B) eye.

to dissemination of epitopes and induced autoimmunity¹⁶; and 3) increasing the risk of ocular toxicity with combined use of BRAF and MEK inhibitors.¹⁷



Images courtesy of Diem Bu, MD

Figure 3. A 47-year-old White woman with a history of metastatic melanoma was on oral 960 mg vemurafenib twice per day and oral 60 mg cobimetinib daily for 2 days with onset of blurry vision and reports of seeing black circles. Her UCVA was 20/25 OD and 20/25 OS. OCT demonstrated subretinal fluid and intraretinal fluid in the macula in the right (A) and left (B) eye. Resolution of fluid in the right (C) and left (D) eye occurred 1 month after cessation of vemurafenib and cobimetinib treatment.

Cancer vaccines have not yet been linked to significant retinal side effects; however, given the experience of patients undergoing other immunotherapies, it is rational to consider the possibility of immune-related adverse ocular events.

DIAGNOSIS AND TREATMENT OF TOXIC OCULAR MANIFESTATIONS

Diagnosis of immune-related ocular adverse events requires careful ophthalmic examination and review of multimodal imaging (Figures 1-3).^{4,14,18} In managing patients undergoing cancer treatment, clinicians must always consider each possible diagnosis, as these patients are at increased risk for infectious and metastatic disease. Slit-lamp examination can demonstrate inflammatory cells in the anterior or vitreous chamber. Fundus examination can reveal optic nerve involvement, retinal vascular disease, sensory detachments, or single or multiple yellowish areas of retinal elevation, all of which may be symmetrical. OCT is a necessary adjunct to confirm the presence and location of fluid and track disease progression over time and after treatment; choroidal thickening may also be visualized via OCT.

Fluorescein angiography may fail to demonstrate a leak or reveal any vascular disturbance, as in the case of MEK-associated retinopathy. Alternatively, it may reveal multiple leaks, mimicking VKH in patients with CPI-associated retinopathy.

Patients starting anticancer treatments should be screened at baseline and then approximately 1 to 2 months after initiating therapy. If MEK inhibitor-associated retinopathy develops, it often resolves on its own without treatment. Steroid treatment (either topical, periocular, intravitreal, or oral) is the standard of care for patients experiencing significant adverse events and can often be administered concomitantly with cancer therapy.⁴

Discontinuation of the cancer agent may not be required if the ocular side effects are mild and easily treated. However, if ophthalmic side effects persist despite treatment and are vision-threatening, it is prudent to discuss with the patient's oncologist the possibility of discontinuation of the cancer immunotherapy and consider the addition of other immunosuppressants, such as intravenous immunoglobulin.¹³

COORDINATED CARE

Although ocular immune-related adverse events are relatively rare side effects of newer cancer therapies, these patients should undergo baseline and regular ophthalmic examination. Close communication with oncology is recommended, with the overarching goal of extended disease-free survival with minimal ocular morbidity. ■

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(Continued from page 47)

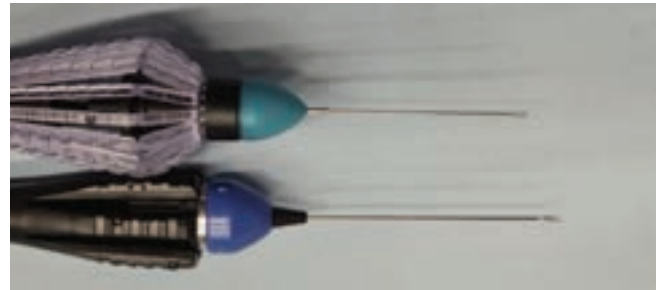


Figure 4. Myopic cutting forceps (Pinnacle 360, Bausch + Lomb) that have a longer shaft (Bottom) than routine ILM forceps (Top) were used in this procedure.

in eyes with a long axial length. Myopic forceps provide additional benefit over standard forceps with an additional 5 mm of length (37 mm vs 32 mm), allowing easier access to the membranes in eyes with a posterior staphyloma (Figure 4). The Pythagorean theorem helps estimate the length of the forceps needed in myopic eyes.¹¹ Complete resolution of the schitic cavity may take 6 to 9 months.¹² With the correct choice of surgery, suitable instruments, and an uncomplicated procedure, these complex cases can achieve successful outcomes. ■

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CODING ADVISOR

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FIVE RETINA CODING UPDATES FOR 2024



Enter the new year with a better understanding of what to expect in your billing department.

BY JOY WOODKE, COE, OCS, OCSR

Each year, there are coding changes that impact the retina practice. Along with identifying these updates, it is crucial to ensure practice resources are revised accordingly and the entire team is on the same page. Here, I highlight five changes you need to be ready to handle this year.

1. NEW CATEGORY I CPT CODE

New to CPT in 2024 is Category I code, 67516, suprachoroidal space injection of pharmacologic agent (separate procedure), which replaced the deleted Category III code, 0465T.

For example, an injection of triamcinolone acetonide (Xipere, Bausch + Lomb and Clearside Biomedical) into the suprachoroidal space is performed in the left eye, with 4 mg/0.1 mL injected and 32 mg/0.8 mL discarded. The correct coding for this case is as follows:

- 67516–LT
- J3299, 4 units
- J3299–JW, 32 units

2. NEW CATEGORY III CODE

Effective July 1, 2023, a new Category III code was added, 0810T, subretinal injection of a pharmacologic agent, including vitrectomy and one or more retinotomies.

For example, a subretinal injection of voretigene neparvovec-rzyl (Luxturna, Spark Therapeutics), pars plana vitrectomy, and retinotomy is performed in the right eye at

an ambulatory surgery center. The physician would report 0810T, and the facility would bill the facility fee and drug.

3. NEW DRUG TREATMENTS

A permanent HCPCS code, J2781, was assigned for 1 mg pegcetacoplan intravitreal injection (Syfovre, Apellis Pharmaceuticals), effective October 1, 2023, for the treatment of geographic atrophy. This new code should be reported in both the office and facility setting, as the previous facility code, C9151, was deleted as of September 30, 2023.

For example, an intravitreal injection of 15 mg/0.1 mL pegcetacoplan is performed in the right eye. Residual medication (overfill) less than 1 unit was discarded. The correct coding for this case is as follows:

- 67028–RT
- J2781–JZ, 15 units

Another drug treatment for geographic atrophy was FDA approved last summer, avacincaptad pegol intravitreal solution (Izervay, Iveric Bio/Astellas). As a new drug treatment, it should be reported with a not otherwise classified (NOC) HCPCS until a permanent code is assigned.

For example, an intravitreal injection of avacincaptad pegol is performed in the left eye. Residual medication (overfill) less than 1 unit was discarded. The correct coding in this case is as follows:

- 67028–LT
- J3490–JZ, 1 unit

TABLE. NEW AND ESTABLISHED OFFICE VISIT CODES AND TIMING PER CODE			
E/M New Patient - Office	Meet or Exceed (minutes)	E/M Established Patient - Office	Meet or Exceed (minutes)
99202	15	99212	10
99203	30	99213	20
99204	45	99214	30
99205	60	99215	40

- Report in item 19 of the CMS-1500 the method of administration, medication name, and dosage as intravitreal injection of 2 mg/0.1 mL avacincaptad pegol

Also new to the retina practice is the recently FDA approved 8 mg aflibercept (Eylea HD, Regeneron). This new drug should also be billed with an NOC code until the permanent code is assigned in the near future. For updates to all new retina drugs, visit aao.org/retinapm.

4. ICD-10-CM CODES FOR SICKLE CELL RETINOPATHY

Both nonproliferative and proliferative sickle cell retinopathy now have specific ICD-10-CM codes to report these conditions. Previously, this disease was billed with unspecified codes. Effective October 1, 2023, report with the following codes:

- H36.811: Nonproliferative sickle cell retinopathy, right eye
- H36.812: Nonproliferative sickle cell retinopathy, left eye
- H36.813: Nonproliferative sickle cell retinopathy, bilateral
- H36.821: Proliferative sickle cell retinopathy, right eye
- H36.822: Proliferative sickle cell retinopathy, left eye
- H36.823: Proliferative sickle cell retinopathy, bilateral

For example, an intravitreal injection of 1.25 mg/0.05 mL bevacizumab (Avastin, Genentech/Roche) is performed in the right eye of a patient with nonproliferative sickle cell retinopathy on Medicare Part B. The Medicare Administrative Contractor for this patient is Noridian, which updated its local coverage article (LCA) A53008 effective October 1, 2023, with the new ICD-10-CM codes, payable for intravitreal injections. The correct coding for this case is as follows:

- 67028-RT
- *J7999-JZ, 1 unit
- Report in item 19 of the CMS-1500 the method of administration, medication name, and dosage as intravitreal injection of 1.25 mg/0.05 mL bevacizumab
- ICD-10-CM code linked to both 67028 and J7999, H36.811

WITH NEW DRUG TREATMENTS ON THE HORIZON AND PAYER POLICIES CONSTANTLY BEING UPDATED, CLINICIANS MUST STAY VIGILANT WITH THEIR CODING KNOWLEDGE.

*Note: HCPCS code J7999 should be reported for bevacizumab for ophthalmic use per Noridian's LCA. For other payers, confirm the appropriate HCPCS code per their unique policies.

5. MODIFICATION OF E/M CODE DESCRIPTORS

A slight update has been made to the E/M office visit family of codes related to the criteria when coding based on total physician time on the date of the encounter (Table). For 2024, the amount of time for each code must meet or exceed the designated amount. Previously, there was a range. This revision is meant to streamline the selection process.

For example, the descriptor for CPT code 99203 is "office or other outpatient visit for the evaluation and management of a new patient, which requires a medically appropriate history and/or examination and low level of medical decision making." From 2021 to 2023, when using time for code selection, 30 to 44 minutes of total time must have been spent on the date of the encounter. In 2024, when using total time on the date of the encounter for code selection, 30 minutes must be met or exceeded.

STAY CONNECTED

With new drug treatments on the horizon and payer policies constantly being updated, clinicians must stay vigilant with their coding knowledge. Access current AAO resources on the Retina Practice Management and Coding webpage at www.aao.org/practice-management/coding/retina. ■

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Leanne M. Clevenger, MD

RISING STARS IN RETINA

Get to know outstanding
retina fellows from
the class of 2024.

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Retina Today: When did you first know that you wanted to become a retina specialist?

I was introduced to retina during my residency at the Cole Eye Institute at the Cleveland Clinic. I was amazed by the complex pathology I saw in clinic and the unique surgical decision making that retina requires.

RT: Who do you look to as mentors in the field?

I am extremely grateful to my mentors for their guidance and support throughout my training. Our fellowship program director, Sunil K. Srivastava, MD, is an outstanding clinician and all-around phenomenal person who dedicates himself to ensuring each of his trainees is fulfilled both personally and professionally.

I cannot express enough thanks for the incredible training and advice I've received from Sumit Sharma, MD; Katherine E. Talcott, MD; Alex Yuan, MD, PhD; Aleksandra Rachitskaya, MD; Peter K. Kaiser, MD; and each of the retina faculty at the Cole Eye Institute, including our exceptional chairman Daniel F. Martin, MD. I could write pages on the many other mentors I've been lucky to learn from.

RT: What has been one of the most memorable experiences of your fellowship thus far?

I remember vividly my first opportunity, as a first-year fellow, to teach a resident during a scleral buckle procedure while on call with Dr. Talcott. I found so much joy in introducing fundamental concepts to the resident and watching their hesitation turn to caution and then excitement. The experience solidified my career choice in academic ophthalmology.

RT: What are you hoping to accomplish once you are in practice?

I look forward to starting my career as a vitreoretinal surgeon at the University of Kentucky in 2024. I hope to encourage enthusiasm for retina in my own residents and fellows. It's my goal to give them the confidence and skillset necessary to tackle difficult pathology and the humility to recognize when to seek advice. I look forward to staying involved at the society level and hope to advance the field through involvement in clinical trials.

FIRST CAREER MILESTONE

Dr. Clevenger will be joining the University of Kentucky as an assistant professor of Ophthalmology.

RT: What advice can you offer to residents who are considering retina?

Approach every patient with an open mind, as even the most seemingly routine case has something to teach you. Say "yes" to new projects, and follow through with them. Value your relationships with peers and mentors, and trust your inner circle when the path forward seems unclear. ■

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AI IN MEDICINE FOR THE RETINA FELLOW



Two experts in the field weigh in on this hot topic.

BY NIKHIL K. BOMMAKANTI, MD

The release of the AI chatbot ChatGPT (OpenAI) in November 2022 led to a renewed interest in the potential applications of AI in medicine.¹ As of December 16, 2023, a PubMed search for “ChatGPT,” “large-language model,” and “AI chatbot” yielded 1,942, 330, and 106 results, respectively, likely because chatbots have the potential to assist in several aspects of health care, including patient education, medical training, and administrative tasks, such as generating clinical notes and summarizing treatment courses.²⁻⁵

As fellows embarking on a career in one of the most dynamic, exciting, and technologically advanced fields in medicine, we would benefit from having a basic understanding of AI and how it may affect the field of retina. I interviewed two experts on this topic: J. Peter Campbell, MD, MPH, an associate professor of Ophthalmology at the Oregon Health & Science University School of Medicine in Portland, and Daniel Shu Wei Ting, MBBS (Hons), M Med (Ophth), FAMS, PhD (UWA), an associate professor and senior consultant at the Singapore National Eye Center in Singapore. Below are their thoughts.

NIKHIL K. BOMMAKANTI, MD: WHAT SHOULD RETINA FELLOWS KNOW ABOUT AI?

Dr. Campbell: AI is a broad topic. It includes, but is not limited to, applications in essentially all imaging devices, electronic health record analytics, patient scheduling, and beyond. It's important to think about each unique AI application based on its indication for use, such as autonomous screening of diabetic retinopathy (DR), detection of Parkinson disease on OCT, and automated quantification of fluid in patients with diabetic macular edema. As a retina specialist, just like with any new imaging modality, you need to take the time to understand what

AI can and can't do and be prepared to leverage it as a tool whenever appropriate.

DR. BOMMAKANTI: WHAT ARE SOME WAYS THAT AI IMPROVES PATIENT CARE IN RETINA?

Dr. Ting: Deep-learning algorithms can be used with color fundus photographs to screen for conditions such as DR, AMD, retinopathy of prematurity, and inherited retinal degeneration. OCT segmentation can also help streamline the clinical workflow.

Dr. Campbell: The most useful applications will involve assessing disease severity in ophthalmic imaging, such as measuring subretinal and intraretinal fluid in AMD.

There are, of course, many potential “moonshot” applications, such as predicting future systemic disease development from OCT scans. There are also numerous potential ways, when incorporated into the health care system, that AI could improve the efficiency of retina clinic scheduling (such as identifying urgent referrals) that we have yet to optimize. In addition, figuring out how to develop health care systems that can leverage the advantages of autonomous AI could be a game-changer in terms of secondary prevention of retina diseases, such as AMD and DR.

DR. BOMMAKANTI: WHAT ARE SOME WAYS THAT AI CAN IMPROVE OUR DAY-TO-DAY WORKFLOW?

Dr. Campbell: If we ignored reimbursement issues, all of the many inefficiencies built into our system could be avoided. AI is a tool that can probably do some of the things that we typically do every day—and do it better than we can. We need to focus on the uniquely human aspects of patient care and use AI to help us be better at what we do.

AS A RETINA SPECIALIST, JUST LIKE WITH ANY NEW IMAGING MODALITY, YOU NEED TO UNDERSTAND WHAT AI CAN AND CAN'T DO AND BE PREPARED TO LEVERAGE IT AS A TOOL WHENEVER APPROPRIATE.

Dr. Ting: Large-language models could aid with patient counselling and education. For example, these models could summarize complex notes and help draft letters to general practitioners or other members of a patient's health care team.

DR. BOMMAKANTI: WHAT ARE SOME OF THE PITFALLS THAT WE SHOULD KNOW ABOUT?

Dr. Campbell: I remember when OCT angiography was new, and we as a field published hundreds of papers with new findings, many of which we now realize were wrong based on image artifacts and other issues. AI has several limitations that are important to understand as well.

Dr. Ting: AI's limitations include bias, which may lead to worse or inaccurate performance for certain populations of people, and unclear generalizability, meaning that models may not perform as well across diverse populations or conditions. Decisions provided by AI should be interpretable by clinicians who must be able to trust and effectively use the insights. It's important that AI respects patient autonomy and privacy and does not exacerbate health care disparities.

There are also other practical considerations, such as how AI can be integrated into clinical workflows and how it will be reimbursed.

DR. BOMMAKANTI: WHAT ARE SOME MISUNDERSTANDINGS THAT DOCTORS HAVE ABOUT AI? WHAT ARE SOME BLIND SPOTS THAT ENGINEERS HAVE ABOUT MEDICINE?

Dr. Ting: When prompted with these questions, here is what ChatGPT had to say: "Doctors may misunderstand AI as a technology that can fully replace human judgment, not appreciating that AI is designed to augment rather than replace their expertise. They might also underestimate the complexity of AI's decision-making process, expecting it to be infallible, or overestimate the readiness of AI to handle nuanced clinical scenarios.

"Conversely, engineers may have blind spots regarding the variability and complexity of medicine. They might not fully grasp the importance of clinical context and the

subtleties of patient interactions, which can be critical for diagnosis and treatment. Additionally, engineers may not always appreciate the regulatory and ethical considerations unique to health care, such as patient consent and the consequences of errors."

DR. BOMMAKANTI: HOW CAN RETINA FELLOWS WORK EFFECTIVELY WITH COMPUTER SCIENTISTS AND ENGINEERS?

Dr. Ting: It's important to be patient, collaborative, and clearly describe the intended clinical uses of AI. Retina specialists can assist computer scientists and engineers by providing insight into patients' perspectives and by troubleshooting the challenges of real-world adoption to make deployment as seamless as possible.

DR. BOMMAKANTI: ANY LAST THOUGHTS ABOUT AI, RETINA, AND THE FUTURE?

Dr. Ting: I'm excited about how AI could be used in medical imaging analysis, drug discovery, and personalized health care.

Dr. Campbell: Remember that AI is only the latest hot thing. It will soon be old news when we have the next thing, and we will soon take AI—and what it can do for us—for granted, exactly like we do now with OCT. Nonetheless, I'm excited to see how this will play out and what's next for retina. ■

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intraretinal hyperreflective dots, bright plaques on top of the Bruch membrane-RPE complex, outer retinal tubulations, macular hole, cystoid macular edema, macular neovascular membrane, and subfoveal neurosensory detachment.^{3,4}

Choroidal caverns were first defined by Querques et al in patients with geographic atrophy.⁵ These are small lesions within the choroid that appear as circular areas of low reflectivity, mainly located in the Sattler and Haller layers of the choroid on OCT sections. Histologic studies have demonstrated that choroidal caverns are lipid globules and may represent a common normal physiologic lipid depot for photoreceptor metabolism.⁶

Choroidal caverns have been reported in eyes with pachychoroid spectrum disease, Stargardt disease, Best vitelliform dystrophy, rod-cone dystrophy, and choroidal osteoma, as well as in normal eyes.^{7,8} To the best of our knowledge, this is the first reported case of choroidal caverns in the presence of BCD. ■

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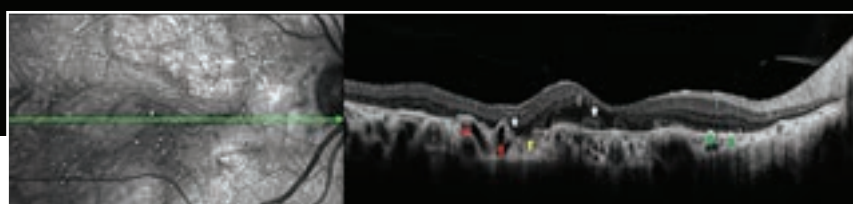
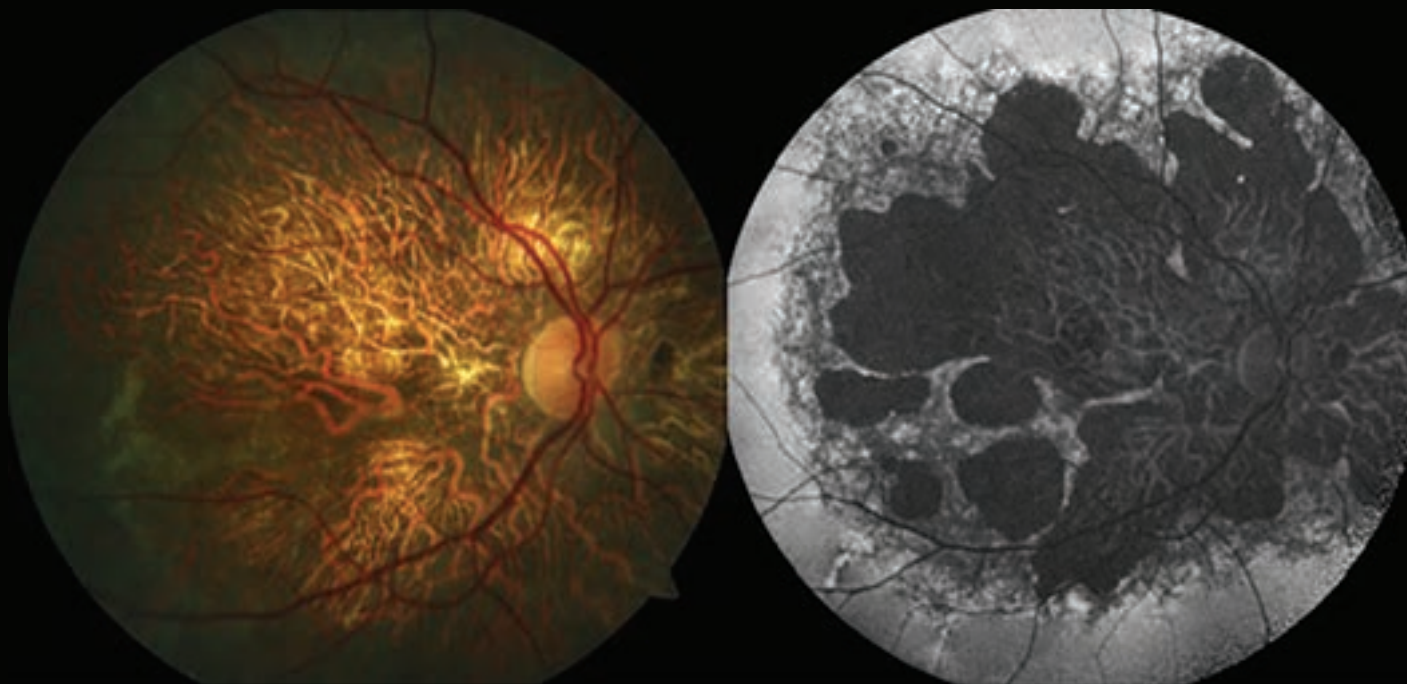
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BIETTI CRYSTALLINE DYSTROPHY WITH CHOROIDAL CAVERNS



Is this a possible sign of a rare genetic ocular condition?

BY MUSTAFA KAYABASI, MD, AND ALI OSMAN SAATCI, MD

A 54-year-old otherwise healthy woman with a diagnosis of Bietti crystalline dystrophy (BCD) has been followed by our clinic for 15 years. In her last routine visit, her BCVA was 20/40 OD. The anterior segment examination was unremarkable, and no corneal crystals were found, although we noted chorioretinal atrophy and a few retinal crystalline deposits at the posterior pole of her right eye (Figure).

On OCT (Inset), we noticed the presence of choroidal caverns (red arrows), intraretinal hyperreflective dots (white arrows), bright plaques on top of the Bruch

membrane-retinal pigment epithelium (RPE) complex (green arrows), mild epiretinal membrane, incomplete posterior vitreous detachment, and parafoveal choroidal excavation (yellow arrow).

AN UNEXPECTED FINDING WITH BCD

BCD is a rare, genetically determined chorioretinal dystrophy characterized by intraretinal crystalline deposits and varying degrees of progressive chorioretinal atrophy, commencing at the posterior pole. In some cases, there may also be concomitant corneal crystals.^{1,2} OCT findings include

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 Periocular Infections

SYFOVRE is contraindicated in patients with ocular or periocular 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.

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. Perfusion 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 839 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

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

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 ischemic 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.

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

Females: 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.

Pediatric Use

The safety and effectiveness of SYFOVRE in pediatric patients have not been established.

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 neovascular AMD, endophthalmitis, and retinal detachments. 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.

Manufactured for:
Apellis Pharmaceuticals, Inc.
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Waltham, MA 02451

SYF-PI-17Feb2023-1.0

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SYFOVRE[®]

(pegcetacoplan injection)
15 mg / 0.1 mL

GA unravels so much
**SAVE RETINAL TISSUE
BY SLOWING
PROGRESSION¹⁻³**

**SYFOVRE achieved continuous reductions
in mean lesion growth rate* vs sham
pooled from baseline to Month 24^{1,4}**

Monthly	Every Other Month (EOM)
OAKS trial (mm ²): (3.11 vs 3.98) 22%	OAKS trial (mm ²): (3.26 vs 3.98) 18%
DERBY trial (mm ²): (3.28 vs 4.00) 18%	DERBY trial (mm ²): (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 24.¹

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 18.¹

GA=geographic atrophy;
SE=standard error.



Explore the
long-term data

The CMS-assigned permanent J-code for
SYFOVRE is J2781—effective 10/1/23¹

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

- 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 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.

• 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. Perfusion of the optic nerve head should be monitored following the injection and managed as needed.

ADVERSE REACTIONS

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

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

Trial Design: SYFOVRE safety and efficacy were assessed in OAKS (N=637) and DERBY (N=621), multi-center, 24-month, Phase 3, randomized, double-masked trials. Patients with GA (atrophic nonexudative age-related macular degeneration), with or without subfoveal involvement, secondary to AMD were randomly assigned (2:2:1:1) to receive 15 mg/0.1 mL intravitreal SYFOVRE monthly, SYFOVRE EOM, sham monthly, or sham EOM for 24 months. Change from baseline in the total area of GA lesions in the study eye (mm²) was measured by fundus autofluorescence (FAF).^{1,4}

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