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RETINA SPECIALIST

VOL. 9, NO. 3 · MAY/JUNE 2025

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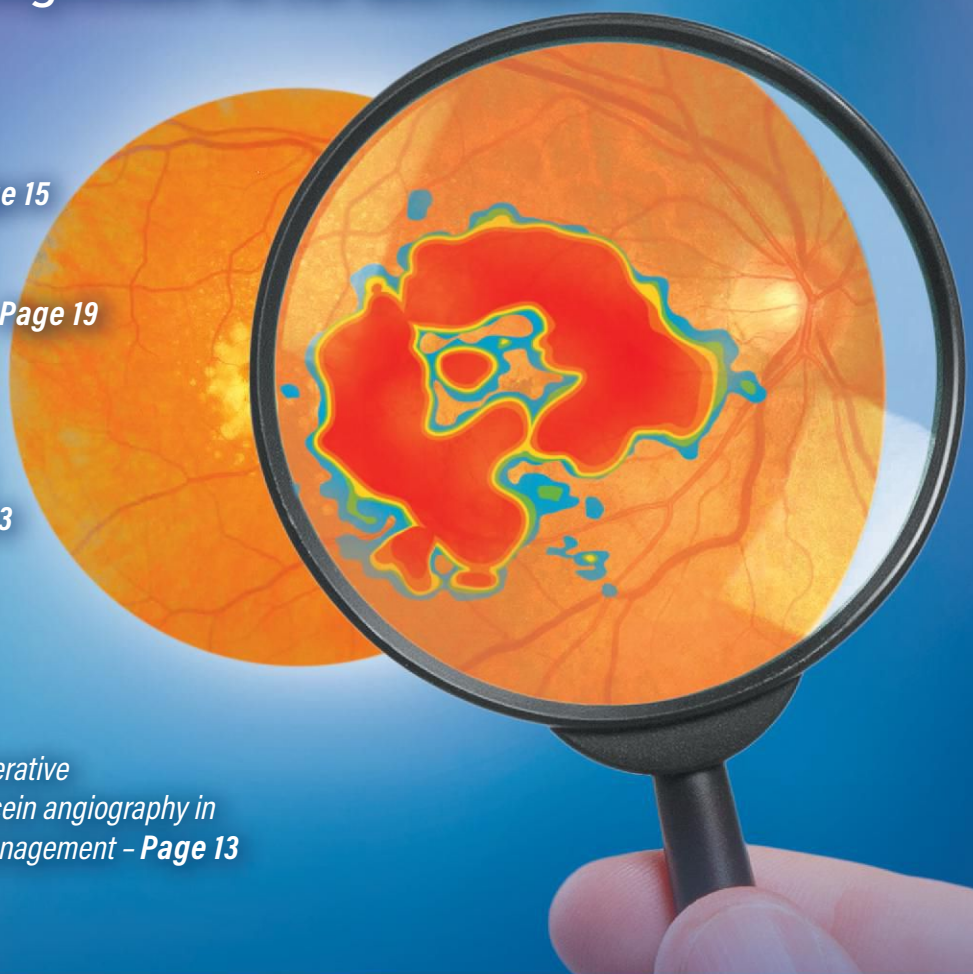
New Insights in Imaging

How OCT is helping improve the management of DR and AMD.



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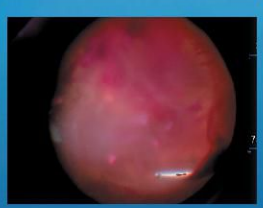
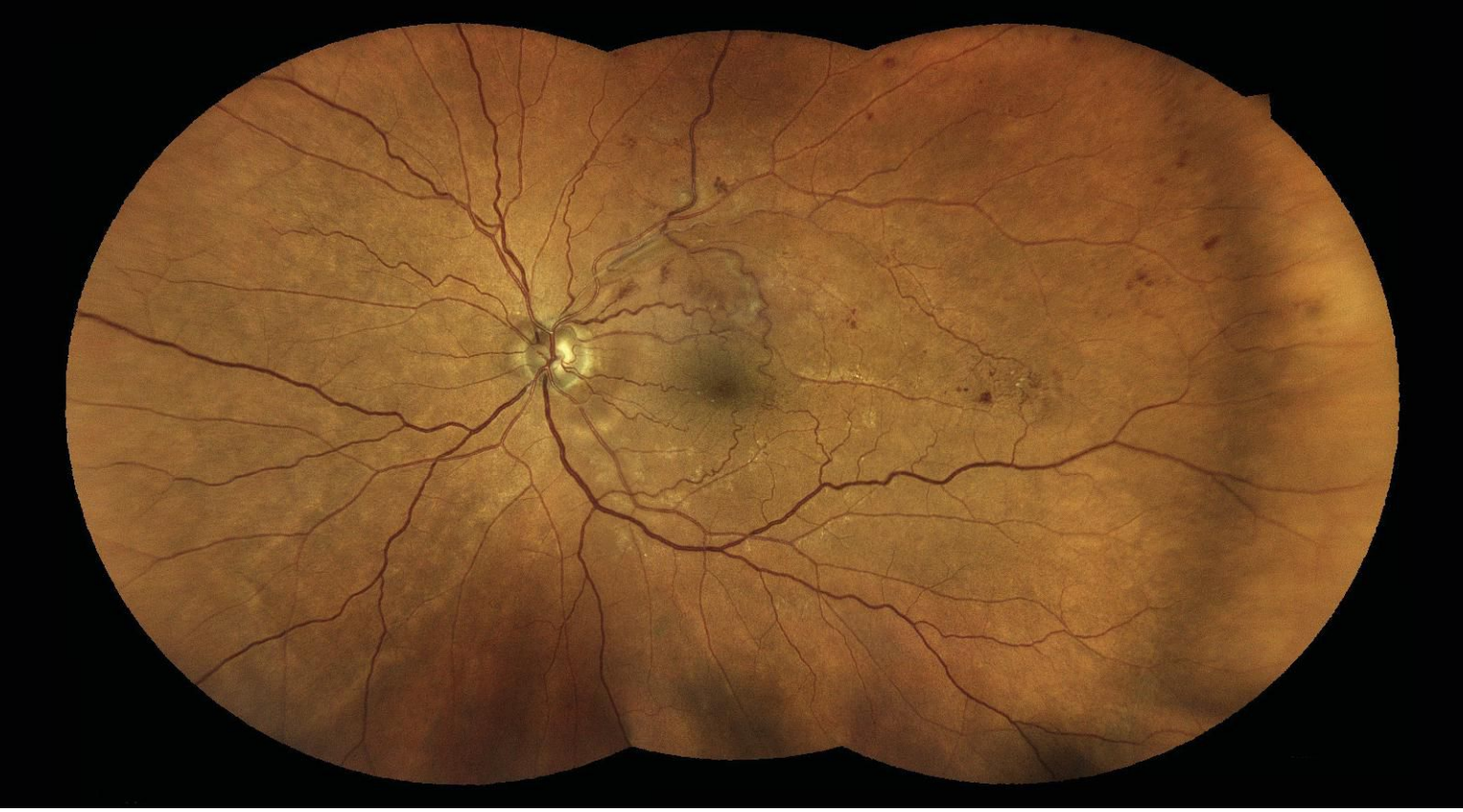


- *Intraoperative fluorescein angiography in PDR management* – ***Page 13***



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

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EDITORIAL

By Jason Hsu, MD

The Inner Game of Vitreoretinal Surgery

As spring turns into summer, graduation ceremonies start sprouting up everywhere. For those who work with trainees, it's another reminder of time marching on as the next generation heads into the subsequent phase of their careers. While this is a joyful period for the graduates, it can be a time of trepidation for the attendings as a new class comes in and the training cycle resets.

I recently had the honor of being guest faculty for the Duke fellows' advanced vitreous surgery course. It was a wonderful experience with interactive, hands-on opportunities for fellows and residents to learn different techniques from a variety of mentors. One topic that came up in conversation was how to prepare for the OR, especially when first learning to operate on the retina. We all have witnessed tremors during membrane peels, especially in the beginning. This brings up the question: What's the best way to become a competent surgeon? Many believe that more practice is the key ingredient, and certainly repetition is an important element of mastering any new skill.

Ultimately, I believe a large part of surgical skill boils down to state of mind. Practice may help by diminishing the anxiety and self-doubt that lead to greater difficulty. One of my mentors in fellowship would always remind us to drop our shoulders and relax our hands as we operated since the vice-like grips on instruments would hinder dexterity. I often add to that by encouraging relaxation techniques during procedures with steady breathing and calming your mind. One of my favorite books is *The Inner Game of Tennis* by W. Timothy Gallwey, which has great advice that extends to all aspects of life. One theme is quieting the inner voice that is commenting on our every win and mistake rather than trusting our subconscious mind to perform at our best. While it is certainly important to recognize mistakes, it is counterproductive to berate ourselves as that only increases the anxiety level and chances of making even more mistakes.

As the academic year comes to an end, I wish to congratulate the graduating fellows and wish them all the very best as they start their careers in this great field. I'm also excited to meet the incoming class and pass along my bits of wisdom from over the years. Let's continue to inspire one another and keep paying it forward. RS

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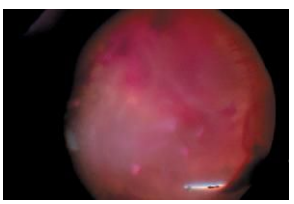
FEATURES

DEPARTMENTS



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- *Infections: Increased susceptibility to new infection and increased risk of exacerbation, dissemination, or reactivation of latent infection.*
- *Elevated blood pressure, salt and water retention, and hypokalemia: Monitor blood pressure and sodium, potassium serum levels.*
- *GI perforation: Increased risk in patients with certain GI disorders.*
- *Behavioral and mood disturbances: May include euphoria, insomnia, mood swings, personality changes, severe depression, and psychosis.*
- *Decreases in bone density: Monitor bone density in patients receiving long term corticosteroid therapy.*
- *Live or live attenuated vaccines: Do not administer to patients receiving immunosuppressive doses of corticosteroids.*
- *Negative effects on growth and development: Monitor pediatric patients on long-term corticosteroid therapy.*
- *Use in pregnancy: Fetal harm can occur with first trimester use.*
- *Weight gain: May cause increased appetite.*

Adverse Reactions

- Based on a review of the available literature, the most commonly reported adverse events following ocular administration of triamcinolone acetonide were elevated intraocular pressure and cataract progression. These events have been reported to occur in 20-60% of patients.
- Less common reactions occurring in up to 2% of patients include: endophthalmitis (infectious and non-infectious), hypopyon, injection site reactions (described as blurring and transient discomfort), glaucoma, vitreous floaters, detachment of retinal pigment epithelium, optic disc vascular disorder, eye inflammation, conjunctival hemorrhage and visual acuity reduced. Cases of exophthalmos have also been reported.

Drug Interactions

- *Anticoagulant Agents* – Corticosteroids may enhance or diminish the anticoagulant effect of anticoagulant agents. Coagulation indices should be monitored.
- *Antidiabetic Agents* – Corticosteroids may increase blood glucose concentrations. Dose adjustments of antidiabetic agents may be required.
- *CYP 3A4 Inducers and Inhibitors* – CYP 3A4 inducers and inhibitors may respectively increase or decrease clearance of corticosteroids, necessitating dose adjustment.
- *NSAIDs* – Concomitant use of NSAIDS, including aspirin and salicylates, with a corticosteroid may increase the risk of GI side effects.

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References: 1. TRIESENCE Prescribing Information. Harrow IP, LLC; 2023. **2.** Maia M, Farah ME, Belfort RN, *et al* Effects of intravitreal triamcinolone acetonide injection with and without preservative. *British Journal of Ophthalmology* 2007;91:1122-1124. **3.** Dyer, David Md; Callanan, David Md; Clinical Evaluation Of The Safety And Efficacy Of Preservative-Free Triamcinolone (Triesence® [Triamcinolone Acetonide Injectable Suspension] 40 Mg/Ml) For Visualization During Pars Plana Vitrectomy. Retina 29(1):P 38-45, January 2009. | Doi: 10.1097/Iae.0b013e318188c6e2 **4.** Data on file.

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- Initial recommended dose for all indications except visualization: 4 mg (100 microliters of 40 mg/mL suspension) with subsequent dosage as needed over the course of treatment.
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WARNINGS AND PRECAUTIONS

- TRIESENCE® is a suspension; it should not be administered intravenously.
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- Hypothalamic-pituitary-adrenal (HPA) axis suppression, Cushing's syndrome, and hyperglycemia: Monitor patients for these conditions and taper doses gradually.
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- *Antidiabetic Agents* – Corticosteroids may increase blood glucose concentrations. Dose adjustments of antidiabetic agents may be required.
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- *NSAIDs* – Concomitant use of NSAIDS, including aspirin and salicylates, with a corticosteroid may increase the risk of GI side effects.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Two prospective case control studies showed decreased birth weight in infants exposed to maternal corticosteroids in utero. Triamcinolone acetonide was shown to be teratogenic in rats, rabbits, and monkeys at inhalation doses of 0.02 mg/kg and above and in monkeys, triamcinolone acetonide was teratogenic at an inhalation dose of 0.5 mg/kg (1/4 and 7 times the recommended human dose)..Corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Infants born to mothers who received corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism.

Nursing Mothers

Corticosteroids are secreted in human milk. The risk of infant exposure to steroids through breast milk should be weighed against the known benefits of breastfeeding for both the mother and baby.

Pediatric Use

The efficacy and safety of corticosteroids in the pediatric population are based on the well-established course of effect of corticosteroids which is similar in pediatric and adult populations. The adverse effects of corticosteroids in pediatric patients are similar to those in adults.

Geriatric Use

No overall differences in safety or effectiveness were observed between elderly subjects and younger subjects, and other reported clinical experience with triamcinolone has not identified differences in responses between the elderly and younger patients.

PATIENT COUNSELING INFORMATION

Patients should discuss with their physician if they have had recent or ongoing infections or if they have recently received a vaccine.

Patients should be advised of common adverse reactions that could occur with corticosteroid use such as elevated intraocular pressure, cataracts, fluid retention, alteration in glucose tolerance, elevation in blood pressure, behavioral and mood changes, increased appetite, and weight gain.

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Study Analyzes DME Patients' Response to Therapy

Anti-VEGF injections are a mainstay of management for various retinal conditions. With diabetic macular edema, patients may receive injections on a fixed schedule, but a new study published in *Ophthalmology Science* assessed whether outcomes upon treatment cessation would be adequate and remain stable.[1]

The retrospective investigation included 81 eyes (62 patients) who met inclusion criteria and had a follow-up of ≥24 months; treatment interruption was defined as a treatment-fee interval of ≥25 weeks after the last injection, happening for any reason. With a maximum follow-up of up to 10 years and a median of five, patients received 22.6 ±14.9 (median 20) injections. One planned treatment cessation occurred in 70.4 percent of patients and four eyes experienced an unplanned interruption of treatment. Cessation was seen in 65.4 percent of eyes at a median of 42 weeks after treatment initiation for 106.2 ±110.4 (median 54) weeks. One eye (1.9 percent) had treatment cessation due to wishing to stop treatment against medical advice, was physician-driven in 38 eyes (71.7 percent) that had stable visual acuity despite persisting residual retinal fluid seen with OCT and was OCT-driven in 14 eyes (26.4 percent) with no intraretinal fluid on OCT. Overall, cessation was seen in 70 percent of DME eyes during the first year.

Due to patients who had treatment cessation having no negative impact on long-term outcomes, the authors of the study write that "this calls for a discussion about a possible systematic assessment of disease stability by omitting a single injection in eyes with stable retinal fluid."

The authors wrote that treatment cessation was possible for almost two years (106 weeks), underscoring a robustness of stability under the persisting fluid-tolerant treatment protocol—mapping onto a relevant reduction in treatment burden for patients. After an average of 65 weeks, eyes became widely dry with tolerance of excess central retinal thickness of ≤10 percent, indicative of a generally favorable anatomic response after intensive treatment (mean 7.7 injections) in the first year. They also report only a small 5 percent of patients being lost to follow-up over a mean of 5.7 years.

Because of the nature of these results, the authors contend that "stable fluid may be tolerated which triggers a reconsideration of the best treatment approach. The currently fluid-driven protocol is not necessarily the ideal patient-supported one."

Instead, they offer the suggestion that "eyes with a supportable amount of persistent, but stable fluid may benefit from an individualized strategy with 'diagnostic' treatment interruption." They highlight that this strategy differentiates DME from non-proliferative age-related macular degeneration, in which only complete dryness indicates control of disease activity.

REFERENCE

1. Saucedo L, Pfister IB, Schild C, et al. Treatment cessation in patients with diabetic maculopathy under intravitreal anti-VEGF therapy following a treat-and-extend protocol. Ophthalmol Sci. June 2, 2025. [Epub ahead of print].

(Continued on page 26)

CELEBRATING A RICH CAREER

This issue of *Retina Specialist* is special in a couple of ways.

This specific issue marks Rich Kirkner's last one as Editor, as he's moving on to a well-earned retirement. Since the magazine's inception, it's been Rich's baby. He's worked tirelessly with retinal specialists to select the best topics and then used his keen editorial eye to make sure each topic was thoroughly and compellingly explored.

Rich honed these abilities over nearly 40 years of working in various publications, from business and general surgery to eye care. He's won 31 journalism awards and has overseen magazines that ranked #1 in their field. Rich was multi-tasking before it was even a term: writing and editing articles; managing large staffs of editors and art directors; managing medical conferences and staying on top of complex medical topics. I've known him personally for many of these years—having started on *Review of Ophthalmology*, a sister publication, as a junior editor back in the 1990s—and never once did he lose his trademark wry sense of humor, or the respect of his staff. His work always made everyone else's work better. So, Rich, from all of us at *Review* and Jobson Publishing, thank you for all you've done and we wish you nothing but the best in your retirement!

Also, in addition to Rich's riding off into the sunset, 2025 marks *RS*' 10th year of publication (also thanks to Rich's efforts). Thanks to all of you for your loyal readership and contributions over the past decade. Here's to many more years!

— WB

Vit-Buckle Society's tips for challenging retina cases

A roundup of this year's standout talks highlights surgical and teaching pearls.


Yuxi Zheng, MD


Richmond L. Woodword, MD


Nikhil Bommakanti, MD


David Zhang, MD

By Yuxi Zheng, MD, Richmond L. Woodward, MD, Nikhil Bommakanti, MD, and David Zhang, MD

The 13th Annual Vit-Buckle Society conference brought together retina specialists from across the country for an engaging meeting in Austin, Texas. The conference showcased innovative surgical techniques and spirited debates on the most pressing issues in retina. With the hallmark VBS energy, this year's event was truly the "Wild Wild VBS."

The conference started with outstanding tips about some common challenging retina cases.

Lasso that lens

Archana Seethala, MD, from Atrius Health opened the session with an engaging and insightful presentation on secondary intraocular lens techniques, focusing on the Gore-Tex sutured Akreos and scleral-fixated Yamane techniques—tools that are essential in the retina surgeon's armamentarium.

• ***Akreos lens with Gore-Tex fixation***. Dr. Seethala emphasized the stability of the Akreos lens, citing its four points of fixation and foldable design, which facilitates small-incision insertion. She walked the audience through meticulous marking techniques and emphasized the directionality of the Gore-Tex suture when threading the lens. She also emphasized centering the lens before locking the sutures, and rotating the suture knot into the sclerotomy. She provided high-yield pearls including using iris hooks for small pupils, and demonstrating a technique to salvage tangled and caught sutures. Despite the lens's material and potential for opacification, its predictable refractive outcome and teachability make it an attractive option.

• ***Yamane technique***. Transitioning to the sutureless technique, Dr. Seethala covered the Yamane technique using three-piece IOLs (MA60AC, CT Lucia, AR40). For MA60AC lenses, she noted that while this lens can result in quick postoperative recovery due to smaller wound size, the haptics can be flimsy and the lens can tilt. The CT Lucia may be unstable at the optic-haptic junction and she suggests using endolaser to stabilize the optic-haptic junction more. The AR40 haptic provides rigidity but risks exposure and breakage. Real-world surgical videos highlighted both seamless cases and common pitfalls. These served as reminders of the unpredictable nature of these cases.

Key takeaways of this talk included: No perfect lens exists, but selecting the right lens for the right patient is critical; setting realistic expectations is essential; and mastery of multiple techniques builds surgical resilience.

Operating one mile high: Altitude considerations for gas-filled eyes

Scott Oliver, MD, from the University of Colorado drew on his experiences treating patients in the Denver area to share practical strategies for managing patients who live at or travel to elevated regions. He pointed out that at higher elevations, reduced atmospher-

BIOS

Dr. Zheng is a vitreoretinal surgery fellow at Duke Eye Center.

Dr. Woodward is a vitreoretinal surgery fellow at Mass Eye and Ear.

Dr. Bommakanti is a vitreoretinal surgery fellow at Wills Eye Hospital/ Mid Atlantic Retina.

Dr. Zhang is a resident at Vanderbilt University Medical Center

DISCLOSURES: The authors have no relevant financial disclosures.

ic pressure can affect surgical instruments, in particular Venturi-based systems which experience decreased vacuum efficiency. Dr. Oliver next reinforced the dangers of air travel with intraocular gas, citing multiple case reports of severe eye pain, vision loss and elevated IOP in patients who flew against medical advice. Cabins are pressurized, but typically only to 8,000 feet, and patients are advised to avoid flying until the gas bubble dissipates.

Dr. Oliver also emphasized the importance of incorporating the patient's home elevation and anticipated travel into surgical plans. If patients must fly or travel to higher elevations, options include avoiding gas by considering scleral buckling or silicone oil tamponade. If gas is used, he advises his patients to stay in the Denver metro area for a month. And before driving home, his patients are equipped with a map and directions to avoid dangerous elevations. When driving home with a partial gas fill, acetazolamide or other ocular hypotensives are prescribed.

Altitude and gas-filled eyes can be a risky combination. To ensure patient safety, verify the patient's home elevation and discuss travel expectations; use oil when appropriate; and equip patients with education, maps and medications to prevent complications.

Approach to biopsies (vitreous, choroidal, retinal biopsies)

Phoebe Lin, MD, PhD, from the Cole Eye Institute presented a clinical vignette to highlight planning strategies and useful techniques for diagnostic vitrectomy. Success begins with a thorough systemic evaluation and communication with cytopathology and hematopathology teams before the day of surgery. Dr. Lin also pointed out the importance of a meticulous specimen collection strategy, including preparing necessary media and requisitions, sequentially obtaining non-dilute and dilute samples, and using Luer-lock syringes and red caps to prevent loss of small-volume specimens. Her intraoperative tips included tailoring port placement to avoid active snowbanks or retinal detachment sites. False negatives can result from low cellularity or degraded samples, making it crucial to freeze and preserve unused vitreous for future testing.

Dr. Lin then turned to chorioretinal biopsy, typically reserved for suspected neoplasm or metastases after non-diagnostic vitrectomy, or for atypical infection. She presented another clinical vignette and pointed out some key surgical techniques, including removal of any residual vitreous skirt for visualization and control, and double-pass diathermy to outline the biopsy site and preempt bleeding. Tissue dissection with multi-cut pneumatic scissors can help achieve clean specimen margins.

Diagnostic vitrectomy and chorioretinal biopsy are powerful tools in diagnosing atypical intraocular inflammation or neoplasia; preparation, multidisciplinary communication, and refined surgical techniques while tailoring the surgical plan to the patient's systemic condition and goals of care are keys to success.

A buckle ain't just for cowboys! How to start if you're a tenderfoot

Chirag D. Jhaveri, MD, from Retina Consultants of Austin/Dell School of Medicine discussed the importance of scleral buckling and shared tips to become more comfortable with this procedure. He explained that buckling is the only surgical method that truly alters force vectors, and argued that primary SB and PPV/SB showed better outcomes in the PRO study reports.

To get started, he advised beginners to perform a PPV/SB, but to treat the buckle portion like a true primary buckle—marking the break and ensuring the buckle supports it directly rather than just "supporting the vitreous base." He noted that a chandelier could be used before transitioning fully to indirect ophthalmoscopy.

Dr. Jhaveri recommended avoiding the microscope to maintain consistent movements while suturing, and to begin with simpler cases such as single-quadrant detach-

These are retinas with broad areas of fibrosis and firm attachment of membranes to the optic disc; the absence of any PVD creates a challenge, as it's difficult to induce a PVD using usual techniques.

ments. Buckling elements should be familiar and simple—he prefers the 510 sponge for segmental buckles and typically uses 41 or 42 bands.

He presented several case examples, including a multifocal IOL patient with superior and inferotemporal tears managed with a 510 sponge (with no change in refractive error), and a young phakic patient with a chronic inferior detachment who underwent segmental buckling instead of vitrectomy. Dr. Jhaveri explained that cryopexy only causes PVR when done poorly, and he noted that treatment of the RPE is sufficient with bullous detachments where the probe may not reach the neurosensory retina. He also described suture techniques such as horizontal mattress and figure-eight patterns for effective imbrication.

For drainage, he suggested a cut-down approach followed by laser to the choroidal bed to achieve hemostasis before entering with a needle (similar to when placing a port delivery implant). He closed by encouraging early adopters to "phone a friend" and ask experienced surgeons for guidance.

During the discussion, Edward Wood, MD, shared his experience with having fellows examine and perform cryopexy before prepping, as the maneuvers are more familiar, although he said he's still looking for a good way to mark the break. Dr. Jhaveri noted that this is a good technique, although it can be more traumatic if the break is under a muscle. Shilpa Desai, MD, noted that it can take some time to develop confidence that the fluid will resolve when buckling without external drainage, because we're used to PPV where we can drain the fluid intraoperatively.

Tips for uveitic retinal detachments

Noy Ashkenazy, MD, from UT Southwestern Medical Center shared several cases of retinal detachments associated with retinitis, which have a variety of presentations both with and without proliferative vitreoretinopathy or atrophy.

In a case of toxoplasmosis-associated giant retinal tear with extensive PVR, she illustrated the utility of MVR picks for tight membranes. PFO can be used for anterior breaks, with a low threshold for silicone oil use in uveitic retinal detachments. Sub-Tenon's steroid injections should be avoided in these infectious cases.

In retinal detachments with retinitis that's healing or progressing to atrophy, PVR can still occur. If no breaks are identified, the borders of the retinitis should be lasered. Once again, scleral buckling is a strong consideration.

Teaching and learning advanced diabetic vitrectomy

James Rice, MBBCh, MRCOphth, FCOphth(SA), MPH, of the University of Cape Town in South Africa, discussed the education process involved in learning advanced diabetic vitrectomy. A strong understanding of the pathophysiology and interface between vitreous and retina is needed. These are retinas with broad areas of fibrosis and firm attachment of membranes to the optic disc; the absence of any PVD creates a challenge, as it's difficult to induce a PVD using usual techniques.

In his practice, anti-VEGF injections are used in all diabetic dissections to decrease bleeding. Obtaining access and finding the correct surgical plane sets up the surgeon for success. He then demonstrated the "c-pull" technique for extending the hyaloidal elevation, working close and tangential to the retinal surface.

He shared his strategy for learning surgical steps. By tracking surgical progress with individual steps on a spreadsheet, elements that require more practice can be identified. He shared examples of simulation with low-cost plastic models allowing for practice with real instruments and bimanual techniques. By incorporating feedback with intraoperative mentorship, this allows the trainee to understand when to change tactics, when to stop a procedure and how to manage complications. RS

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ABOUT RICK

Rick Bay served as the publisher of *The Review Group* for more than 20 years.
To those who worked for him, he was a leader whose essence was based in a fierce and boundless loyalty.
To those in the industry and the professions he served, he will be remembered for his unique array of skills and for his dedication to exceeding the expectations of his customers, making many of them fast friends.

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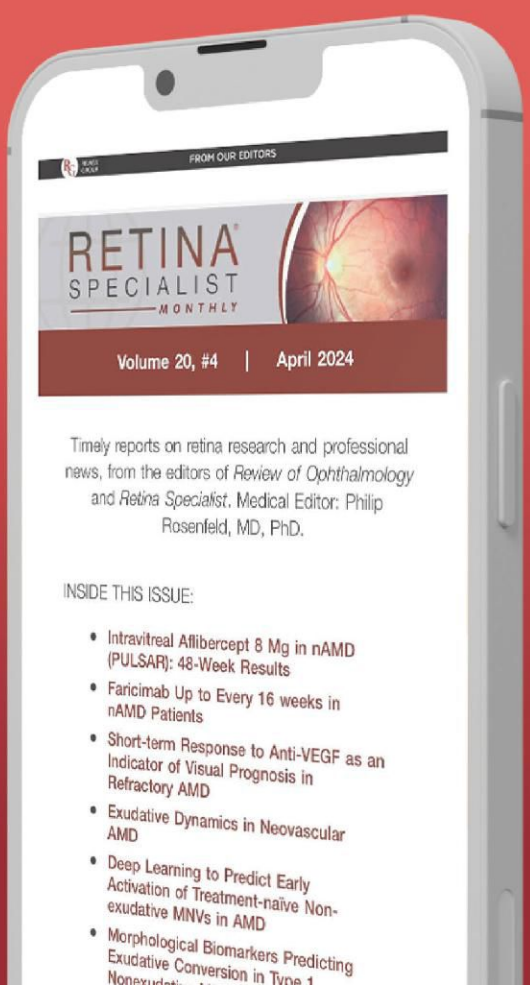


Intraoperative Fluorescein Angiography in the management of PDR

Intraoperative FA is a useful tool to reduce risk of recurrent postoperative vitreous hemorrhage

Joaquín Sosa-Lockward, MD, Alan J. Franklin, MD, Diana Flores, MD, Jeannette Dominguez, MD, and Nassim Abreu-Arbaje, MD

Joaquín Sosa-Lockward, MD

Alan J. Franklin, MD

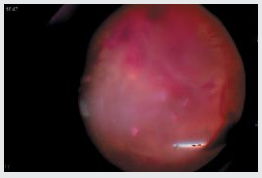
Diana Flores, MD

Jeannette Dominguez, MD

Nassim Abreu-Arbaje, MD

View the Video

The authors demonstrate their approach for using intraoperative fluorescein angiography to prevent a postoperative vitreous hemorrhage after proliferative diabetic retinopathy. Go to: https://bit.ly/VideoPearl-46 or scan the QR code.



Vitreous hemorrhage is a common complication and cause of persistent visual loss after surgery for proliferative diabetic retinopathy with a reported incidence ranging from 20 to 75 percent.[1,2] Early postoperative vitreous hemorrhage, occurring in the first four weeks, is caused either by postoperative leakage of the remnant vessels or dissected tissue or by lysis of residual blood in the cavity.[3]

Early postoperative vitreous cavity hemorrhage, which occurs within the first few days after surgery, hinders visual recovery due to its persistence and lack of clearance. It can lead to elevated intraocular pressure and can make further treatment for diabetic retinopathy difficult.[3] Although spontaneous resolution occurs in most cases, non-clearing postoperative vitreous cavity hemorrhage requires revision surgery in 10 percent of the cases to address any underlying causes.[4]

Intraoperative fluorescein angiography enables detection of residual retinal neovascularization as active leakage which may be treated with laser or diathermy. This will, in turn, reduce the risk of early postoperative vitreous cavity hemorrhage and expedite visual recovery, reduce complications and improve surgical outcomes for patients.

Surgical management and practical tips for intraoperative FA

This is the case of a 56-year-old male with a longstanding vitreous hemorrhage and proliferative diabetic retinopathy. Preoperative vision was hand motion. A conventional 25G pars plana vitrectomy was performed. After initial vitrectomy, ILM peeling was executed at the macular area and the attached nasal hyaloid was addressed completing the procedure.

In this case, a classic intraoperative FA image was obtained with a 485 nm bandpass filter installed on the light module of our Constellation vitrectomy system. The

Figure 1. Adapted optical exciter filter.

BIOS

Dr. Sosa is a vitreoretinal surgeon, associate professor at the Retina Department at Hospital Dr. Elias Santana (CCSM), Santo Domingo, Dominican Republic. **Financial disclosure:** none.

Dr. Franklin is a retina specialist at the Diagnostic and Medical Clinic, Mobile, Alabama. **Financial disclosure:** Consultant (Alcon, AsclepiX, Neuracle, OcuTerra, Outlook Therapeutics); Founder/CEO (ForwardVue Pharma). *(Cont'd, next page)*

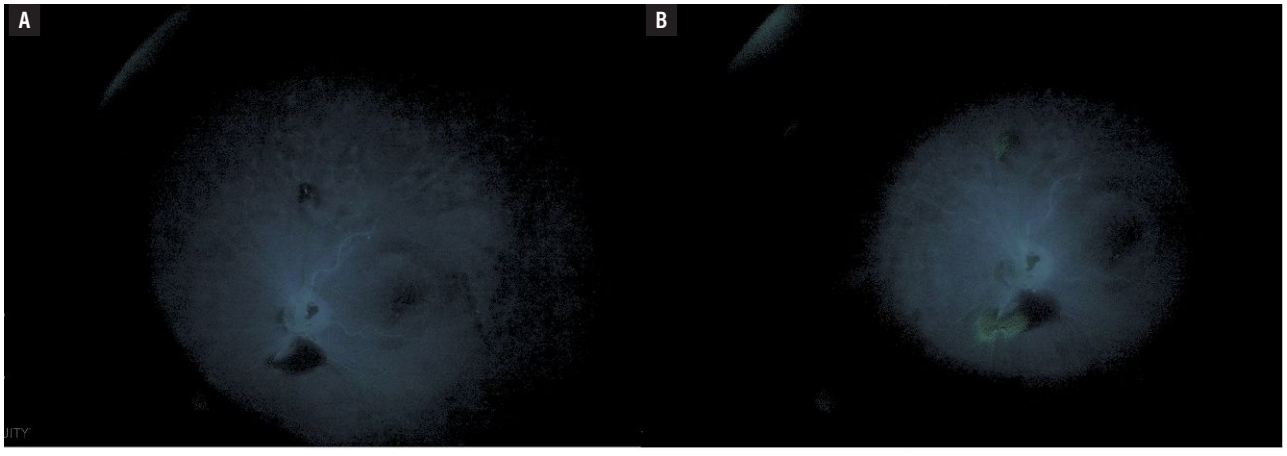


Figure 2. (A) Early intraoperative angiography phases (10 seconds). (B) Late intraoperative angiography phases (90 seconds).

barrier filter was achieved digitally with the Alcon NGenuity visualization system, creating a new filter and modifying the color, saturation, contrast and hue to enhance the green and produce a grayscale image similar to the in-office FA.

Prior to administration, the IOP was lowered to less than 30 mmHg to facilitate faster fluorescein entry into the eye and enhance image quality. The intravenous fluorescein was injected firmly with a constant speed over five to seven seconds. The iris camera was opened, and the gain was adjusted to improve image brightness. With the aid of the intravenous fluorescein, leaking vessels were identified, and continuous endolaser was applied to promote accurate hemostasis with less damage to the surrounding tissue.

At postoperative month three, the patient preserves a BCVA of 20/30 in his left eye, with no complications observed during follow-up visits, thus demonstrating that intraoperative fluorescein angiography is an outstanding tool in cases of any retinal vascular disease, leading to an accurate diagnosis and faster visual recovery.

Benefits of intraoperative FA

Intraoperative FA has many benefits in vitrectomy for PDR including:

1. Identifying angiographic biomarkers such as:

a. Ischemic areas

b. Intraoperative leakage that is not evident during surgery

2. Guiding both delamination and laser in the posterior pole and the periphery.[5,6]

Intraoperative FA is a valuable tool for detection and management of neovascularization in patients undergoing PPV for proliferative diabetic retinopathy.

Dr. Flores is a retina and vitreous surgery fellow at Hospital Dr. Elias Santana (CCSM), Santo Domingo, Dominican Republic.
Financial disclosure: None

Dr. Dominguez is a vitreoretinal surgeon and associate professor at the Retina Department at Hospital Dr. Elias Santana (CCSM).
Financial disclosure: none

Dr. Abreu is a vitreoretinal surgeon, and associate professor at the Retina Department at Hospital Dr. Elias Santana (CCSM).
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Using SS-OCTA to forecast progression in intermediate AMD

Learn how a single scan can detect numerous biomarkers that help predict the onset of GA.

By Alessandro Berni, MD, and Philip J. Rosenfeld, MD, PhD

Alessandro Berni, MD

Philip J. Rosenfeld, MD

Take-home points

- A single macular swept-source OCT angiography raster scan can assess multiple high-risk biomarkers in intermediate AMD that predict disease progression to choroidal hypertransmission defects, an early feature of geographic atrophy.
- Combining *en face* and B-scan imaging, a single scan can easily identify OCT biomarkers including hyperTDs, drusen volume, hyperreflective foci and calcified drusen.
- Central macular drusen volume is a robust, fully automated biomarker for stratifying the risk of progression from iAMD to GA.
- The total macular burden of HRF, including both intraretinal and retinal pigment epithelium-associated lesions, can be easily detected using a slab from beneath the RPE by the appearance of choroidal hypotransmission defects, and these HRF outperform drusen volume in predicting disease progression.
- Calcified drusen, also easily detected as hypoTDs on *en face* sub-RPE slabs and distinguished from HRF by using corresponding B-scans, serve as independent predictors of disease progression from iAMD to GA.

Predicting the progression of an eye with intermediate age-related macular degeneration to geographic atrophy is challenging, due to such factors as limitations of imaging biomarkers, variability in AMD's phenotype and an incomplete understanding of the individual risk factors. Here, we'll show how new imaging approaches can help more accurately stratify the risk of progression to GA.

The challenge of AMD

The threat of AMD is constant, as it remains the leading cause of irreversible blindness in individuals aged 60 years and older.[1] Intermediate AMD is the stage prior to the late stage of AMD that is characterized by significant vision loss associated with the onset of GA or exudative AMD.[2] iAMD is characterized by structural changes such as the accumulation of drusen and pigmentary abnormalities.

Although anti-VEGF therapy is effective in managing exudative neovascular AMD by controlling macular neovascularization and reducing exudation, it doesn't address the underlying progression of nonexudative AMD toward GA.[3] Similarly, emerging therapies such as complement inhibitors can modestly slow the rate of GA enlargement, but they aren't curative and don't reverse vision loss that has already occurred.[4,5] These limitations underscore the urgency to identify therapies for iAMD to slow the progression to late AMD. The need to identify eyes with iAMD at high risk for progression to late-stage disease is obvious. Testing potential disease-modifying therapies in clinical trials can be completed within one to two years, rather than requiring five years of follow-up.

High-risk OCT biomarkers in iAMD

The development of optical coherence tomography has greatly improved our

BIOS

Dr. Berni was a retina research fellow at Bascom Palmer Eye Institute in Miami and is completing an ophthalmology residency at San Raffaele Hospital in Milan, Italy. **Dr. Rosenfeld** is a professor of ophthalmology at Bascom Palmer Eye Institute.

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ability to visualize and quantify structural changes in the retina and choroid associated with the stages of AMD and serve as harbingers of disease progression. OCT biomarkers have become central to detecting high-risk features in iAMD that offer potential pathways for early intervention.[6] Several OCT biomarkers have been proposed as reliable predictors of disease progression from iAMD to GA. These include the central macular drusen volume,[7,8] the area of hyperreflective foci (HRF),[9,10] the presence of calcified or hyporeflective-core drusen,[11-13] vitelliform material,[14] subretinal drusenoid deposits (also known as reticular pseudodrusen)[15] and decreased perfusion in the macular choriocapillaris.[16]

Among these, central macular drusen volume remains a core biomarker. Advanced image segmentation algorithms now permit accurate, reproducible quantification of drusen volume using commercial spectral-domain OCT devices. Research by Yehoshua et al. and Abdelfattah et al. showed that a central drusen volume >0.03 mm^3 was easily measured and could serve as an OCT biomarker that was associated with disease progression from iAMD to late exudative AMD.[7,17]

More recently, Liu et al.[8] used swept-source OCT angiography and an automated algorithm for measuring drusen volume and identifying large hypertransmission defects (hyperTDs). Large hyperTDs represent an early structural sign of impending GA, and this OCT biomarker is now FDA-approved as a clinical trial endpoint for studying the progression from iAMD to GA. Large hyperTDs are defined as bright areas at least 250 µm in greatest linear dimension identified on *en face* sub-retinal pigment epithelium slabs with boundaries positioned 64 µm to 400 µm beneath Bruch's membrane. The use of *en face* images derived from dense macular raster scans allows for the simultaneous evaluation of multiple biomarkers without the need to scroll through every B-scan. Using longitudinal data from a prospective cohort of iAMD eyes, the researchers[8] used drusen volume to identify eyes at higher risk of disease progression and designed a clinical trial to test therapeutic strategies targeting hyperTD formation and growth.

Building upon this framework, Berni et al.[9,10] proposed an alter-

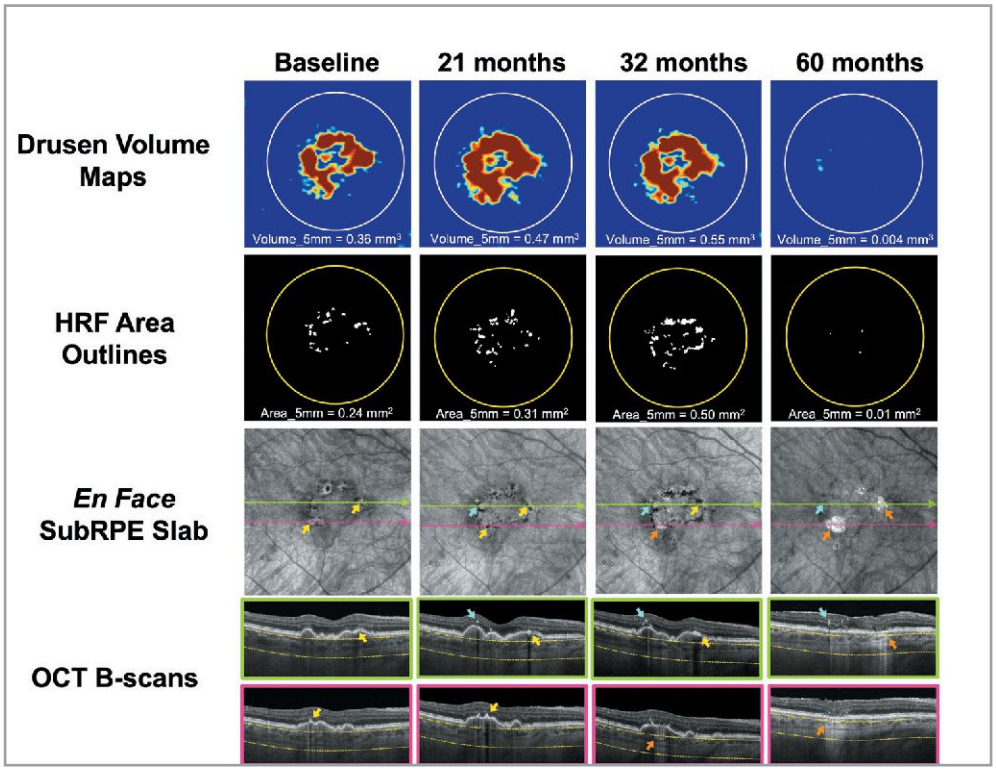

Figure 1. Longitudinal SS-OCTA imaging from an iAMD eye with a large drusen volume and HRF located both intraretinally (blue arrows) and along the RPE (yellow arrows), developing large choroidal hyperTDs (orange arrows) over 60 months of follow-up. ***(Adapted and reprinted with permission from Berni A, Shen M, Cheng Y, et al. The total macular burden of hyperreflective foci and the onset of persistent choroidal hypertransmission defects in intermediate AMD. Am J Ophthalmol. 2024;267:61-75.)***

native approach for stratifying risk by incorporating HRF into the risk assessment.

HRF are typically observed on OCT B-scans as discrete intraretinal lesions with reflectivity equal to or greater than that of the RPE band. These foci may correspond to different cell types or debris depending on the disease. In AMD, these HRF correspond to migrating RPE cells, activated microglia, lipid-laden macrophages or photoreceptor remnants. Moreover, in AMD, intraretinal HRF are frequently observed during progression from iAMD to both GA and exudative AMD. In dry AMD, iHRF likely represent RPE cells detaching and migrating from the monolayer, as supported by histologic and longitudinal imaging studies. However, not all HRF are intraretinal. Some remain confined to the RPE monolayer, referred to as rpeHRF. These rpeHRF are usually seen as areas of RPE thickening with increased reflectivity, and while not elevated above the monolayer, they're considered important in predicting disease progression.

In longitudinal studies of iAMD, researchers observed that eyes could progress to hyperTDs even in the absence of a large drusen volume.[9,10] Using the same SS-OCTA raster scans as used by Liu et al., they applied a semiautomated algorithm capable of identifying and quantifying the area of HRF based on their enhanced optical properties. While both iHRF and rpeHRF scatter both incident and reflected light and can be easily identified by detecting choroidal hypoTDs on the same *en face* subRPE slabs used to identify hyperTDs, Berni et al.[9] were able to quantify the total area of HRF in the central macula, including both iHRF and rpeHRF. While the univariable analysis showed that the total HRF burden included both iHRF and rpeHRF predicted disease progression, the multivariable model revealed that only rpeHRF was the most predictive biomarker. However, for simplicity, when using a quantitative biomarker to predict disease progression, we propose that it's easier to use the total HRF area as a practical metric for identifying high-risk eyes. Of note, measurements of the total macular HRF area outperformed drusen volume in predicting disease progression when both variables were included in a multivariable model. However, when considered separately, drusen volume still remained a valid marker of progression.

When separately considering drusen volume and the area of HRF, Berni et al.[9] showed that eyes with a baseline HRF area ≥0.07 mm² had a 90-percent likelihood of developing a hyperTD within five years, compared to an 87-percent likelihood in eyes with drusen volumes of 0.22 mm³ or more. While both markers performed well, drusen volume has the advantage of being

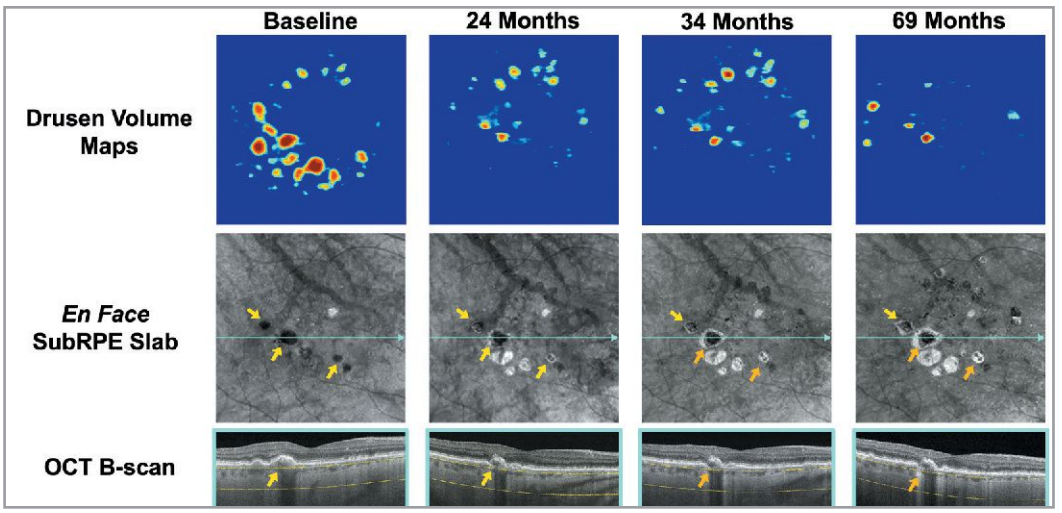

Figure 2. Longitudinal SS-OCTA imaging from an iAMD eye with multiple calcified drusen evolving into large choroidal hyperTDs (orange arrows) over 69 months of follow-up.

automatically measured using OCT software widely available in clinical settings. In contrast, HRF assessment still requires semi-automated segmentation and manual refinement, which can be more time-consuming and technically demanding. Thus, while HRF burden may offer stronger predictive accuracy in clinical trials, drusen volume still remains a pragmatic and accessible biomarker for large-scale screening in clinical practice.

Calcified drusen are another clinical biomarker for AMD progression. CaD represent an advanced form of drusen degeneration and are considered robust OCT biomarkers of disease severity in iAMD. These lesions are easily recognized on structural OCT as highly reflective drusen, often with hyporeflective cores. On *en face* OCT, they produce choroidal hypoTDs similar to HRF, owing to their strong light-blocking properties, and they're distinguished from HRF by reviewing the corresponding B-scans. Liu et al.[12] first described this hallmark *en face* OCT appearance and linked CaD to the formation of large hyperTDs.

More recently, El-Mulki et al. (paper currently under revision) demonstrated that the mere presence of CaD, irrespective of their size or area, significantly elevates the risk of hyperTD development. As CaD often signify advanced pathological remodeling, eyes with these lesions may be less responsive to therapeutic intervention, further emphasizing their clinical relevance.

For this reason, identifying CaD at the time of clinical trial enrollment is crucial. Their presence may skew treatment outcomes if not appropriately accounted for, as they disproportionately elevate the baseline risk of progression. As a result, clinical studies should either ensure balanced distribution of CaD across study arms or consider excluding these eyes from early-phase intervention trials. While exclusion may reduce recruitment speed, it enhances study reliability and ensures a clearer assessment of therapeutic efficacy in treatable cases.

Bottom line

High-risk OCT biomarkers, particularly drusen volume, HRF and CaD, provide vital prognostic harbingers of progression from iAMD to GA. Their early identification through advanced imaging modalities like SS-OCTA enables timely intervention, personalized monitoring and improved clinical trial design. Continued research into OCT biomarkers will be instrumental in enhancing AMD management and preserving vision in at-risk populations. RS

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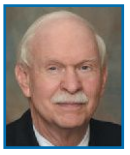
Optical coherence tomography in the management of diabetic retinopathy

Tips on what to look for when using this technology to assess and follow patients with DR.

Landon J. Rohowetz, MD, and Harry W. Flynn Jr., MD

Landon J. Rohowetz, MD



Harry W. Flynn Jr., MD

Take-home points

- OCT provides precise, objective assessment of diabetic macular edema, guiding treatment decisions and enhancing patient engagement.
- OCT allows physicians to evaluate treatment response in patients with diabetic retinopathy both in the clinical and research settings.
- OCT biomarkers such as DRIL and ellipsoid zone disruption support individualized therapy and help predict treatment response in diabetic retinopathy.
- Emerging technologies including swept-source OCT and OCT angiography expand diagnostic capabilities by enhancing field of view and noninvasively identifying microvascular abnormalities.

Diabetic retinopathy remains one of the leading causes of vision impairment and blindness in working-age adults worldwide.[1] As the global burden of diabetes increases, retina specialists are tasked with not only treating the sight-threatening complications of DR but also detecting and monitoring the disease earlier and more effectively. Optical coherence tomography, with its ability to provide high-resolution cross-sectional images of the retina, has become a cornerstone in the evaluation and management of DR. From identifying subclinical changes to guiding individualized treatment regimens, OCT plays a pivotal role in improving patient outcomes and enhancing clinical decision-making. Here, we'll review OCT's capabilities in this area, as well as take a look at what benefits newer technologies might bring.

Early Detection and Risk Stratification

Traditional staging systems for diabetic retinopathy, such as the Early Treatment Diabetic Retinopathy Study classification, rely heavily on fundus photography and clinical examination. While these tools remain fundamental, they often miss early structural changes, particularly those affecting the macula. Optical coherence tomography enables the detection of subtle alterations such as thickening of the retina, early intraretinal cysts or signs of neuroretinal dysfunction before they're visible clinically. Indeed, OCT has been an important tool used in the Diabetic Retinopathy Clinical Research Network trials.[2,3]

More specific pathologic changes such as disorganization of the retinal inner layers (DRIL; *Figure 1*) can be appreciated only through OCT and have been identified as markers of visual potential and predictors of DR progression.[4] Similarly, outer retinal disruption *(Figure 2)* and early photoreceptor damage may indicate more advanced disease with poor visual prognosis.[5]

By incorporating OCT findings and these evolving technologies into the clinical workflow, retina specialists can identify patients at higher risk of progression, allowing for earlier intervention and more tailored

BIOS

Dr. Rohowetz is a vitreoretinal surgery fellow at Bascom Palmer Eye Institute, University of Miami Miller School of Medicine.

Dr. Flynn is the J. Donald M. Gass Distinguished Chair in Ophthalmology at the University of Miami's Miller School of Medicine, and a professor of ophthalmology at Bascom Palmer.

Disclosures: None

follow-up intervals. This is particularly useful in patients with diabetes who do not yet meet criteria for treatment but warrant closer surveillance.

Monitoring diabetic macular edema

One of the most impactful contributions of OCT to diabetic eye care has been in the management of diabetic macular edema, the leading cause of vision loss in DR.[6] While ophthalmoscopy can detect clinically significant macular edema, OCT provides a far more sensitive and quantitative assessment of retinal thickening and the presence of intraretinal or subretinal fluid.[7]

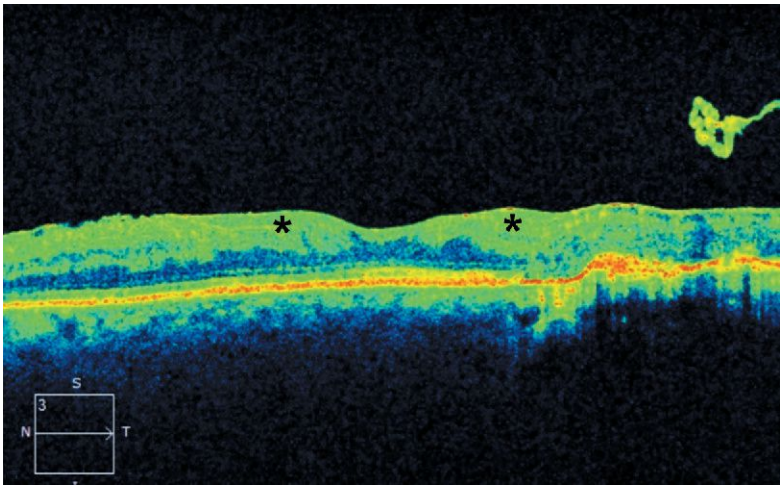


Figure 1. Optical coherence tomography of a 41-year-old male with a history of proliferative diabetic retinopathy demonstrating disorganization of the retinal inner layers (asterisks).

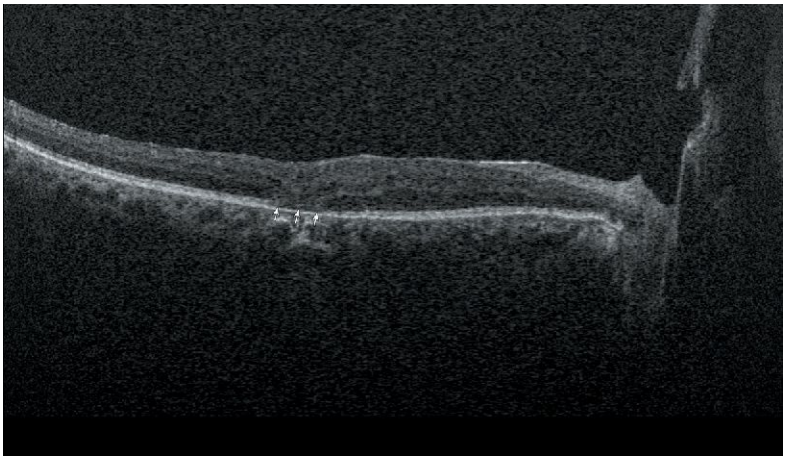


Figure 2. Optical coherence tomography of a 59-year-old with a history of proliferative diabetic retinopathy demonstrating outer retinal disruption (arrows).

Optical coherence tomography enables precise measurement of central subfield thickness, which is often used as a surrogate endpoint in clinical trials and treatment protocols. It also allows for the characterization of fluid patterns and identification of structural features such as hyperreflective foci or hard exudates.

These features not only guide initial treatment decisions but also help retina specialists assess disease activity over time. For instance, persistent intraretinal fluid despite multiple anti-VEGF injections may prompt a switch to an alternative agent while resolution of fluid may justify extension of treatment intervals.[8]

Artificial intelligence–assisted OCT interpretation is also emerging as a tool for earlier and more standardized detection of DME. AI algorithms trained on large imaging datasets can identify patterns of disease activity, flag subtle anatomic changes, and potentially support more consistent and proactive management.[9] In parallel, home-based OCT platforms are being developed to enable remote monitoring of patients with macular disease such as DME. These devices may allow for more frequent assessments, earlier detection of fluid recurrence and timely treatment adjustments, particularly beneficial for patients who face challenges with frequent clinic visits.[10]

Furthermore, OCT imaging facilitates shared decision-making with patients, who can visualize the impact of their therapy and understand the importance of treatment adherence. The ability to track objective improvements in retinal architecture can enhance patient engagement and satisfaction *(Figure 3)*.

Assessing treatment response and guiding individualized therapy

The era of one-size-fits-all therapy in diabetic retinopathy is evolving toward a more personalized approach, and OCT is at the heart of this shift. Response to intravitreal therapy is highly variable, and struc-

tural outcomes on OCT often correlate imperfectly with changes in visual acuity. However, certain OCT biomarkers, such as the presence of DRIL, ellipsoid zone disruption or persistent cystoid spaces, can offer prognostic insights that help guide long-term management.[4,11] For example, in patients undergoing anti-VEGF therapy, OCT is invaluable for determining retreatment intervals under treat-and-extend or PRN regimens. Evidence suggests that patients with persistent or recalcitrant fluid respond better to shorter intervals, whereas stable patients can often tolerate extension.[12] Corticosteroid agents including dexamethasone implants, fluocinolone implants and triamcinolone acetonide offer alternative strategies for chronic DME, and OCT monitoring can help determine treatment response and optimal intervals.[13]

In surgical contexts, OCT can also aid in planning by identifying tractional elements or vitreomacular adhesion that may necessitate vitrectomy. Postoperatively, serial OCT scans can document resolution of edema and retinal reattachment, allowing for a more objective assessment of surgical outcomes.

OCT angiography: A new frontier in DR evaluation

More recently, OCT angiography has emerged as a powerful adjunct in the evaluation of diabetic retinopathy. This noninvasive imaging modality captures motion contrast from blood flow, providing a detailed view of retinal and choroidal microvasculature without the need for fluorescein dye.[14]

Optical coherence tomography angiography allows clinicians to identify areas of capillary nonperfusion, microaneurysms and enlargement of the foveal avascular zone—hallmarks of ischemia that are closely linked to disease severity.[15] Unlike fluorescein angiography, OCTA can be repeated frequently and noninvasively, making it a valuable tool for longitudinal monitoring.

In eyes with nonproliferative DR, OCTA can detect progressive microvascular changes even in the absence of overt clinical signs, potentially identifying patients who may benefit from closer observation or early intervention.[16] In proliferative disease, OCTA can complement ophthalmoscopy and widefield imaging by delineating neovascular networks and their response to panretinal photocoagulation or anti-VEGF therapy *(Figure 4)*.[17]

While traditional OCTA does have limitations—such as a smaller field of view compared to ultra-widefield FA and vulnerability to motion artifacts—it represents a promising step toward more comprehensive, noninvasive retinal vascular imaging.

Surgical planning and postoperative evaluation

Though many patients with diabetic ret-

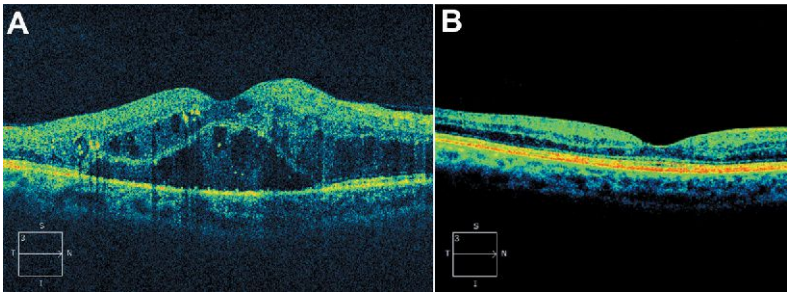


Figure 3. (A) Optical coherence tomography of a 47-year-old male with a history of nonproliferative diabetic retinopathy demonstrating the presence of subretinal fluid, intraretinal fluid and intraretinal deposits. (B) Optical coherence tomography six years after initiation of regular intravitreal anti-VEGF therapy demonstrating resolution of intraretinal and subretinal fluid.

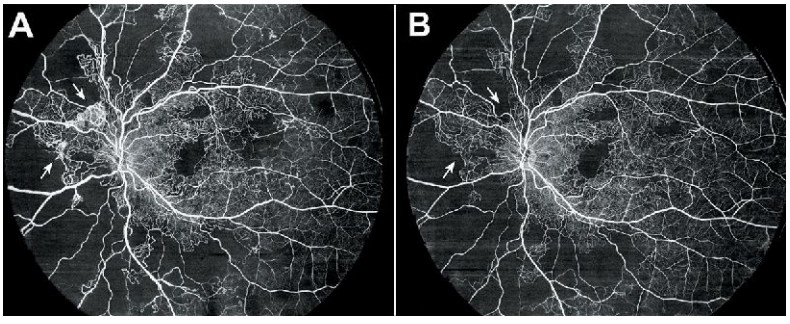


Figure 4. (A) Optical coherence tomography angiography of a 40-year-old female with a history of proliferative diabetic retinopathy demonstrating capillary nonperfusion and peripapillary neovascularization elsewhere (arrows). (B) Optical coherence tomography angiography one year after treatment with intravitreal bevacizumab demonstrating regression of the neovascularization (arrows).

inopathy are managed medically, surgical intervention remains an option for complications such as non-clearing vitreous hemorrhage, tractional retinal detachment and dense epiretinal membranes. Optical coherence tomography provides essential preoperative information in these cases, particularly in identifying signs of progression or foveal involvement.[18]

Postoperatively, OCT can be used to monitor retinal architecture, detect recurrent or residual edema, and assess the integrity of the ellipsoid zone and other photoreceptor layers. This information can be critical in counseling patients regarding visual prognosis and planning adjunctive treatments if needed.

Limitations and considerations

Despite its many advantages, OCT isn't without limitations. Image artifacts can result from media opacities, patient movement or segmentation errors, which may lead to misinterpretation. Moreover, traditional OCT generally provides only a limited view of the peripheral retina, where proliferative changes and ischemia may occur outside the macula.[19] However, new widefield technologies are being developed to improve image quality and expand the field of view.

It's also important to remember that OCT is an adjunct—not a replacement—for clinical examination and functional testing. In some cases, visual acuity changes may precede structural changes on OCT, underscoring the need for comprehensive assessment.

Cost, access and reimbursement also play a role, particularly in practices that serve underserved populations or operate in resource-limited settings. As OCT and OCTA are bundled with some evaluation codes or imaging services, it's not always separately reimbursed, and this may influence usage patterns in clinical practice.

Bottom line

Optical coherence tomography has transformed the way retina specialists diagnose, monitor and treat diabetic retinopathy. Its ability to detect subtle structural changes, quantify disease activity, and guide individualized therapy has elevated the standard of care and improved outcomes for millions of patients. As OCT technology continues to evolve—with advances such as swept-source OCT, AI-assisted interpretation and home-based monitoring devices—the future of diabetic eye care will be even more precise, personalized and proactive. By integrating OCT into a comprehensive management strategy, retina specialists can stay one step ahead of diabetic retinopathy and preserve vision in a growing population at risk.

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Obstructive sleep apnea: A risk factor for DR progression

A look at the relationship between the two conditions and the possible effects of OSA over time.

Katie Carrillo, BS, Amer Alsoudi, MD, and Ehsan Rahimy, MD

Katie Carrillo, BS

Amer Alsoudi, MD

Ehsan Rahimy, MD

Take-home points

- Obstructive sleep apnea and diabetic retinopathy share common risk factors, associated comorbidities and pathophysiological overlap within the retinal microvasculature.
- Recent evidence suggests that OSA may be associated with an increased risk of DR progression to vision-threatening complications such as proliferative disease and diabetic macular edema.
- Patients with concomitant DR and OSA may be more likely to require treatment with intravitreal pharmacotherapy and laser photocoagulation.
- Routine screening for OSA for patients with DR using tools such as the STOP-BANG survey can help facilitate earlier detection and management of the condition, improving patient outcomes.

Established risk factors for the development and progression of DR, a leading cause of vision loss,[1] include poor glycemic control, hypertension, hyperlipidemia and tobacco use/nicotine dependence.[2,3] In recent years, however, obstructive sleep apnea has emerged as a potentiating risk factor for the progression of DR to more advanced stages, resulting in greater visual impairment and an increased treatment burden.[2] Recognition of OSA as an underlying risk factor presents an opportunity for physicians to improve ocular as well as systemic outcomes for patients with DR by properly screening for potential OSA and ensuring timely referral and proper management of this condition. Here, we review existing evidence on DR progression rates in patients with and without OSA, highlighting a recent aggregate, electronic health record (EHR)-based study on the progression of non-proliferative DR over a five-year period.

Current understanding of OSA and DR

Obstructive sleep apnea is a chronic breathing disorder that causes cessation of airflow due to an obstruction of the upper airway during sleep.[4] There's an established association between diabetes and OSA, with OSA affecting 58 to 86 percent of individuals with diabetes.[2,5] OSA is also associated with other ophthalmic conditions, specifically in the retina, including retinal vein occlusion and central serous chorioretinopathy.[6,7,8]

More recently, emerging evidence has supported a positive association between OSA and DR. In one study, researchers evaluated diagnoses in 317 patients and found that severe OSA is associated with both prevalence and severity of DR.[9] Patients with severe OSA were found to be at greater risk of developing DR, PDR and DME compared to patients with mild-to-moderate OSA. Another investigation evaluated 170 patients with type 2 diabetes and concurrent OSA of varying severity.[10] Findings from this group included a higher prevalence of DR in patients with severe OSA than in patients with mild-to-moderate OSA. However, a separate study with a larger cohort of 556 patients didn't find

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Katie Carrillo is a medical scribe at the Palo Alto Medical Foundation. Dr. Alsoudi is an ophthalmology resident focusing on surgical retina and ocular oncology at Baylor College of Medicine, Houston.

Dr. Rahimy is a vitreoretinal specialist at Palo Alto Medical Foundation as well as an adjunct clinical assistant professor of ophthalmology at Byers Eye Institute at Stanford University, both in Palo Alto, California.

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a significant difference in DR prevalence when comparing patients with mild OSA and moderate-severe OSA.[11]

The overlapping relationship between OSA and DR may be potentiated by the shared risk factors, associated comorbidities and underlying pathophysiological commonalities exerted within the retinal microvasculature. Comorbidities of OSA—hypertension, hyperlipidemia, CAD, obesity and hypothyroidism—are also potential risk factors for DR progression and vice versa, creating a complex, interwoven relationship between the two conditions.[2] How studies choose to mitigate and interpret the confounding impact of this overlap may result in different observed effects of OSA on DR. This presents a challenge in establishing a direct causal relationship between OSA and DR.

Within the retina, OSA may adversely impact tissue structural integrity, microcirculation, resultant tissue ischemia and release of pro-angiogenic factors, all of which are associated with onset of PDR and macular edema,[12] including retinal manifestations. Literature highlighted the clear association between OSA and numerous ocular conditions including glaucoma and papilledema. This comprehensive and narrative review aims to summarize up-to-date clinical research concerning the association of OSA and vascular conditions that affect the retina. OSA is associated with central serous chorioretinopathy. It's also been recognized as an independent contributing factor to the development of insulin resistance, subsequently leading to poor glucose regulation.[13] It's therefore hypothesized that OSA may have a greater impact on the progression of DR to more advanced forms compared to the prevalence of DR in diabetic patients without concurrent OSA.

Table 1a. STOP-BANG Questionnaire

Risk Factor	Question	Answer	N
Snoring	Do you snore loudly (loudly enough to be heard through closed doors or your bed-partner elbows you for snoring at night)?	Y	N
Tiredness	Do you often feel tired, fatigued or sleepy during the daytime?	Y	N
Observed apnea	Has anyone observed you stop breathing or choking/gasping during your sleep?	Y	N
High Blood Pressure (hypertension)	Do you have or are you being treated for high blood pressure?	Y	N
Body Mass Index (BMI)	Is your Body Mass Index greater than 35 kg/m^2?	Y	N
Age	Are you older than 50 years old?	Y	N
Neck circumference	Is your neck circumference greater than 16 inches (40 cm)?	Y	N
Gender	Are you male?	Y	N

Modified from Chung et al. questionnaire

Table 1b. STOP-BANG Scoring Algorithm

Total Score (number of Y answers)	Risk Assessment
0-2	Low risk
3-4	Moderate risk
5-8 2+ of STOP questions + male 2+ of STOP questions + BMI > 35 kg/m^2 2+ of STOP questions + neck circumference >16 in (40cm)	High risk

Modified from the Chung et al. scoring algorithm

OSA as a risk factor for DR progression

A recent large-scale retrospective cohort study investigated the progression of DR over a five-year period in patients with NPDR divided into two study groups: 11,931 patients with OSA and 11,931 matched individuals without OSA.[2] The study used a multicenter aggregate EHR research network, TriNetX, which encompasses more than 300 million patient lives worldwide, including data from more than 64 U.S. institutions. Control group participants were selected for by propensity score matching to balance for various baseline characteristics, systemic comorbidities (i.e., hypertension, cardiovascular disease, renal disease), nicotine use/dependence, medication use (i.e., glucagon-like peptide-1 (GLP1-) agonists) and laboratory values (i.e. hemoglobin A1c (HbA1c), body mass index).

Long-term outcomes of NPDR patients in each group were compared during the course of the study period and measured at one, three and five years. Results of the study revealed that patients with OSA demonstrated significantly faster progression to PDR and DME from baseline NPDR. Progression to PDR was significantly higher in the cohort with concurrent OSA at all three time points

(one-year RR: 1.34, p<0.001; three-year RR: 1.31, p<0.001; five-year RR: 1.28, p<0.001) as well as DME (one-year RR: 1.31, p<0.001; three-year RR: 1.19, p<0.001); five-year RR: 1.18, p<0.001). This translated to a higher need for treatment with intravitreal injections of anti-VEGFs (one-year RR: 1.59, p<0.001; three-year RR: 1.58, p<0.001; five-year RR: 1.54, p<0.001) and laser photocoagulation in this study group compared to patients without OSA. Furthermore, there was a significant difference observed in the baseline HbA1c levels, a known modifiable risk factor for DR, in patients with concurrent OSA and NPDR (7.96 ± 1.96 percent) versus those without OSA (8.07 ± 1.93 percent; p<0.001).

Patients with OSA were observed to have lower HbA1c levels at baseline but still experienced a higher rate of DR progression over five years. While the prevalence of diabetic tractional retinal detachments and resulting need for surgical intervention didn't differ significantly between groups, authors attribute this to increased utilization of treatments that mitigate progression to end-stage DR.

Individuals with NPDR and OSA also experienced significantly higher rates of stroke (one-year RR: 1.80, p<0.001; three-year RR: 1.56, p<0.001; five-year RR: 1.49, p<0.001), myocardial infarction (one-year year RR: 1.51, p<0.001; three-year year RR: 1.46, p<0.001; five-year RR: 1.43, p<0.001), and mortality (one-year RR: 1.31, p<0.001; three-year RR: 1.19, p<0.001; five-year RR: 1.15, p<0.001) compared to those without OSA. These findings underscore the substantial impact of OSA on the course of DR and the health outcomes of patients.

Practical implications and current gaps in care

Increasing awareness of the relationship between OSA and DR may help address a current overreliance on traditional pharmacotherapy by emphasizing early co-management of OSA as a risk factor for DR progression. Typical treatment of OSA has included lifestyle modifications (diet, exercise, weight loss, reducing alcohol/caffeine consumption, etc.), oral devices worn during sleep to prevent blocked airways and/or positive airway pressure ventilation. Notably, on December 20, 2024, the FDA approved tirzepatide (Zepbound, Eli Lilly, Indianapolis), a potent GLP-1 agonist, as the first prescription medication for the treatment of moderate-to-severe OSA in adults with obesity.

Screening for OSA should include three main strategies: identifying retinal symptoms associated with OSA, such as the presence of cotton wool spots in patients with NPDR; use of the STOP-BANG questionnaire to identify OSA risk factors; and confirming suspected cases of OSA through formal diagnostic polysomnography testing.[2] The STOP-BANG questionnaire assesses the eight major risk factors for OSA, which include snoring, tiredness, observed apnea, high blood pressure, body mass index, age, neck circumference and gender *(Tables 1a and 1b)*.[14]

Other studies have demonstrated that management with continuous positive airway pressure can result in more optimal DR outcomes. One study concluded that CPAP use enhanced response to VEGF therapy, with patients requiring fewer injections of Avastin (bevacizumab) compared to individuals with untreated OSA.[15] This introduces a potential gap in care for DR if patients aren't properly screened for OSA and the condition isn't addressed. Furthermore, OSA is associated with an increased risk of systemic vascular events, including death, underscoring its broader impact on patient health.[2] Implementing the STOP-BANG questionnaire in eye clinics could help identify high-risk patients, ultimately improving both ocular and overall health outcomes.

Due to the nature of the EHR-based study (referenced above) and its reliance on aggregate data, there was the potential for misclassification of DR stages due to inaccuracies in ICD-10 diagnoses and CPT coding. Additionally, the study wasn't able to account for the severity of OSA or patient compliance with CPAP therapy, thereby limiting observation on how the severity of OSA might affect DR progression and outcomes. It can't

be concluded based on the dataset that was used if compliant management with CPAP positively mitigates the risk of DR progression and to what extent, so this is an area that warrants future interventional studies. Assessing whether CPAP compliance influences DR risk could have significant therapeutic implications. Regardless, there were still observed differences in the rate of progression to more advanced stages and the need for intervention by ophthalmologists.

While complex, the relationship between OSA and DR has been demonstrated to be significant both in the rate of DR progression locally, as well as for systemic morbidity and mortality of afflicted patients. Given that OSA is widely underdiagnosed despite its high prevalence and potential severity, there's a need to better understand the nature of OSA and its impact on DR in patients so that ophthalmologists can be more proactive in managing these patients and referring them for an appropriate higher level of care.

Bottom line

Ultimately, OSA has been demonstrated to be a risk factor for the progression of DR to more severe stages, PDR and DME, and a greater risk of visual impairment as well as increased treatment burden. Earlier recognition of OSA and referral for treatment offer an opportunity to improve outcomes through proper screening and management, potentially mitigating their DR progression as well as their risk of systemic complications. Further research is needed to better understand the complex nature of the association between OSA and DR.

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(Continued from page 7)

AI May Help Increase DR Patient Follow-ups

Catching diabetic retinopathy as early as possible is key to preserving patients' vision. But despite the frequent implementation of large-scale screening efforts, adherence to annual eye exams still lag, with rates presently at 67 percent in high-income countries and 39 percent in low- and middle-income countries, according to research. Those patients with referable DR have also been slow to attend referral appointments.

To probe for ways to improve adherence, a group of researchers recently compared human graders and computer-based artificial intelligence assessment of images in diabetic retinopathy screening programs. Their review study published recently in *Eye* showed that AI algorithms are associated with an increased uptake in follow-up exams because they give patients actionable information right away.[1]

The researchers screened articles in several major health sciences databases. Their review yielded data from 20,108 patients with diabetes across six studies, 6,476 of which were graded using artificial intelligence and 13,632 who were graded by humans. The random effects model showed that initial AI assessment for diabetic retinopathy significantly increased the number of scheduled follow-up appointments (OR 1.89). Patients under 21 in particular demonstrated higher uptake (OR 11.06) compared with adults (OR 2.75).

"AI-assisted DR screening allows real-time classification of severity of DR at the point-of-care, in any clinical setting, irrespective of availability of skilled ophthalmic personnel; this in turn allows patients to be informed of any need for onward referral sooner than can be achieved with human graders," the researchers explained in their paper. "AI based DR screening systems accelerate the analysis of fundus images and provide DR grading results faster than human grader-based systems."

The researchers concluded that this increased uptake in follow-up exams is "likely due to instant results being made available with AI-based algorithms when compared to a delay in the communication assessment outcomes achieved with human graders."

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Revisiting pneumatic retinopexy: Past, present, and future

Evolving evidence, practical considerations and forthcoming directions for this practical, in-office procedure.

Fares Antaki, MDCM, FRCSC, and Aleksandra Rachitskaya, MD

Fares Antaki, MDCM, FRCSC

Aleksandra Rachitskaya, MD

Take-home points

- Pneumatic retinopexy is a minimally invasive, office-based treatment for select cases of rhegmatogenous retinal detachment that offers favorable visual outcomes.
- Careful patient selection is critical for maximizing single-surgery success with PnR.
- Despite strong evidence supporting its use, PnR remains underutilized in the United States due to training gaps and surgeon preference for operating room-based procedures.
- In the future, emerging artificial intelligence technologies may enhance patient selection and outcome prediction, potentially expanding the role of PnR in personalized retinal care.

Despite having several things going for it pneumatic retinopexy continues to be underused in the United States due to how surgeons are trained and their preferences for procedures such as vitrectomy. However, PnR's strong outcomes data and the convenience of being an in-office procedure make it a worthwhile option that surgeons shouldn't ignore for the treatment of retinal detachment. Here, we'll take a look at PnR's pros and cons, and how it can be beneficial in selected patients.

Pneumatic retinopexy's development

The evolution of PnR for retinal detachment repair stems from numerous innovations dating back to the early 20th century,[1] culminating in its first formal introduction by Alfredo Domínguez of Madrid, Spain, in 1985.[2] The technique was later coined and popularized by George F. Hilton and W. Sanderson Grizzard, former professors at the University of California Medical Center in San Francisco, in 1986.[3] Early evidence emerged in 1989 when San Diego's Paul Tornambe, MD, reported a single-surgery success rate of 73 percent for PnR in patients with detachments associated with breaks in the superior two-thirds of the retina.[4] However, the modern resurgence of PnR is largely driven by a growing body of evidence-based literature comparing it to other surgical approaches. For example, the landmark PIVOT trial demonstrated an 80.8 percent initial success rate for PnR, along with superior visual acuity and less vertical metamorphopsia, but lower primary anatomic success compared to pars plana vitrectomy.[5]

There's a growing interest in medicine toward office-based and outpatient treatments aimed at reducing hospital utilization and overall costs. PnR exemplifies this shift, offering an alternative that eliminates the need for anesthesia and an operating room. However, careful patient selection is essential to achieving optimal outcomes. In general, ideal candidates are phakic patients with an RRD involving a single break (or a few breaks spanning no more than 1 clock hour) between the 8 and 4 o'clock meridians. It's

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Dr. Antaki is a vitreoretinal surgery fellow at the Cleveland Clinic Cole Eye Institute.

Dr. Rachitskaya is a vitreoretinal surgeon at the Cleveland Clinic Cole Eye Institute.

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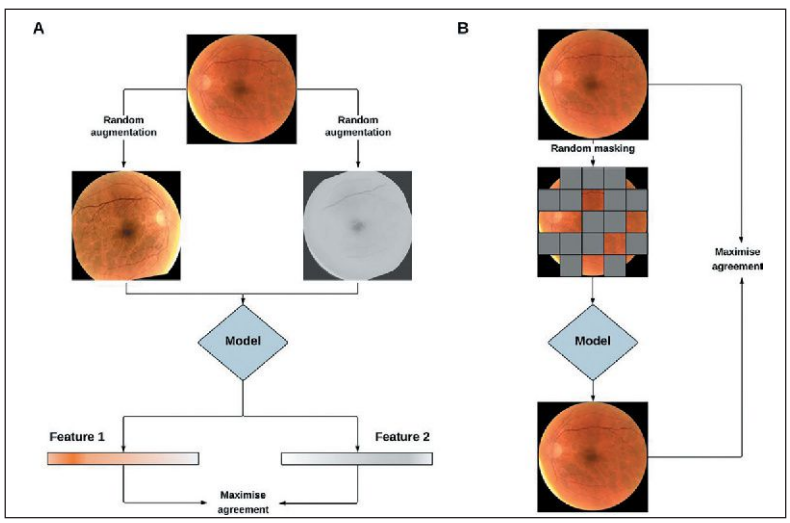
recommended to avoid cases with inferior retinal pathology. That said, the PIVOT criteria included patients with breaks or lattice degeneration anywhere in the attached retina, as well as pseudophakic patients.[5] Once PnR is chosen for RRD repair, several technical factors can influence the procedure's success. These include the choice of gas tamponade, the use of cryotherapy versus laser retinopexy and the patient's ability to maintain appropriate positioning.

Real-world results

While randomized controlled trial data suggest a high success rate for PnR, real-world data indicate lower success rates in practice. For example, an analysis of IRIS Registry data (2013 to 2022) reported a single-surgery success rate of only 59.82 percent for PnR overall, with pseudophakic eyes having an even lower success rate.[6] A key limitation of such large-database data is the inability to account for clinical criteria used to determine whether a patient with RRD is an appropriate candidate for PnR. Moreover, in the study, operation failure was defined as the need for additional procedures, like repeat PnR, scleral buckle, PPV or complex retinal detachment repair. This may lead to an underestimation of the true success rate of PnR. For instance, in the early postoperative period, some surgeons may opt for further intervention to flatten the retina in the presence of persistent subretinal fluid, even though the retina might have reattached with observation without additional procedures in select cases. PnR is a non-drainage procedure that relies on the retinal pigment epithelium to pump out most of the fluid. Therefore, generally, if the break is sealed and no new breaks are present, residual fluid could sometimes be observed—as is common in SB surgery—and the case shouldn't be considered a failure as long as the fluid resolves.

Even when PnR is considered successful, its durability may be questioned, as the underlying vitreous traction causing the retinal breaks isn't addressed—unlike with SB or PPV. This is a valid critique of the approach, given that relieving traction is generally considered a core principle in the management of RRD. In a post-hoc analysis of the PIVOT trial with over five years of follow-up, both PnR and PPV were associated with very low rates of long-term redetachment.[7] The authors suggest that eliminating vitreous traction through PPV may not be necessary for long-term reattachment in most RRDs. They draw a parallel with lasered horseshoe tears, which rarely cause detachments despite persistent traction. Older studies on PnR also support the long-term durability of this surgery.[8]



AI advances such as foundation modeling may help predict the outcomes of retinal detachment. Shown here are methods of training foundation models. (A) A contrastive self-supervised learning task, which randomly augments images and trains the model to maximize the agreement of matching image pairs. (B) A generative self-supervised learning task, which masks points of an image and trains the model to redevelop it. ***Chia MA, et al. Foundation models in ophthalmology. Br J Ophthalmol 2024. 108:10:1341-1348. Creative Commons License: https://creativecommons.org/licenses/by/4.0/.***

Current usage patterns

Overall, PnR appears to be underutilized in the United States, despite many detachments fitting the typical configuration for traditional PnR. For example, in 2021, only 36.1 percent of retina specialists responding to the ASRS Preferences and Trends Survey reported they would treat a phakic, superior, macula-on RRD with a single superior tear using PnR, and 58.1 percent said they

performed PnR less than once per month.[9] Its use varies significantly depending on the region, operating room availability and, to a large extent, surgeon comfort. Because PnR isn't routinely taught in U.S.-based fellowships[10]—and given the greater familiarity with SB and PPV—surgeons tend to favor procedures they're more comfortable performing. A laddered approach may be reasonable—starting with PnR and proceeding to PPV or combined SB/PPV if PnR fails. This strategy is supported by clinical trial evidence indicating that attempting PnR doesn't compromise final reattachment rates or visual outcomes.[4,5,11] Some evidence suggests, however, that the single-surgery anatomic success rate of PPV or SB following failed PnR may be lower—around 75 percent,[12] compared to the higher success rates of 80 to 90 percent typically seen when PPV and/or SB are used as primary interventions for RRD.[13,14]

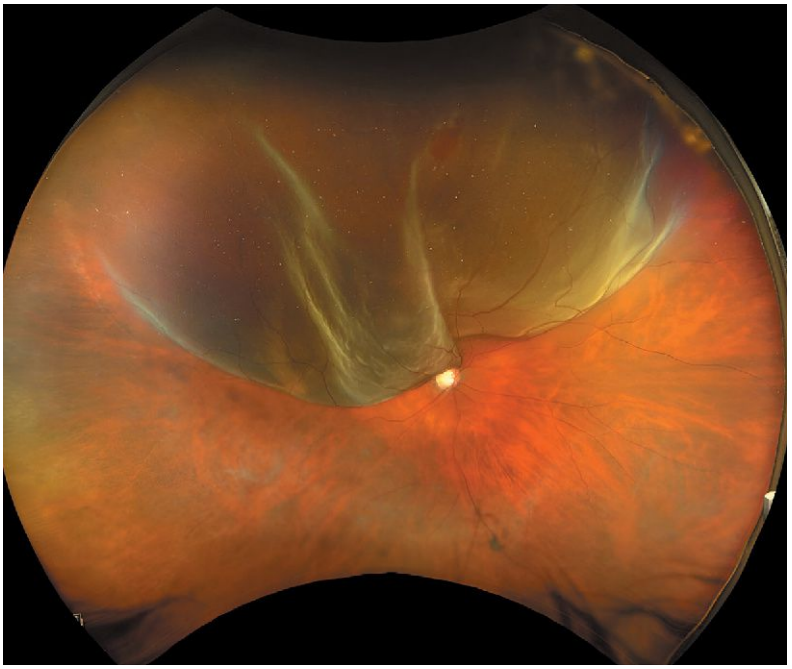
There is compelling evidence to use PnR as a first-line treatment for RRD because it's been associated with better vision-related functioning (including higher mental health scores and improved ability to carry out daily activities) and less metamorphopsia compared to PPV.[15,16] While those factors aren't routinely measured in the clinic, from a practical standpoint, we also need to consider the risk of cataract progression.

In the PIVOT trial, 65 percent of phakic patients in the PPV arm underwent cataract surgery within one year, compared to 16 percent in the PnR group.[5] This is a key practical consideration we routinely face after performing PPV or SB/PPV for RRD in phakic patients. The majority will require cataract surgery in the operated eye.

When planning subsequent cataract surgery, because these patients are often myopic in the fellow eye, intraocular lens calculations must take into account the risk of symptomatic aniseikonia. There are two main approaches: performing bilateral cataract surgery with refractive targets closer to plano; or operating only on the eye that developed a post-PPV cataract, targeting a moderate or high myopic outcome to match the fellow eye. The latter may represent a missed opportunity to improve the patient's quality of life by achieving spectacle independence for distance vision.

The Cost Question

Regarding cost-effectiveness, it's intuitive to assume that PnR, as an office-based procedure, is less expensive than PPV or SB, which require an operating room. The lower overhead and administrative costs in outpatient settings likely drive the perception of PnR as a more economical option.[17] This may be significant for societies with a single-payer health-care system, where substantial savings could be realized when PnR is clinically appropriate. However, any economic analysis must also consider a broader range of factors beyond the initial procedure, such as follow-up visits, management of complications and the necessity for additional treatments. A recent economic analysis actually found that PPV was the most cost-effective primary procedure for



Superior macula-splitting retinal detachment with a single horseshoe tear located between 12 and 1 o'clock in a phakic patient, an ideal candidate for pneumatic retinopexy.

primary RRD from the health-care payer perspective over a lifetime.[18] This was attributed to PPV's higher single-operation success rate, which helps avoid the additional costs associated with treatment failures.

AI's potential impact

Recent advances in artificial intelligence have sparked early interest in applying these techniques to predict outcomes in RRD.[19,20]

For instance, one study explored the use of preoperative patient factors to predict the success of PnR.[19] As large datasets of RRD cases become increasingly available—ideally enriched with ultra-widefield imaging and detailed clinical variables such as break location, extent of detachment and patient age—there is potential to build robust AI-based predictive models. We speculate that, eventually, by training models on thousands of RRD cases with known outcomes, AI could provide individualized predictions.

For example, a model could analyze a fundus image along with patient-specific factors to estimate the likelihood of success with PnR. It might even do better than the usual decision-making shortcuts doctors use by picking up on subtle features we might miss. Of course, we recognize that even with comprehensive datasets, numerous nuanced variables such as surgeon skill and patient compliance remain difficult to quantify. Still, the emergence of multimodal models that incorporate imaging, videos and even data from wearable sensors (e.g., tracking postoperative positioning) may bring us closer to personalized, AI-driven retinal care. Foundation models may play a key role in enabling this next frontier.[21]

Bottom line

In conclusion, PnR represents a compelling, safe, effective, first-line option for selected cases of RRD. Despite variability in real-world success rates and potential underutilization due to training gaps and surgeon preference, evidence from clinical trials supports its efficacy and long-term durability. With the rise of AI-driven predictive tools in medicine and growing interest in outpatient retinal care, PnR may play an increasingly important role in the future of personalized RRD management.

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Department Editor ***Meera Sivalingam, MD***

Tattoo-associated Uveitis

Asking the right questions and taking complete images help ensure this diagnosis isn't missed.

By Flavius Beca, MD

Flavius Beca, MD

A 27-year-old female initially presented to the emergency room with three months of photophobia, tinnitus, hearing loss and headaches.

Workup and imaging

Visual acuity was 20/25 in the right and left eye. Exam showed 2+ anterior chamber cell with mild anterior vitreous spillover, as well as disc edema in both eyes. Although idiopathic intracranial hypertension was suspected based on the confluence of symptoms, body habitus and demographics, the concurrent bilateral anterior uveitis prompted a thorough workup which included neuroimaging, lumbar puncture and broad infectious inflammatory laboratory workup which were all consistent with IIH alone.

The patient was referred to the retina clinic where multimodal imaging, which included spectral domain macular OCT, fundus autofluorescence and fluorescein angiogram were unremarkable excepting mild disc leakage in the late phase angiogram *(Figure 1)*. The anterior uveitis was successfully treated with topical steroids and subsequent taper, while the patient saw neuro-ophthalmology for the management of the concurrent IIH with oral acetazolamide and weight loss.

Figure 1. Patient fundus photo with mild optic disc edema and unremarkable fluorescein angiogram at initial presentation.

The patient then presented nearly four months later with new sudden painless vision loss in the right eye. At this time vision was 20/50 in the affected eye and examination revealed a peripapillary subretinal hemorrhage and again bilateral anterior chamber cell but no evidence of posterior inflammation. A peripapillary macular neovascular membrane and secondary hemorrhage was suspected, likely in the setting of chronic IIH, an uncommon though well-established entity *(Figure 2)*. However, upon further review of symptoms, the patient acknowledged having "itchy and raised" rash within several of her tattoos reported as chronic for the preceding six months, corresponding with the time of the original symptom onset *(Figure 4)*.

Repeat multimodal imaging was performed, this time including indocyanine-green angiogram. The FA confirmed the MNV but once again showed no vasculitis or disc leakage (*Figure 2*). However, the ICG angiogram revealed bilateral scattered small hypofluorescent lesions consistent

BIO

Dr. Beca is a vitreoretinal surgeon at Wills Eye Hospital/Mid-Atlantic Retina in the Philadelphia region. He has no disclosures to report.

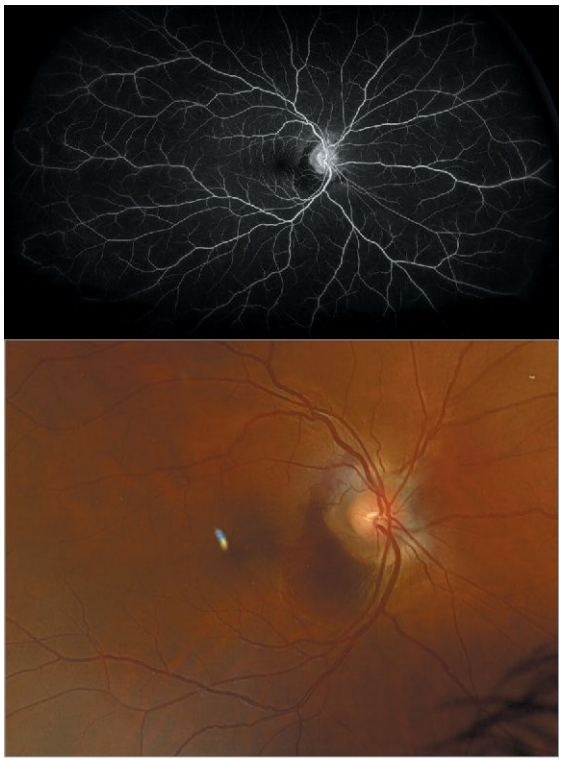

Figure 2. Fluorescein angiogram is once again unremarkable beyond the MNV and blockage by the subretinal hemorrhage (top). The fundus photo taken at second presentation depicts peripapillary MNV with subretinal hemorrhage.

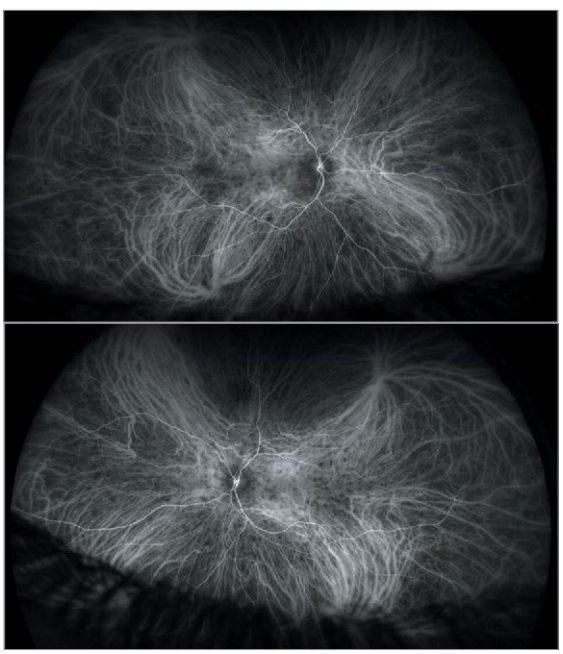

Figure 3. Patient ICG angiogram depicts bilateral scattered hypofluorescent choroidal lesions consistent with sarcoid granulomas.

with choroidal granulomas as are often seen in patients with sarcoid uveitis or tattoo-associated uveitis *(Figure 3)*.

The patient was treated with a single bevacizumab intravitreal injection as well as 60 mg of oral prednisone with a subsequent taper. Treatment resulted in improvement in vision and apparent resolution of the MNV and subretinal hemorrhage with vision improving to 20/25 in the right eye and the pruritic tattoo rash. Notably, once the oral steroids were tapered off, the patient developed recurrence of anterior chamber cell as well as the pruritic rash. At this point the patient was referred to rheumatology to initiate systemic immunosuppression.

Discussion

Peripapillary neovascular membranes can occur in a wide variety of conditions. In a large retrospective series of over 1,100 cases, only six developed peripapillary MNVs. Although rare, MNVs can occur in patients with IIH and reported treatment approaches include observation, management of the IIH, and anti-VEGF injections.[1,2,3] Unlike other MNVs, most reports in the literature suggest that once treated and the underlying condition is controlled, the MNVs don't recur.[1]

In the setting of chronic uveitis, secondary MNVs occur rarely (~2 percent) but can be suspected in the setting of just about any cause of chronic inflammation.[1,2] Among causes of infectious uveitis, ocular histoplasmosis is the most common entity where MNVs, including peripapillary MNVs, are common. In addition, toxoplasmosis, tuberculosis and West Nile Virus are infrequent causes (all with incidences of less than 5 percent). Among causes of non-infectious uveitis, multifocal choroiditis/punctate inner choroidopathy are the most common causes with 50 percent or more of cases developing an MNV. However, serpiginous choroiditis (10 to 25 percent) and Voyt-Koyanagi-Harada disease (9 to 15 percent) are also reported to have significant rates of MNV development.[1,2] Untreated sarcoidosis very infrequently has also been reported as a cause of secondary MNVs.[4,5] Treatment patterns vary, however, many providers treat with anti-VEGF with concurrent management of any underlying inflammation.

Tattoo-associated uveitis is an entity that remains poorly understood but likely exists on a shared spectrum with sarcoidosis.[6] As such, imaging and clinical presentations can mimic sarcoidosis.[7] Inflammation of the tattoo can be concurrent or precede an episode of uveitis, sometimes by many years. Patients often ignore or fail to appreciate the significance of their inflamed, bumpy or itchy tattoos, particularly in the context of other bothersome visual symptoms. In particular, the darker pigmented inks are more frequently associated with inflammation.[6] Careful history and complete imaging are critical in making the diagnosis. Like sarcoidosis, patients often experience recurrent symptoms requiring chronic

(Continued on page 34)

Incorporating AI into your retina practice

This tool can offer value in many areas, from creating patient education materials to bridging language barriers.

By Jayanth Sridhar, MD

This month, I interviewed John Kitchens, MD, who practices in Lexington, Kentucky, to learn how he uses artificial intelligence to increase efficiency and improve patient care at his retina practice.

A disclaimer from Dr. Kitchens: To keep the process efficient and natural, I dictated my responses on the fly using my Plaud pin [a wearable AI voice recorder], which automatically transcribes voice to text. I then copied that text into ChatGPT-4o and used it, along with Jay's original questions, to refine and shape the final answers. This workflow allowed me to keep the tone conversational while organizing my thoughts clearly and coherently. It's a great example of how AI can enhance productivity and creativity, even in something as simple as responding to an email interview. It took me a total of about 15 minutes.

1. What apps are you currently using as a retina doctor for your day-to-day productivity, and how have they benefited your quality of life?

JK: Right now, the app I use most frequently in my day-to-day life as a retina specialist is ChatGPT. I've found it incredibly versatile; it's become my go-to tool for everything from composing emails and crafting thoughtful responses to performing literature searches on disease states. I also rely on it to help create patient education materials that are easy to understand and visually appealing. Another area where it's been helpful is summarizing research papers. Whether I'm preparing for a talk, reviewing the latest studies or trying to digest a particularly dense publication, AI tools like this have streamlined my workflow and helped me manage my time more effectively.

2. Are you using AI for your digital media creation? If not, do you think you will in the near future?

JK: Absolutely—I've been using AI for digital media creation for a while now, especially when it comes to presentations. I like my presentations to be visually engaging and thought-provoking, so I often use tools like MidJourney, Ideogram or ChatGPT to generate striking images that complement the narrative. Lately, I've also been experimenting with Sora AI to create short, funny videos that add personality and depth to my talks. These kinds of tools allow me to communicate complex ideas more effectively, especially when speaking at conferences or educational events. I've also started using AI to help generate graphs and charts, making my Keynote or PowerPoint slides more compelling and easier for audiences to follow. Over the past two and a half years, AI has certainly elevated the way I create and share content.

Quotable

"[ChatGPT] has become my go-to tool for everything from composing emails and crafting thoughtful responses to performing literature searches on disease states. I also rely on it to help create patient education materials that are easy to understand and visually appealing."

3. Do you have any ethical concerns about AI that have changed how you use it in practice?

JK: The biggest ethical concern I have is around patient privacy, specifically HIPAA compliance. Whenever I upload images—

BIO

Dr. Sridhar is an associate professor of clinical ophthalmology at Bascom Palmer Eye Institute, Miami.

DISCLOSURES: Dr. Sridhar is a consultant to Alcon, DORC, Genentech/Roche and Regeneron Pharmaceuticals. Dr. Kitchens is a consultant for Alcon, Allergan, Alimera, Bayer, Genentech, Optos, Regeneron Pharmaceuticals and ZEISS.

Photo Credit: Plaud.AI

Dr. Kitchens used a Plaud NotePin—a wearable AI note-taker—to record and transcribe his answers to the prompts in this column.

like OCT scans—for assistance or a second opinion using AI, I'm very careful to de-identify or exclude any personal patient information. I don't want to inadvertently expose sensitive data. That said, I feel more comfortable using AI when it's strictly for training or translation purposes. One incredibly helpful feature of ChatGPT, for example, is its ability to serve as a real-time translator during clinical interactions. You can tell it to translate spoken English into Korean, or vice versa, and it facilitates communication in a way that feels seamless. It's an amazing tool for breaking down language barriers with patients and improving care.

4. If someone reading this hasn't used any AI, including large language models, what first steps should they take to familiarize themselves and get comfortable using these new tools?

JK: For someone who's just getting started, I'd recommend beginning with some YouTube videos or online tutorials. These can offer a good overview of how different AI tools work and introduce you to a variety of platforms in a user-friendly way. Once you've gotten the lay of the land, try out the free versions of popular AI tools; see which one fits your workflow or needs the best, and then stick with it long enough to learn it well. At that point, upgrading to a paid version can be worthwhile to unlock premium features and gain access to the most advanced capabilities. That said, not all platforms are equally priced. For instance, the pro version of ChatGPT with access to Sora and other advanced features can cost up to $200 per month, which I wouldn't recommend for most people. More affordable options like Google Gemini or Claude fall in the $15 to $20 range and offer great value. The key is to start small, experiment and gradually build your comfort level.

Tattoo-associated Uveitis

(Continued from page 32)

Figure 4. Patient tattoos depict an elevated and symptomatically pruritic rash localized to the darkly pigmented tattoos.

immunosuppression. Removal of the tattoos hasn't been definitively shown to alter the disease course and is often not viable with large tattoos.

Bottom line

When TAU or sarcoidosis are suspected, a careful tattoo history is important. In addition, multimodal imaging should include ICG in addition to FA, as in some cases like the one reported, choroidal granulomas can be silent on fluorescein angiograms alone. While the definitive cause for the peripapillary MNV can't be determined, treatment requires management of the underlying inciting disease entity.

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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.
Hypersensitivity
SYFOVRE is contraindicated in patients with hypersensitivity to pegcetacoplan or to any of the excipients in SYFOVRE. Systemic hypersensitivity reactions (e.g., anaphylaxis, rash, urticaria) have occurred.

WARNINGS AND PRECAUTIONS

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

Postmarketing Experience
The following adverse reactions have been identified during postapproval use of SYFOVRE. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Eye disorders: retinal vasculitis with or without retinal vascular occlusion. Systemic reactions: anaphylaxis, rash, and urticaria.

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

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Save more retinal tissue

Through Year 2, in OAKS and DERBY, SYFOVRE slowed GA lesion growth vs sham pooled.[1]

SYFOVRE slowed GA lesion growth with **increasing effects over time** **up to 42%** in Year 3 (GALE) vs projected sham in patients without subfoveal lesions[1,2]

- Through Year 2 (OAKS and DERBY), SYFOVRE slowed GA lesion growth (mm^2) vs sham pooled by 22% (3.11 vs 3.98) and 18% (3.28 vs 4.00) monthly, and by 18% (3.26 vs 3.98) and 17% (3.31 vs 4.00) EOM[1,2]
- Through Year 3 (GALE), SYFOVRE slowed GA lesion growth (mm^2) vs sham pooled/projected sham by 25% (4.46 vs 5.94) monthly and 20% (4.74 vs 5.94) EOM. The greatest differences were observed in Year 3[2]
  - Reductions in patients without subfoveal lesions at baseline through Year 3: 32% (5.10 vs 7.54 (n=95)) monthly and 26% (5.60 vs 7.54 (n=104)) EOM. In this subset of patients, there was a 42% reduction with monthly SYFOVRE in Year 3 vs projected sham

SE in trials (monthly, EOM, sham pooled/projected sham): OAKS: 0.15, 0.13, 0.14; DERBY: 0.13, 0.13, 0.17; GALE (total population): 0.16, 0.16, 0.19; GALE (without subfoveal): 0.26, 0.31, 0.41[1,2]

EOM=every other month; GA=geographic atrophy; SE=standard error.

GALE Trial Limitations: GALE is an ongoing open-label, multi-center extension study, subject to patient dropouts over time. The analysis for the first year of GALE utilized a projected sham and may not reflect rate of change of all patients with GA. Projected sham assumes linear growth rate from Months 24-36 (GALE Year 1) based on the average of the mean rate of change of each 6-month period of sham treatment in OAKS and DERBY and natural history studies, which have shown there is a high correlation between prior 2-year growth rates of GA lesions and subsequent 2-year growth rates. This is a prespecified analysis but there is no statistical testing hierarchy, therefore the results on the individual components need cautious interpretation. Open-label studies can allow for selection bias.[2,3]

Discover more at SyfovreECP.com

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, in patients with active intraocular inflammation, and in patients with hypersensitivity to pegcetacoplan or any of the excipients in SYFOVRE. Systemic hypersensitivity reactions (e.g., anaphylaxis, rash, urticaria) have occurred.

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.
- **Retinal Vasculitis and/or Retinal Vascular Occlusion**
  - Retinal vasculitis and/or retinal vascular occlusion, typically in the presence of intraocular inflammation, have been reported with the use of SYFOVRE. Cases may occur with the first dose of SYFOVRE and may result in severe vision loss. Discontinue treatment with SYFOVRE in patients who develop these events. Patients should be instructed to report any change in vision without delay.
- **Neovascular AMD**
  - In clinical trials, use of SYFOVRE was associated with increased rates of neovascular (wet) AMD or choroidal neovascularization (12% when administered monthly, 7% when administered every other month and 3% in the control group) by Month 24. Patients receiving SYFOVRE should be monitored for signs of neovascular AMD. In case 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 ≥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.

OAKS and DERBY Trial Design: SYFOVRE safety and efficacy were assessed in OAKS (N=637) and DERBY (N=621), multi-center, 2-year, 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 every other month, sham monthly, or sham every other month, for 2 years. Change from baseline in the total area of GA lesions in the study eye (mm^2) was measured by fundus autofluorescence (FAF).[1,2]

GALE Trial Design: GALE (N=790) is a multi-center, 3-year, Phase 3, open-label extension study to evaluate the long-term safety and efficacy of pegcetacoplan in subjects with geographic atrophy secondary to age-related macular degeneration. Patients enrolled in GALE include those who completed OAKS or DERBY after 2 years and 10 patients from Phase 1b Study 103. Patients with GA (atrophic nonexudative age related macular degeneration) with or without subfoveal involvement, secondary to AMD were assigned to receive 15 mg/0.1 mL intravitreal SYFOVRE monthly or SYFOVRE EOM for 3 years. The first visit was required to be within 60 days of the final visit in OAKS and DERBY.[2]

References: 1. SYFOVRE (pegcetacoplan injection) [package insert]. Waltham, MA: Apellis Pharmaceuticals, Inc.; 2024. **2.** Data on file. Apellis Pharmaceuticals, Inc. **3.** Sunness JS, Margalit E, Srikumaran D, et al. The long-term natural history of geographic atrophy from age-related macular degeneration: enlargement of atrophy and implications for interventional clinical trials. *Ophthalmology*. 2007;114(2):271–277. doi:10.1016/j.ophtha.2006.09.016.

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