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RETINA SPECIALIST®

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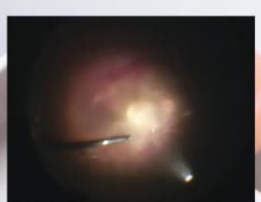
What's Coming Down the DR/DME Pipeline

An update on the trials and what future therapy might look like - ***Page 15***

Also Inside

Online Video



- *The "grazing" technique for repair of diabetic tractional retinal detachments* – ***Page 9***

Ken is a real patient with GA, and Dr. Arshad Khanani is his retina specialist who treats his GA with IZERVAY.

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izervay™ (avacincaptad pegol intravitreal solution) 2 mg

*In 2 clinical trials of 624 people, IZERVAY was proven to reduce the annualized rate of GA lesion growth by 18%-35% in one year compared to those who were not treated.

†Based on Symphony data from 3/24-7/25. May not represent entire patient population.

Dr. Arshad Khanani is a compensated physician.

INDICATION

IZERVAY™ (avacincaptad pegol intravitreal solution) is indicated for the treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD)

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Endophthalmitis and Retinal Detachments

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

Neovascular AMD

- In clinical trials, use of IZERVAY was associated with increased rates of neovascular (wet) AMD or choroidal neovascularization (7% when administered monthly and 4% in the sham group) by Month 12. Over 24 months, the rate of neovascular (wet) AMD or choroidal neovascularization in the GATHER2 trial was 12% in the IZERVAY group and 9% in the sham group. Patients receiving IZERVAY should be monitored for signs of neovascular AMD.

Increase in Intraocular Pressure

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

ADVERSE REACTIONS

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

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

References: 1. Holz FG, Strauss EC, Schmitz-Valckenberg S, van Lookeren Campagne M. Geographic atrophy: clinical features and potential therapeutic approaches. *Ophthalmology*. 2014;121(5):1079-1091. **2.** Izervay. Package insert. Northbrook, IL: Astellas Pharma US, Inc.; 2025. **3.** Astellas Pharma US, Inc. Izervay. Data on File.

astellas

IZERVAY™ (avacincaptad pegol intravitreal solution)
Rx only
Brief Summary: This information is not comprehensive. Visit IZERVAYecp.com to obtain the FDA-approved product labeling or call 800-707-4479.

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

2 DOSAGE AND ADMINISTRATION
2.1 General Dosing Information
IZERVAY must be administered by a qualified physician.
2.2 Recommended Dosage
The recommended dose for IZERVAY is 2 mg (0.1 mL of 20 mg/mL solution) administered by intravitreal injection to each affected eye once monthly (approximately every 28 ± 7 days).

4 CONTRAINDICATIONS
4.1 Ocular or Periocular Infections
IZERVAY is contraindicated in patients with ocular or periocular infections.
4.2 Active Intraocular Inflammation
IZERVAY is contraindicated in patients with active intraocular inflammation.

5 WARNINGS AND PRECAUTIONS
5.1 Endophthalmitis and Retinal Detachments
Intravitreal injections may be associated with endophthalmitis and retinal detachments. Proper aseptic injection techniques must always be used when administering IZERVAY in order to minimize the risk of endophthalmitis. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay, to permit prompt and appropriate management.
5.2 Neovascular AMD
In the GATHER1 and GATHER2 clinical trials, use of IZERVAY was associated with increased rates of neovascular (wet) AMD or choroidal neovascularization (7% when administered monthly and 4% in the sham group) by Month 12. Over 24 months, the rate of neovascular (wet) AMD or choroidal neovascularization in the GATHER2 trial was 12% in the IZERVAY group and 9% in the sham group. Patients receiving IZERVAY should be monitored for signs of neovascular AMD.
5.3 Increase in Intraocular Pressure
Transient increases in intraocular pressure (IOP) have been observed after an intravitreal injection, including with IZERVAY. Perfusion of the optic nerve head should be monitored following the injection and managed as needed.

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

- Ocular and periocular infections
- Active intraocular inflammation
- Endophthalmitis and retinal detachments
- Neovascular AMD
- Increase in intraocular pressure

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.
The safety of avacincaptad pegol was evaluated in 733 patients with AMD in two sham-controlled studies (GATHER1 and GATHER2). Of these patients, 292 were treated with intravitreal IZERVAY 2 mg (0.1 mL of 20 mg/mL solution). Three hundred thirty-two (332) patients were assigned to sham.
Adverse reactions reported in ≥2% of patients who received treatment with IZERVAY pooled across GATHER1 and GATHER2, are listed below in Table 1.

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

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

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

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy Risk Summary
There are no adequate and well-controlled studies of IZERVAY administration in pregnant women. The use of IZERVAY may be considered following an assessment of the risks and benefits.
Administration of avacincaptad pegol to pregnant rats and rabbits throughout the period of organogenesis resulted in no evidence of adverse effects to the fetus or pregnant female at intravenous (IV) doses 5.5 times and 3.4 times the human exposure, respectively, based on Area Under the Curve (AUC), following a single 2 mg intravitreal (IVT) dose (see Data).
In the U.S. general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15%-20%, respectively.
Animal Data
An embryo fetal developmental toxicity study was conducted with pregnant rats. Pregnant rats received daily IV injections of avacincaptad pegol from day 6 to day 17 of gestation at 0.1, 0.4, 1.2 mg/kg/day. No maternal or embryofetal adverse effects were observed at any dose evaluated. An increase in the incidence of a non-adverse skeletal variation, described as short thoracolumbar (ossification site without distal cartilage) supernumerary ribs, was observed at all doses evaluated. The clinical relevance of this finding is unknown. Plasma exposures at the high dose were 5.5 times the human AUC of 999 ng·day/mL (23976 ng·hr/mL) following a single 2 mg IVT dose.
An embryo fetal developmental toxicity study was conducted with pregnant rabbits. Pregnant rabbits received daily IV injections of avacincaptad pegol from day 7 to day 19 of gestation at 0.12, 0.4, 1.2 mg/kg/day. No maternal or embryofetal adverse effects were observed at any dose evaluated. Plasma exposure in pregnant rabbits at the highest dose of 1.2 mg/kg/day was 3.4 times the human AUC of 999 ng·day/mL (23976 ng·hr/mL) following a single 2 mg IVT dose.
8.2 Lactation
There is no information regarding the presence of avacincaptad pegol in human milk, or the effects of the drug on the breastfed infant or on milk production. Many drugs are transferred in human milk with the potential for absorption and adverse reactions in the breastfed child. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for IZERVAY and any potential adverse effects on the breastfed infant from IZERVAY.
8.4 Pediatric Use
Safety and effectiveness of IZERVAY in pediatric patients have not been established.
8.5 Geriatric Use
Of the total number of patients who received IZERVAY in the two clinical trials, 90% (263/292) were ≥65 years and 61% (178/292) were ≥75 years of age. No significant differences in efficacy or safety of avacincaptad pegol were seen with increasing age in these studies. No dose adjustment is required in patients 65 years and above.

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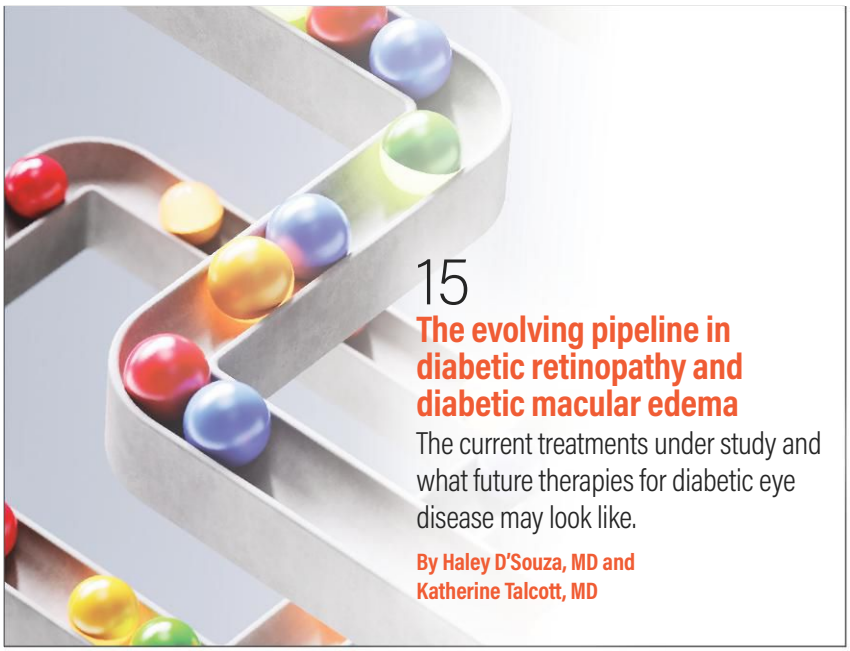
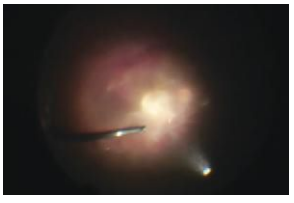
FEATURES



DEPARTMENTS

Online Video



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EDITORIAL

By Jason Hsu, MD

Honoring our Mentors

The phrase, "We stand on the shoulders of giants" resonated throughout the Atlantic Coast Retina Club/Macula 2026 meeting.

In our field, we often think of those who set our subspecialty in motion: Robert Machemer; Charles Schepens; Jules Gonin; and Arnall Patz, amongst a myriad of others whose inquisitive nature and daring pushed our field forward into its current iteration.

As we also celebrated the 65th anniversary of the Wills Eye Retina Service, I was reminded of how relatively young our field is and yet how many greats have come before me, including P. Robb McDonald, Charles Rife, William Annesley, William Tasman, and Lov Sarin who founded the service.

Kevin Caldwell

Dr. Hsu, his wife, Vatinee Bunya, MD, and Dr. Hsu's mentor, Arunan Sivalingam, MD.

It was a chance to honor living legends, such as our former chief of the Retina Service, William Benson, and our current ophthalmologist-in-chief and CEO, Julia Haller as a new fund supporting the retina research fellowship was inaugurated in their names.

One of the highlights for me was seeing more than 50 former residents and fellows return for the celebration. It was a combination of those whom I have helped train and many others who came before me. Sitting around and hearing stories about the craziness of fellowship really cemented the bond that we have across time through our shared experiences.

The glue that brought everyone back was really our fellowship director, Arunan Sivalingam, who has been in that role for almost a quarter century. Nothing compares to his calm demeanor, his personal investment in getting to know each fellow, and his wardrobe (think bowties and crazy socks). As I look back and think about the people who have influenced my career trajectory the most, Dr. Sivalingam stands out. He has been an advocate for me from the days of my fellowship, offering me my first (and only) job, promoting me in our research department, and mentoring me countless times over the years.

We have all become very busy, which as many patients remind me, is a blessing for our livelihood. However, it's worth taking a breather and thinking about how each of us got here. Remember the mentors who helped you along the way and think about taking a few minutes to make a call or send a message to one (or more) of those mentors who have made a difference in your life.

Inflammatory and fibrogenic factors in PVR development

The evidence and implications behind these key findings.

Niveditha Pattathil, BHSc, and Tina Felfeli, MD


Niveditha Pattathil, BHSc


Tina Felfeli, MD, PhD

As is well-known, proliferative vitreoretinopathy is a major complication that can occur following retinal detachment repair, characterized by the proliferative growth of contractile cellular membranes on the retina and in the vitreous.[1] The fibrotic membranes that grow in PVR are predominantly derived from the retinal pigment epithelium, which undergo a series of inflammatory and myofibroblastic changes within the inner and outer retinal surfaces and hyaloid.[2] The identification of molecular biomarkers implicated in these dysregulated inflammatory and fibrotic etiological processes could be predictive for the development of PVR, which has the potential to help stratify patients by risk and allow for targeted action earlier in the disease process.[2,3]

Factors involved in the stages of post-RD PVR development

PVR goes through five distinct phases in its development cycle:

1) Ischemic phase. Ischemia in the outer retina leads to diffusion of hypoxic products within the retinal space, triggering breakdown of the blood-retinal barrier within the inner retina. Within three days after RD, approximately 20 percent of photoreceptors die via necrosis, caspase-dependent apoptosis or necroptosis. These cell death pathways are mediated by receptor interacting protein kinase (RIPK1 and RIPK3). Continued ischemia triggers the upregulation of angiogenesis, fibrogenesis, glial proliferation, and the release of further growth factors and cytokines.[2,4]

2) Inflammatory phase. The next phase of PVR development is initiated by the release of serum factors such as thrombin into the vitreous. Macrophages secrete growth factors, specifically fibroblast growth factor and transforming growth factor-beta that stimulate the proliferation of fibroblast-like cells within growing membranes. T-helper cells are also involved in this process, as they release various anti- and pro-fibrogenic cytokines, including interleukin-10, antifibrotic interferon-gamma, FGF, TGFβ, platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF).[2–4]

3) Retinal apoptotic phase. Apoptosis is a cell loss process mediated through intrinsic and extrinsic signaling pathways that are triggered by intracellular death receptors, with considerable shared pathways with the pathogenesis of PVR. Pro-apoptotic factors are dysregulated in PVR, specifically Fas and tumor necrosis factor. Fas ligand receptor binding triggers apoptosis in proliferating RPE cells. Therefore, the FasL/Fas system, when in dysregulation, may contribute to PVR through the defective removal of excess RPE cells. TGFβ is a factor also released during this process, which contributes to the blocking of T-cell-mediated apoptosis and upregulates the proliferation of RPE cells.[5–7]

4) Cell migratory and proliferation phase. Epiretinal membranes consist of a collagenous core, transformed and untransformed RPE cells, Muller glia, T-lymphocytes, macrophages, astrocytes and microglia. Post-RD, the initiation of PVR begins with the activation of RPE cells and their epithelial-mesenchymal transition (EMT), leading to further proliferation, the formation of cell groups that migrate into the vitreous space, and the adoption of an extracellular matrix (ECM) and profibrot-

BIOS

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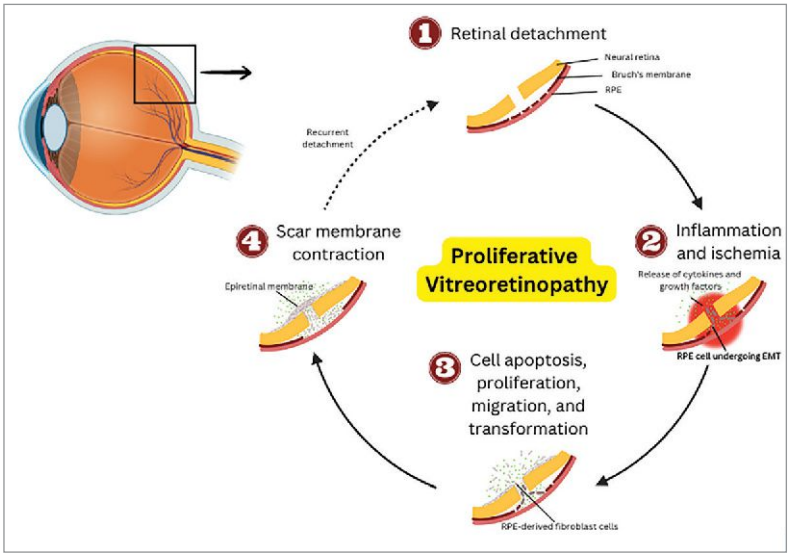
The authors have no relevant disclosures.



Summary diagram of pathophysiology of proliferative vitreoretinopathy .

ic secretory phenotype. Fibronectin initiates the production of further fibronectin, thrombospondin and other proteoglycans, while also inducing the deposition of collagen from fibroblasts. Muller glia also proliferate and release ECM and profibrotic and inflammatory mediators.[2,7]

5) Scar contraction phase. Within PVR membranes, transformed cells can differentiate into myofibroblasts through stimulation from IL-1. Annexin A2 mediates contractile ability in myofibroblasts, which releases further RPE cells into the vitreous space and worsens retinal detachment.[2,3,8]

Potential biomarkers for prediction of PVR after RD

In the literature, the following cytokines and growth factors have been identified within subretinal fluid to be potentially predictive of PVR development:

- Interleukins 1a, 2, 3, 6, 11, 15, 18;
- Chemokine Ligands 2, 3, 11, 17, 18, 19, 22;
- CXC Ligands 8, 9, 10;
- CTSS;
- ADIPOQ;
- Leptin;
- ICAM-1;
- VCAM-1;
- PDGF;
- VEGF;
- Fas;
- FasL; and
- TIMP-1.[2,7]

There are also several cytokines and growth factors that have been identified within vitreous samples to be potentially predictive of PVR development:

- IL-6;
- TGFB2;
- FGF-2;
- Tot Prot;
- MMP-2;
- MMP-9;
- Cont Stim Fac;
- Decorin; and
- miR-21.[9,10]

Challenges in the validation of molecular biomarkers

Predictive molecular biomarkers are substances found in a target tissue that can help indicate the risk of developing a specific pathology. Evaluation of biomarkers relies on the reliability of the sampling technique as obtaining consistent samples of subretinal fluid and vitreous fluid can be challenging and therefore lead to highly variable values. Serum samples can be more reliable but may have lower biomarker levels compared to levels in local retinal production. Additionally, surgical techniques for RD repair can vary, which could potentially influence the rates of PVR between various surgical approaches.[2,11]

Therefore, future biomarker studies should consider detailing the specific surgical approaches taken by their sample or include a range of surgeons and techniques in their analyses. In patients with RD, it's challenging to identify biomarkers with high positive predictive value for PVR development because most molecules are also present in RD cases irrespective of PVR development. Therefore, future research

(Continued on page 10)

The "grazing" technique for TRD

Surgical tips for single 27-gauge vitrectomy for navigating through tight surgical planes in tractional retinal detachments.

Hnin Hnin Oo, MBBS, FRCOphth
Helen Mi, MBBS, MMed(Ophth), FRCOphth, FAMS

Hnin Hnin Oo, MBBS, FRCOphth

Helen Mi, MBBS, FRCOphth, FAMS

Diabetic tractional retinal detachment cases are daunting and unpredictable for any vitreoretinal surgeon. The primary concern during surgery is the ability to relieve all tractional components while avoiding the creation of an iatrogenic retinal break. A retinal break increases surgical complexity, often requiring limited retinectomy, silicone oil tamponade, or scleral buckle to relieve traction and enable endolaser uptake.[1] Postoperatively, the risk of proliferative vitreoretinopathy rises, and posterior breaks may lead to poor visual outcomes.[2]

Technological advances have enabled the development and growing popularity of small-gauge vitrectomy, such as the 27-ga. vitrectomy described by Osaka's Yusuke Oshima, MD, PhD, in 2010.[3] 27-gauge vitrectomy has been shown to result in minimal complications and favorable postoperative visual outcomes.[4] Here, we describe a 27-ga. single-gauge pars plana vitrectomy approach for a young diabetic patient with aggressive "wolf-jaw" configuration[5] TRD and vitreous hemorrhage.

View the Video

Drs. Oo and Mi demonstrate their grazing technique for tractional detachments.
Go to https://vimeo.com/1152674035 or scan the QR code.

The surgical "grazing" technique

In this case, the tractional bands were extensive over the posterior pole and the macula. An intravitreal injection of anti-vascular endothelial growth factor was administered three days preoperatively to improve intraoperative safety. A single 27-gauge system was used with a high-speed 10K vitrectomy cutter *(Figure 1)*. Given the patient's young age, we didn't perform a lensectomy. With a concurrent bleached vitreous hemorrhage, core vitrectomy was performed with caution. We find that positioning the cutter facing upwards in the mid-vitreous cavity is relatively safe until better visualization is gained. The posterior hyaloid is then identified and entered to create a surgical plane to relieve the tractional forces on the posterior pole.

Once the posterior pole is isolated, persistence is key in delaminating and segmenting the fibrovascular membrane without causing a break. We used the vitrector with reduced vacuum settings, ensuring the bevel was strictly away from the retina, entering tight retinal spaces to "graze" on the fibrovascular membranes. End-gripping (such as internal limiting membrane) forceps were used

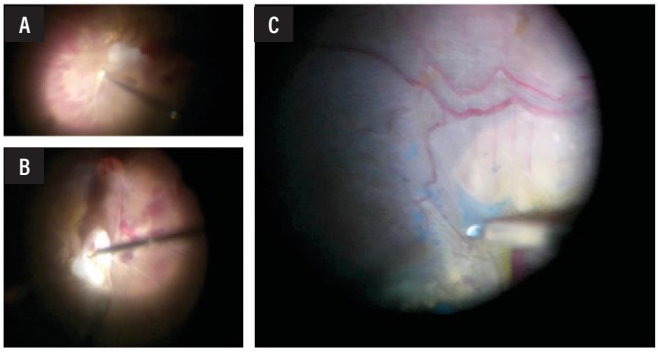


Figure 1. A) Navigating tight surgical spaces with the 27-gauge vitrector to release fibrovascular traction and delamination further with proportion reflux hydro-dissection. B) Using end-gripping forceps to exert gentle tension on the membranes to release any underlying fibrovascular pegs. C) ILM peel is performed over the macula to relieve any residual traction.

BIOS

Dr. Oo is a resident at Tan Tock Seng Hospital.
Dr. Mi is the deputy head of the vitreoretina service and a consultant with the National Healthcare Group Eye Institute (NHGEI) at Tan Tock Seng Hospital.

Disclosures
The authors have no relevant disclosures.

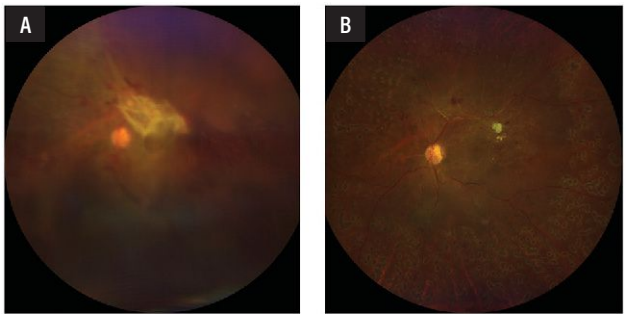


Figure 2. A) Initial preoperative fundus photograph showing central dispersed vitreous hemorrhage, with "wolf-jaw" configuration TRD. B) Postoperative fundus photograph showing reattached retina with isolated residual fibrovascular stump.

when necessary. When using forceps, gentle tension should be applied; if the retina appears too taut, further delamination may be required. The 27-gauge vitrector allows for navigation through tight surgical spaces, and proportional reflux hydrodissection is used as an adjunct to create a fluid-based tissue separation. It's acceptable to leave small, isolated residual fibrovascular pegs as long as all traction is alleviated. ILM peeling is advised when significant macular membrane or distortion is present to further relieve traction and reduce the risk of membrane re-proliferation over the macula.

Completion of panretinal endolaser is essential to reduce ischemic drive postoperatively. In the absence of retinal breaks and with adequate delamination, fluid-air exchange can be performed, leaving only air tamponade in situ.

Color fundus preoperative and postoperative images are illustrated in Figure 2.

The bottom line

With meticulous and purposeful surgical maneuvers, a single 27-gauge vitrectomy allows for precise segmentation and delamination while navigating through tight surgical planes and adherent fibrovascular bands. This approach minimizes the risk of iatrogenic retinal breaks, negates the need for additional chandelier placement, reduces surgical complexity and surgical time, and maintains a good anatomical outcome. RS

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(Continued from page 8)

should focus on combining specific biomarkers and expanding screening methods to include other potential factors in order to improve the prediction methods for PVR.[3,12]

Conclusion

In summary, PVR is the leading cause of failure following surgery for repair of RD. The retinal fibrosis of PVR is triggered by an abnormally regulated array of inflammatory markers, cytokines and growth factors which produce an aberrant inflammatory response at the site of retinal detachment or tear. The process is initiated by RPE-derived fibroblasts that undergo epithelial-mesenchymal transition and start depositing extracellular matrix components and collagen on the retinal surfaces.[2,9,11]

Biomarker profiling holds promise in predicting the development of PVR after surgery, which could help guide management and identify patients earlier who are at risk and may benefit from prophylactic therapy. Current evidence suggests that there are various inflammatory and fibrogenic factors that are associated with RD and can also contribute to the pathogenesis of PVR. Factors with persistent presence into the PVR state may serve as prognostic biomarkers and also be useful as potential targets for anti-PVR treatments.[1,6,10] Individual factors have limited positive predictive value and most have significant overlap between their levels in patients who did and did not go on to develop PVR, which limits utility as a biomarker in isolation. Therefore, the most promising approach is combining multiple clinical and laboratory biomarkers to improve the sensitivity and specificity of PVR prediction.[2,5,7,8] RS

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Managing recurrent retinal detachments without PVR

How to design the best plan of action for a recurrent retinal detachment, and then execute the management properly.

By Theo Bowe, MD, David K. Camacho, MD, Anton Orlin, MD


Theo Bowe, MD


David K. Camacho, MD


Anton Orlin, MD

Take-home points

- Accurately determining whether there is PVR in a recurrent RRD is critical because management strategies differ significantly. Recurrent RRD without PVR is primarily a mechanical problem.
- Successful management depends on identifying the cause of failure and tailoring the repair accordingly.
- Prevention and surgical versatility are key to optimizing outcomes.

Recurrent rhegmatogenous retinal detachment in the absence of proliferative vitreoretinopathy is typically a mechanical process. This is related to new or missed breaks, inadequate treatment of the pathology, persistent vitreoretinal traction or inadequate tamponade. Notably, re-detachments due to the cellular proliferation and traction of PVR are a distinct topic.

The risk of re-detachments has decreased with advances in vitrectomy techniques; however, it still represents a significant issue for vitreoretinal surgeons and patients. Recent studies have noted that recurrent RRD occurs in approximately 2.5 to 8 percent of cases within the United States and 16 to 28 percent globally. The presence of PVR increases the recurrence rate to 25 to 33 percent, with increased rates associated with grade C PVR or worse.[1-5]

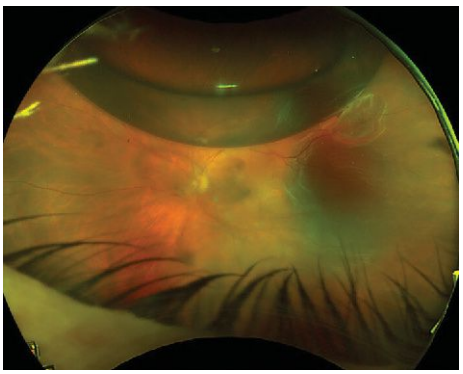
Figure 1. Recurrent retinal detachment caused by a new tear (2:00) in an eye with a previously well treated retinal detachment (with a break at 11:00).

This review summarizes the causes, prevention, and management of recurrent retinal detachments in the absence of PVR.

Etiology

Recurrent RRD without PVR is a mechanical process. Differentiation between the two types of re-detachments is critical. PVR can be characterized as a maladaptive wound healing process associated with cellular proliferation, membrane formation, preretinal, intraretinal and subretinal fibrosis and contraction, which can lead to recurrent RRD. Re-detachments in the setting of PVR require a different approach (possibly adding a scleral buckle, as well as early intervention in PVR RRDs).

The causes of recurrent RRD in the absence of PVR can be separated into the following categories,

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and there may be more than one cause in a single case:

• ***Missed retinal breaks.*** Small tears or retinal defects may be overlooked during the initial surgery, particularly in eyes where the view is compromised by media opacity.

• ***Persistent vitreoretinal traction.*** Residual vitreoretinal traction on the causative break may allow continual accumulation of subretinal fluid.

• ***New break development.*** Continued vitreous traction or vitreous contraction can lead to the development of new breaks *(Figure 1)*.

• ***Inadequate retinopexy.*** Inadequate sealing of the breaks (pexy, or positioning/height of a buckle) may lead to recurrent accumulation of subretinal fluid.

• ***Inadequate tamponade.*** Inadequate tamponade (short-acting, insufficient fill, etc) may fail to support the break until sufficient chorioretinal adhesion is achieved.

Risk factors for re-detachment include:

• ***Surgical and anatomic factors.*** Missed breaks (often in the setting of lattice and/or thin peripheral retina), inadequate vitrectomy, inadequate scleral depression, inadequate pexy or tamponade, or poor selection of method of surgical repair.

• ***Patient factors.*** Inadequate positioning due to various reasons.

Differentiation between PVR RRD and recurrent RRD without PVR is critical due to the differing approaches to fixing them.

Evaluation

Differentiation between PVR RRD and recurrent RRD without PVR is critical, as mentioned above, due to the differing approaches to fixing them.

A thorough history and examination (which may include fundus photography and OCT, and should include a detailed scleral-depressed examination) targeted at understanding the initial method of repair and the reason for the recurrent RRD must be undertaken.

Management

As with any complication or unanticipated outcome, prevention is key. To increase the success rate, a surgeon should be competent in all methods of detachment repair. Although there has been a significant trend towards pars plana vitrectomy in the treatment of retinal detachment,[6] scleral buckling and pneumatic retinopexy remain crucial techniques that have their own advantages. Vitreoretinal Surgery Fellowships should, therefore, ensure trainees are skilled in all these approaches.

Despite our best efforts, recurrent detachments without PVR still occur. The first step to managing a recurrent RRD is correctly identifying the cause (detailed above), as this will guide appropriate treatment.

In cases of failed primary PPV, we have a low threshold to add an encircling scleral buckle during repeat PPV. SB improves success rates in phakic patients and potentially in other cases, such as those with inferior retinal detachments.[7] Although there is conflicting data regarding improved success rates in non-phakic eyes,[7,8] scleral buckling treats persistent peripheral vitreoretinal traction. Additionally, it can support other pathology, such as small peripheral holes or lattice degeneration, which may have been missed in the primary surgery. Adding a buckle is rarely regretted, especially in cases that have already failed one vitrectomy surgery. Meticulous scleral depression is also important to identify and treat all potential pathology. Longer tamponades such as C3F8 or silicone oil may also be more beneficial, particularly in cases with inferior pathology, which may not be adequately supported with SF6. This is determined on a case-by-case basis.

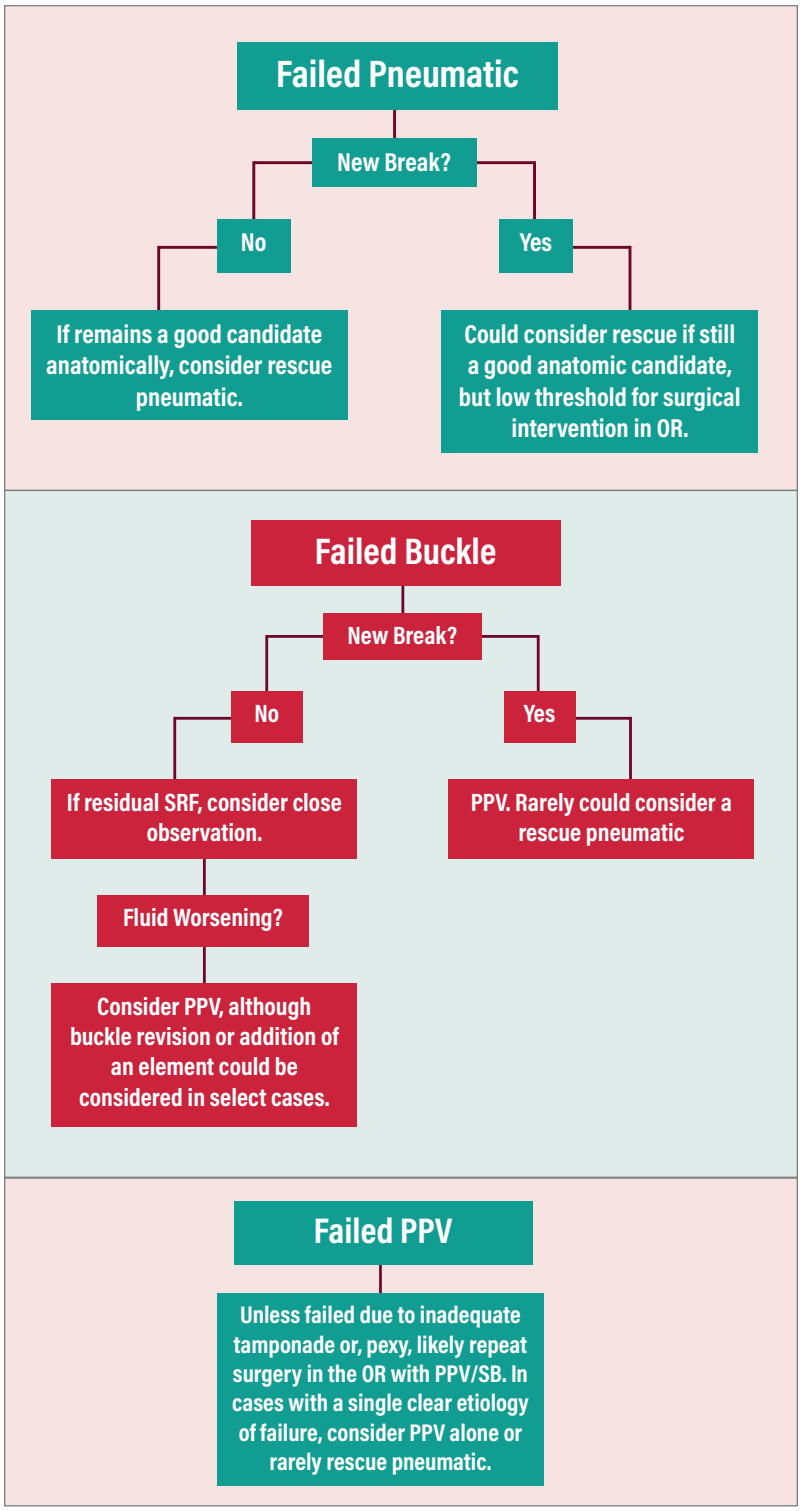
Similarly, when a primary buckle fails to treat a retinal detachment, the cause must be determined so that it can be adequately addressed. Of note, subretinal fluid can take weeks to months to resorb, and this is not considered a failure. We observe these cases, particularly when there is continued resolution of subretinal fluid and the pathology is supported by the buckle. However, if the initial break isn't supported, new breaks occur, or subretinal fluid is worsening, further intervention is necessary. The procedure will depend on both the patient's exam and the

surgeon's skill set. Occasionally, the buckle can be revised if the surgeon feels comfortable doing so. This is particularly useful in younger patients or in those without a posterior vitreous detachment, in which case a vitrectomy may be more challenging.

You can add SB elements if additional areas need to be supported, or the buckle (such as an encircling band) can be repositioned if the original pathology isn't well supported. For other cases, or if the surgeon feels more comfortable doing so, they can perform a PPV. It's important to identify and treat all pathology as previously detailed above. During a vitrectomy, it may be reasonable to apply peripheral laser along the extent of the detachment if suspected pathology is present. Notably, even a rescue pneumatic retinopexy could also be considered in select cases where the characteristics of the detachment and the patient selection are both favorable.

The same algorithm can apply if the initial procedure was a PnR. Patient selection is paramount in considering PnR. An excellent candidate would be phakic, with a break confined to the superior eight clock-hours of retina, without PVR and with a good ability to adhere to positioning. Alternatively, if there are multiple breaks, they should be confined within one clock-hour. Also, any lattice degeneration, or retinal holes/tears should be pretreated with laser or cryopexy.[9] These can still fail because of inadequate pexy, positioning or tamponade. A rescue pneumatic occasionally can be a reasonable choice, if inadequate positioning wasn't the cause of failure. At times, displacement of gas into the anterior chamber is responsible for failure. These can be minimized by optimized head positioning during paracentesis and by minimizing pupil diameter. If rescue pneumatic fails or is inappropriate, escalation to either PPV, SB or PPV/SB should be done promptly. The residual gas bubble can be used to keep the macula attached with face-down positioning while awaiting operative intervention.

Effective management of recurrent RRD requires first determining the underlying



A flowchart for approaching recurrent retinal detachments. Decisions are usually made on a case-by-case basis, however.

cause and understanding how the initial repair may have contributed to failure. Treatment decisions are tailored to the location and number of breaks, adequacy of prior tamponade and positioning, and the presence of factors such as lattice degeneration or high myopia. Depending on these variables, numerous interventions may be suggested. Regardless of the chosen method, success hinges on identifying all breaks, ensuring thorough vitreous removal when performing vitrectomy and applying durable retinopexy to achieve long-term reattachment. Each case must be analyzed individually to come to the best management plan.

Outcomes and prognosis

Recurrent RRD without PVR generally carries a more favorable prognosis than PVR-associated failures, provided that the macula was attached during most of the recurrence, the duration of detachment was short and the causative break or tractional source is accurately identified.

Visual recovery is strongly influenced by macular status; eyes with macula-on recurrence or brief macular detachment often return close to baseline. Importantly, the risk of subsequent recurrence after appropriate re-intervention is low, particularly when a buckle is added in anatomically high-risk cases.

Conclusion

Recurrent RRD in the absence of PVR remains primarily a mechanical problem, and successful management requires careful differentiation from PVR-associated failure. A methodical approach focusing on identifying all breaks, eliminating traction, applying durable retinopexy and providing adequate tamponade can yield excellent anatomic outcomes. With modern surgical techniques and proper case selection, most patients can achieve retinal reattachment with meaningful visual recovery. RS

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The evolving pipeline in diabetic retinopathy and diabetic macular edema

The current treatments under study and what future therapies for diabetic eye disease may look like.

By Haley D'Souza, MD and Katherine Talcott, MD


Haley D'Souza, MD


Katherine Talcott, MD

Take-home points

- Despite the transformative impact of intravitreal anti-VEGF therapy, real-world outcomes in diabetic retinopathy and diabetic macular edema remain limited by treatment burden, incomplete response, and access barriers.
- The current DR/DME pipeline emphasizes extended durability, alternative biologic pathways, and novel delivery platforms—including implants, systemic agents, and gene therapy.
- Over the next decade, management of diabetic retinal disease is likely to shift from frequent intravitreal injections toward durable, mechanism-targeted, and increasingly personalized treatment strategies.

Over the past three decades, the management of diabetic retinopathy and diabetic macular edema has undergone significant transformation. The introduction of intravitreal anti-vascular endothelial growth factor therapy dramatically improved visual outcomes and redefined standards of care, reducing rates of vision loss and delaying disease progression for millions of patients worldwide.[1]

Despite these advances, serial intravitreal anti-VEGF injections supplemented by focal/grid laser, panretinal photocoagulation or corticosteroids remains the cornerstone of therapy for most patients. In real-world practice, visit fatigue, treatment cost, systemic comorbidities and logistical barriers make this treatment model particularly challenging for a working-age population managing chronic diabetes.[1,2] Even among adherent patients, a substantial subset of patients demonstrate persistent retinal fluid or limited functional improvement despite adequate VEGF suppression.

These unmet needs have catalyzed a wave of innovation focused not only on improving efficacy, but also on reducing treatment burden and targeting disease mechanisms beyond VEGF. As the field enters the next decade, the DR/DME pipeline increasingly converges on three overarching goals: enhanced durability; expanded mechanisms of action; and more sustainable, accessible care.

Extended-Delivery and Durable Therapies

The cumulative burden of monthly or bimonthly intravitreal injections affects both patients and retina practices.

On a system-wide level, annual Medicare expenditures for anti-VEGF therapy have risen substantially, increasing from an estimated $2.51 billion in 2014 to $4.02 billion in 2019.[3] Additionally, each injection carries a small but non-negligible risk of complications such as endophthalmitis, retinal tear or vitreous hemorrhage.[4] Therapies that meaningfully extend treatment intervals therefore have the potential to improve access, adherence, and long-term

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outcomes, particularly for underserved populations.

The ranibizumab port delivery system (PDS; Susvimo, Genentech/Roche) is currently one of the most mature durability-focused platforms. It's a surgically implanted reservoir that enables continuous intravitreal delivery of ranibizumab, with refill exchanges approximately twice yearly.

In May 2025, the PDS received FDA approval for the treatment of both diabetic retinopathy and DME.[5] Clinical trial data demonstrate that the PDS can substantially reduce injection frequency while maintaining visual and anatomic outcomes comparable to monthly intravitreal ranibizumab.[6,7]

Corticosteroid-based sustained-release approaches also continue to evolve. In the Phase II RIPPLE-1 trial, 92 percent of patients treated with the IBE-814 high-dose (70 µg) intravitreal dexamethasone insert reached six months without requiring additional therapy.[8]

Migaldendranib (MGB; Ashvattha Therapeutics) is a VEGF receptor tyrosine kinase inhibitor (TKI) designed to suppress VEGF production from macrophages, microglia, and retinal pigment epithelial cells. Unlike other currently available therapies, it's administered subcutaneously.

In a recently completed 40-week Phase II study of MGB in DME and neovascular age-related macular degeneration, migaldendranib was associated with improvements in both visual acuity and retinal anatomy, along with a marked reduction in supplemental anti-VEGF injections from an annualized rate of 8.4 injections to 1.6 injections. It was well tolerated, with no reported ocular or systemic serious adverse events despite subcutaneous route of delivery.[9]

EYP-1901 (Duravyu) is a sustained-release TKI. It's a bioerodible intravitreal insert that delivers vorolanib, a small-mol-

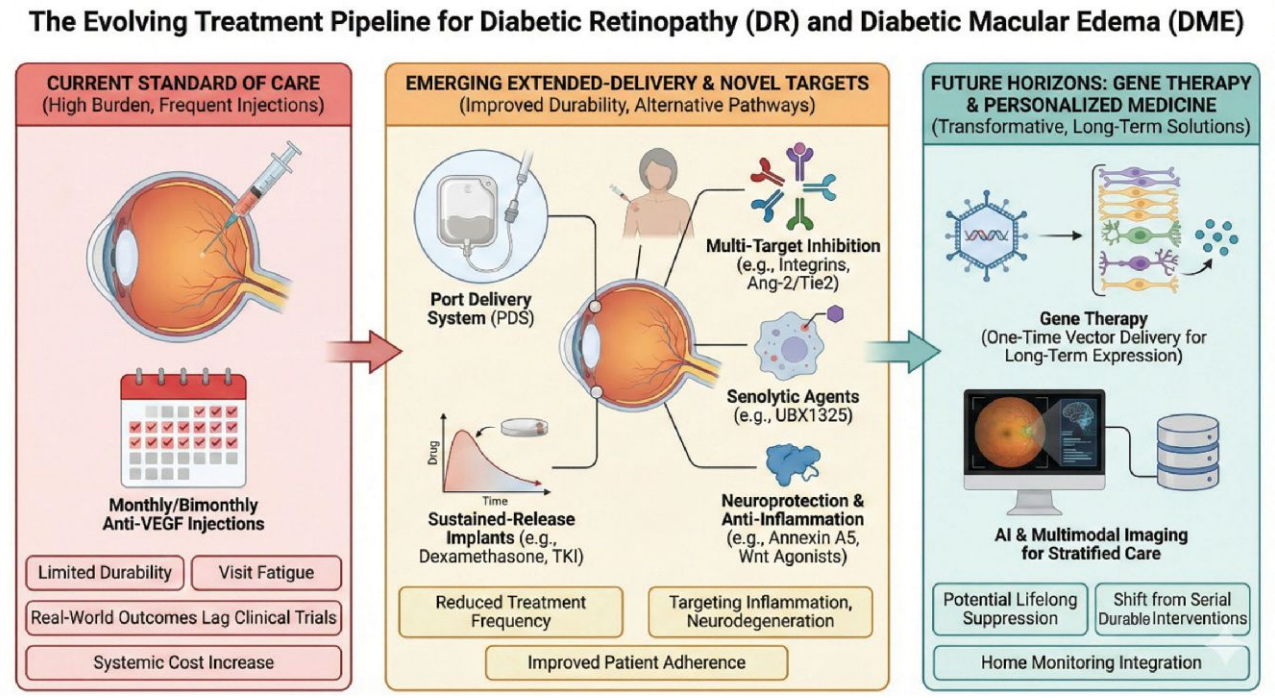

Figure 1. The evolving therapeutic landscape for diabetic retinopathy and diabetic macular edema. The diagram illustrates the progression from the current high-burden anti-VEGF standard of care (left panel) toward emerging extended-delivery systems and novel biologic targets (middle panel), and finally to future gene therapies and AI-driven personalized medicine (right panel).

ecule pan-VEGFR inhibitor that also suppresses IL-6/JAK1–mediated inflammatory signaling, achieving rapid therapeutic intraocular levels and maintaining target inhibition for at least six months. In the Phase II VERONA trial in active DME, a single EYP-1901 dose significantly extended time to first supplemental anti-VEGF treatment compared with aflibercept, with 73 percent of eyes treated with the 2.7-mg dose remaining supplement-free through 24 weeks. Early and sustained improvements in visual acuity and retinal thickness were observed, along with reductions in macular vascular leakage and a favorable safety profile.

Pivotal Phase III trials are now underway evaluating q6-month EYP-1901 dosing versus on-label aflibercept, aiming to maintain visual outcomes while meaningfully reducing injection frequency in diabetic macular edema.[10]

Axpaxli (formerly OTX-TKI) (axitinib; Ocular Therapeutix), delivered via a biodegradable intravitreal implant, demonstrated encouraging results in moderately severe non-proliferative DR, with no treated eyes progressing to proliferative disease or developing DME at 48 weeks compared with 37 percent of control eyes.[11]

Novel Biologic Targets

Diabetic retinal disease is driven by a complex interplay of angiogenesis, inflammation, oxidative stress, vascular dysfunction and neurodegeneration.[1] Recognition of this multifactorial pathophysiology has expanded interest in therapeutic targets beyond VEGF inhibition.

OCU200 (Ocugen) is an integrin-targeting fusion protein that combines tumstatin and transferrin domains to inhibit angiogenesis and vascular leakage through non-VEGF mechanisms. Preclinical and early clinical studies suggest potential benefit in modulating vascular permeability and inflammation, positioning integrin inhibition as a potentially complementary strategy in diabetic eye disease.[12]

Additional targeting includes small-molecule modulation of the Ang-2/Tie2 pathway and melanocortin receptor agonists, both of which are under investigation for anti-inflammatory and neuroprotective effects. The Genentech THAMES study (NCT06850922) is a Phase I/II clinical trial evaluating the novel treatment RO7446603 in patients with DME. The study investigates RO7446603 alone or in combination with faricimab, targeting the Tie2 pathway.

ANXV (Annexin Pharmaceuticals), a recombinant annexin A5 protein, is currently being evaluated in a Phase IIa trial for NPDR in patients with early microvascular changes who don't yet require anti-VEGF therapy. Annexin A5 is thought to protect endothelial cells, reduce leukocyte adhesion and modulate immune activity. The agent previously demonstrated a favorable safety profile in Phase IIa studies for retinal vein occlusion.[13]

Cellular senescence has also emerged as a potential contributor to chronic retinal vascular disease. The senolytic agent UBX1325 (foselutoclax; Unity Biotechnology) was evaluated in patients with DME who had shown suboptimal response to anti-VEGF therapy. Although the study wasn't powered for efficacy, UBX1325 demonstrated an acceptable safety profile and a numerically greater mean gain in best-corrected visual acuity, with a 5.6-letter greater mean gain in ETDRS best-corrected visual acuity at week 48 compared to sham.[14]

Gene Therapy and Transformative Platforms

If extended-release implants represent an incremental advance, gene therapy offers the possibility of a more transformative shift. Advances in vector engineering and ocular delivery have made long-term intraocular expression of therapeutic proteins increasingly feasible after a single administration.[15]

4D-150 (4D Molecular Therapeutics)

If extended-release implants represent an incremental advance, gene therapy offers the possibility of a more transformative shift.

employs a proprietary adeno-associated viral (AAV) vector designed to express dual inhibitors targeting VEGF-A, VEGF-B and placental growth factor. In the Phase III SPECTRA trial in DME, the selected dose (3E10 vg/eye) achieved a 78-percent reduction in treatment burden compared with projected on-label aflibercept dosing through 60 weeks, with a favorable safety profile and no reported cases of intraocular inflammation, vasculitis or retinal artery occlusion.[16,17]

Restoret (EYE103; EyeBio/Eyebiotech) is a trispecific Wnt agonist antibody designed to mimic the activity of Norrin, a ligand critical for maintaining the blood–retinal barrier. Preclinical work has demonstrated Norrin-mediated restoration of barrier integrity and reduction of vascular permeability.[18,19]

In the Phase Ib/II AMARONE trial, intravitreal Restoret was well tolerated, with no drug-related serious adverse events reported at 12-week follow-up. Preliminary data also showed an increase in BCVA of 11.2 EDTRS letters visual acuity and retinal thickness in patients with DME who were concurrently treated with aflibercept.[20]

ABBV-RGX-314 (RegenxBio, AbbVie) is a subretinal gene therapy consisting of an AAV8 vector containing a gene encoding for a monoclonal antibody fragment designed to neutralize VEGF.

Data from the ATMOSPHERE and ASCENT trials assessing the subretinal delivery of RGX-314 in wet age-related macular degeneration are anticipated in 2026. A Phase III study on the use of suprachoroidal delivery with the in-office SCS Microinjector of ABBV-RGX-314 in DR is being planned.

A one-time gene therapy alternative to frequent intravitreal injections has potential for effectively treating disease, and Phase I/II and Phase II data have demonstrated durability and substantial reduction in treatment burden.[21]

FT-003 (Frontera Therapeutics) recently received investigational clearance in China for DR, following earlier development in nAMD and DME. It has shown in trials significant improvements in visual acuity and retinal anatomy, with a marked reduction (or elimination) of the need for anti-VEGF rescue injections over a two-year follow-up.

Clinical studies suggest that a single intravitreal administration may establish sustained intraocular anti-VEGF expression, with prolonged visual and anatomic benefits and reduced need for rescue injections over extended follow-up.[22]

New delivery routes, including suprachoroidal administration, may further refine the safety and efficacy profile of both gene and small-molecule therapies by limiting anterior-segment exposure while maintaining chorioretinal bioavailability.

These innovations will require new procedural skill sets, long-term safety monitoring and thoughtful discussion regarding durability, reversibility and cost.

Looking Ahead

The late-stage DR/DME pipeline is dynamic. Platforms including port delivery systems, gene therapies and novel targeting pathways exemplify a broader shift toward durable, mechanism-targeted therapy. Concurrently, artificial intelligence–based image analysis and large-language-model tools may enhance disease monitoring and individualized medicine as treatment paradigms grow more complex.

Over the next decade, management of diabetic retinal disease is likely to evolve toward increasingly stratified algorithms. Long-acting therapies may be deployed earlier to prevent progression, combination or pathway-specific treatments may be reserved for refractory disease, and gene-based interventions may ultimately offer multi-year stability from a single procedure.

Together, these advances promise to reframe DR and DME from conditions managed through relentless retreatment to diseases addressed with durable, precision-guided interventions. RS

(Ed. note: A version with all of the endnotes is available on our website, retina-specialist.com)

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Optimizing oral fluorescein in angiography

This new method of administering fluorescein for angiography may eliminate many issues with the IV approach.

Guillermo Salcedo Villanueva, MD

By Guillermo Salcedo Villanueva, MD

Take-home points

- IV fluorescein angiography is a key tool but has limitations, such as administration-related adverse events and a limited ability to repeat the test in diseases that might require serial imaging. Oral administration may be a useful alternative.
- We conducted a small study of angiography done with orally administered fluorescein and found that 25% fluorescein produced higher fluorescence but that the 10% concentration also generated adequate visualization of fundus structures.
- Following a second study of oral fluorescein in diabetic retinopathy cases, we've developed practical tips for the use of oral FA in retina practice.

Fluorescein angiography is a fundamental imaging technique in ophthalmology. It provides a dynamic assessment of the anatomy and physiology of the posterior segment by visualizing normal and abnormal filling patterns and leakage in different vascular compartments, principally the retinal and choroidal circulations. Since its development by Novotny and Alvis in the 1960s,[1] FA has served as one of the gold standards for diagnostic imaging in ophthalmology and is generally considered a safe procedure.

However, FA has notable limitations. It's an invasive test that requires intravenous access and is therefore associated with adverse events related to fluorescein administration. These reactions may be mild (1.24 to 17.5 percent), including nausea (0.06 to 15.29 percent), vomiting (0.2 to 8.0 percent) and extravasation (0.1 to 2.65 percent); moderate (0.2 to 6.0 percent), including rash/urticaria (0.2 to 4.5 percent) and syncope/dizziness/hypotension (0.04 to 1.2 percent); or severe (0.04 to 0.59 percent), including anaphylaxis/bronchospasm (0.03 to 0.38 percent) and myocardial infarction (0.01 to 0.15 percent). The estimated mortality rate ranges from 1:100,000 to 1:220,000.[2,3]

Because of the invasive nature of IVFA and the potential for adverse events, frequent repetition of the test is limited, particularly in diseases where serial imaging may be beneficial, such as posterior uveitis, intermediate uveitis and retinal vasculitis. Although newer non-invasive imaging modalities such as optical coherence tomography angiography provide valuable information, there remain clinical scenarios, such as retinal vasculitis, where FA is essential for assessing disease activity.

Recent advances in imaging systems, particularly confocal scanning laser ophthalmoscopes including the Clarus 700 (Carl Zeiss Meditec AG, Jena, Germany) and Optos California (Optos plc, Dunfermline, Scotland), have improved image quality and acquisition speed. Scanning times range from <0.2 to 0.5 seconds, providing optical resolution between 7.3 to 14 μm. Improved visualization of fine details may allow adequate imaging with lower concentrations

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He has no financial interest in the material presented.

of fluorescein or with orally administered fluorescein.

Oral FA has been described primarily in pediatric populations and has been used with various reflectance imaging systems such as the Visucam (Carl Zeiss Meditec AG, Jena, Germany).[4,5] As noted above, improvements in cSLO technology have enhanced OFA image quality.[4] Although fluorescein doses for oral administration have been studied—mainly in children—there's limited information on optimal dosing, absorption kinetics, and transit time in adults.[6,7]

To address these gaps, we conducted a small cross-sectional pilot study to compare 10% and 25% oral fluorescein in healthy young adults.[8] We recruited 19 subjects divided into two groups and administered either 10% or 25% fluorescein. Participants fasted for at least seven hours and then consumed 4 mL of the assigned concentration diluted in 30 mL of cold orange juice, taken in a single gulp if possible. Images were obtained using the Clarus 700, and a timer was started at the moment of ingestion. Images were captured as follows:

- Every minute from 0 to 10 minutes
- Every five minutes from 10 to 30 minutes
- Every 10 minutes from 30 to 60 minutes

All participants were monitored for adverse events during the procedure and for 30 minutes afterward. For image analysis,

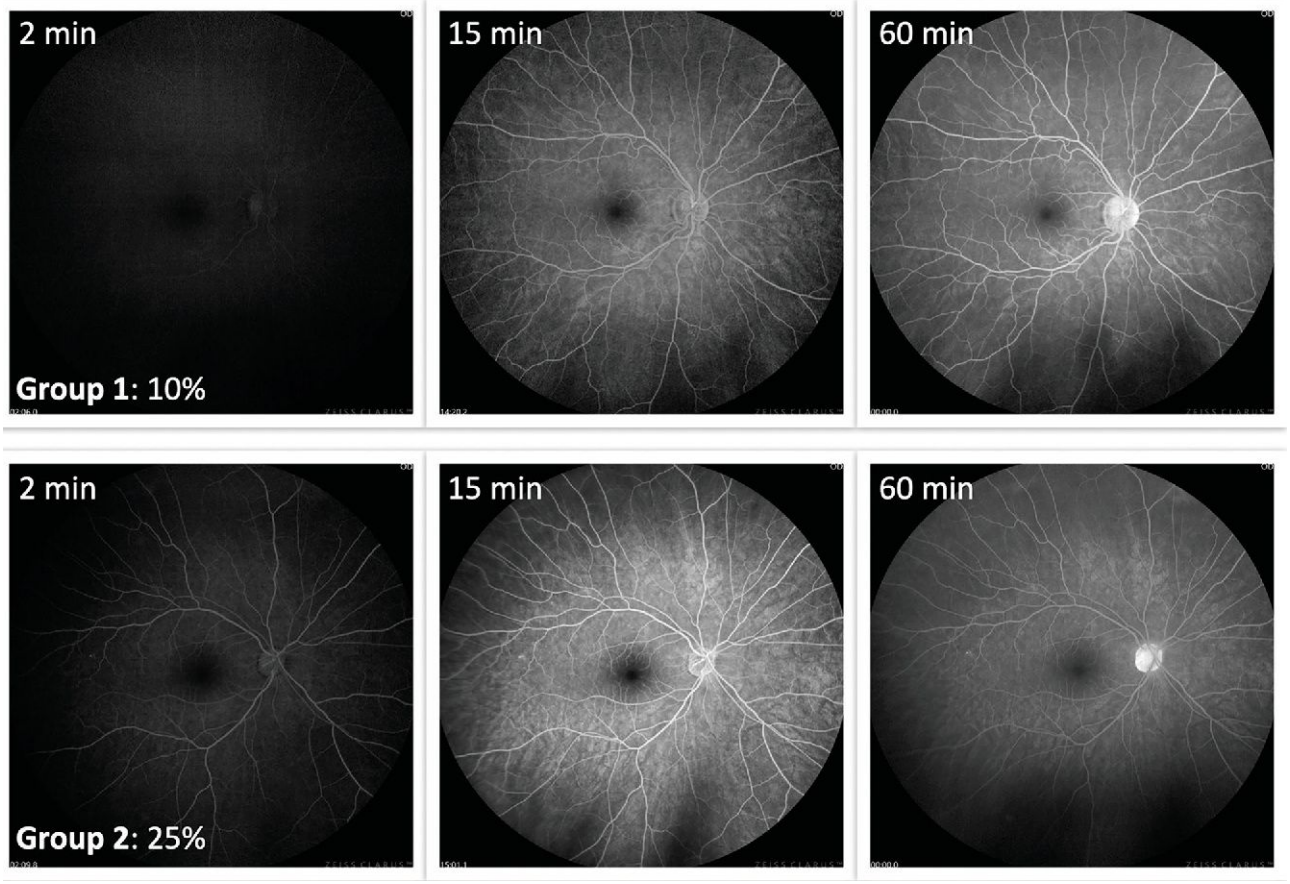

Figure 1. Examples from two subjects that showed early fluorescence at two minutes. Top images show the subject that ingested 10% fluorescein; lower images show the subject that ingested 25% fluorescein. Notice how clear fundus features are observable in both cases. Twenty-five percent shows a brighter image at 15 minutes. However, both concentrations show an adequate fluorescence at 60 minutes. This project was presented at ARVO 2023.[8]

we used ImageJ and applied the histogram function to measure fluorescence intensity through the mean gray value for each image. These values range from 0 (completely dark) to 255 (completely white).

Findings

Mean overall fluorescence was 32.55 pixels (P) (standard deviation [SD]: 24.75) for 10% fluorescein and 38.62 P (SD: 29.68) for 25% fluorescein (p=0.08). Mean time to initial fluorescence was 11.5 minutes for 10% and 8.2 minutes for 25% (p=0.464). Maximal fluorescence reached 62.79 P for 10% and 72.18 P for 25% (p=0.195). No adverse events were observed.

Although 25% fluorescein produced higher fluorescence, the 10% concentration also generated adequate visualization of fundus structures *(Figure 1)*. In the examples provided, early fluorescence was detectable as early as two minutes with both concentrations; image quality improved significantly by 15 minutes and persisted through 60 minutes, providing good visualization of posterior segment structures. Importantly, a notable increase in fluorescence occurred between 10 and 15 minutes. We therefore consider approximately 15 minutes to represent the optimal peak phase for image acquisition. Although fluorescence continues to increase over the first 60 minutes, obtaining the initial and most critical images at around 15 minutes is recommended.

Is oral FA useful in clinical settings?

We believe so. Despite requiring a larger volume of fluorescein and taking longer than IVFA, OFA doesn't require venous access and therefore doesn't disrupt clinic workflow. A patient may ingest the dye while undergoing dilation, and images can be obtained after 15 minutes. When using an ultra-widefield imaging system, just a few images will be enough for a good assessment of the disease. Following brief observation for adverse events, the patient can be discharged.

This offers a practical alternative in conditions where repeated FA might be beneficial. Figure 2 shows a patient with retinal vasculitis due to a probable Behçet's disease. For her follow-up it's important to observe if vasculitis is subsiding with systemic treatment, and OFA has been helpful in providing that information in practically all her appointments *(Figure 2)*.

To explore the clinical applications of OFA, we performed a second experiment assessing image quality in patients with diabetic retinopathy compared with IVFA.[9] Two masked graders evaluated and graded, on a scale from 0 to 3 points, each of the following features:

- Visualization of the retinal vasculature.
- Visualization of the foveal avascular zone (FAZ).
- Visualization of DR features, including diabetic macular edema, neovascularization, and microaneurysms.

Fluorescence intensity was again measured using mean gray value, and safety was assessed through adverse event monitoring.

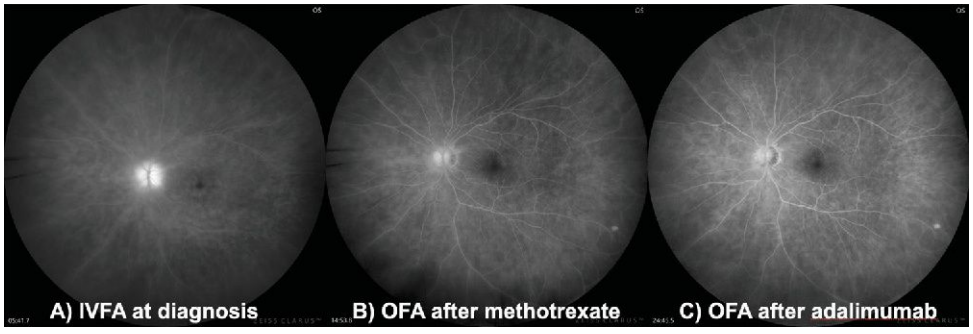

Figure 2. Patient with probable Behçet's Disease. A) The patient at baseline with IVFA. B) Since the patient needed continued evaluation with FA, oral administration was proposed. The patient is shown with methotrexate was initiated. C) After initiation with adalimumab.

Findings

The mean quality score was 8.54 (SD: 1.15) for OFA and 8.89 (SD: 0.24) for IVFA (p=0.285). Image quality was rated excellent in 81 percent of OFA images and 86 percent of

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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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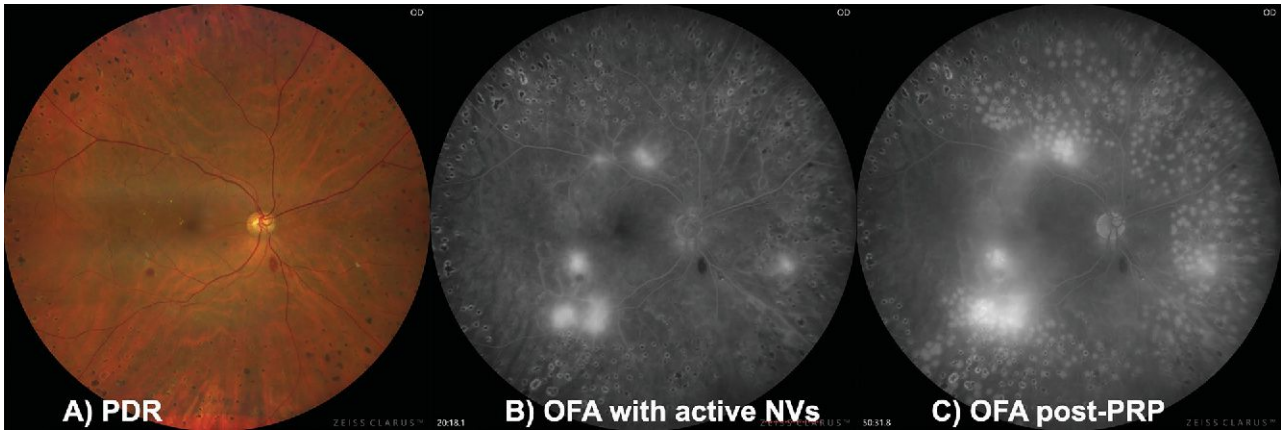

Figure 3. A) Patient with proliferative diabetic retinopathy with active retinal neovascularization. B) The patient undergoes an OFA that pin-points the location of the active NV. C) After laser, that patient can return to complete the FA (with the same initial dose of oral fluorescein) to evaluate if the photocoagulation was adequately administered.

IVFA images; moderate in 17 percent vs. 12 percent; and poor in 2 percent for both. Mean fluorescence was 76.38 p (SD: 21.76) for OFA and 78.79 p (SD: 22.83) for IVFA which showed no statistical significance difference. Unexpectedly, we observed two mild adverse events (3.12 percent) in the OFA group—one case of nausea and one rash—and none in the IVFA group.

Based on these findings, OFA appears to permit excellent visualization of DR features, comparable to IVFA. Fluorescence intensity was similar between modalities, and OFA may represent a useful imaging tool in selected clinical settings, particularly in diabetic patients. For example, you could perform a routine OFA on a proliferative DR patient, where you could easily detect the presence of neovascularization. The patient could get laser photocoagulation and again return for another OFA (with the same, initial dose of fluorescein) to compare and grade how laser was given *(Figure 3)*.

Practical recommendations

Both 10% and 25% concentrations may be used for OFA. In routine practice, we use 25% due to subjectively better image quality, higher fluorescence and faster onset. We recommend:

1. Administer 4 mL of 25% fluorescein diluted in 30 mL of cold orange juice.

2. Start the timer at ingestion; allow absorption while the patient continues dilation in the waiting room.

3. Initial images can be obtained at five minutes, but optimal fluorescence is typically reached after 15 minutes. Repeat imaging if fluorescence appears insufficient.

4. Monitor all of the patients for adverse events. RS

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Management of uveitis in pregnancy

Treatment decisions should be individualized with careful consideration of maternal and fetal safety. Here's guidance.

By Akshay S. Thomas, MD, MS, FASRS

Managing uveitis in pregnancy requires a thoughtful balance between controlling intraocular inflammation to preserve maternal vision and minimizing potential risks to the developing fetus. Pregnancy is a unique physiologic state characterized by substantial hormonal and immunologic shifts, and these changes have important implications for autoimmune and inflammatory diseases, including uveitis. Treatment decisions must simultaneously consider disease subtype, maternal health, fetal safety, medication pharmacology and the timing of exposure. The result is a clinical landscape defined by nuance, shared decision-making and individualized care.

This article summarizes practical principles for evaluating and managing uveitis during pregnancy, integrating evidence-based guidance with real-world considerations commonly encountered in ophthalmology and maternal-fetal medicine practices.

Physiologic and immunologic changes in pregnancy

Pregnancy induces a shifting immunologic environment that's broadly immunosuppressive but highly dynamic. As early as the peri-fertilization period, hormonal and immune modulation shape maternal immune tolerance. Although pregnancy is often described as favoring immune suppression, autoimmune and inflammatory diseases behave inconsistently: Some improve, some remain stable and others worsen.[1-8]

Uveitis often follows a characteristic trend through each stage of pregnancy and immediately after.

- First trimester: This is highly variable on an individual basis. Some patients flare, some improve and some see no change. Early pregnancy may reflect pre-pregnancy disease activity more than pregnancy physiology.
- Second and third trimesters: Many forms of non-infectious uveitis tend to improve as pregnancy progresses and immunologic tolerance increases.
- Postpartum period: Flares are common due to rebound immune activation.

However, not all uveitis subtypes follow the same pattern. Certain groups—particularly HLA-B27-associated acute anterior uveitis and scleritis, especially when related to systemic lupus erythematosus—may worsen during pregnancy. These variants require closer monitoring and proactive management.

Overall, a patient's degree of disease control prior to conception remains the best predictor of flare risk during pregnancy.

Medication safety: Understanding the framework

Historically, clinicians relied heavily on the FDA's pregnancy risk categories (A, B, C, D, X), but this system was discontinued in 2015 because of oversimplification. Many effective and commonly used medications, including steroids, insulin and antibiotics, were categorized as C or D simply due to lack of controlled data, not because they were unsafe. Clinicians should now rely on more detailed drug labeling, multidisciplinary consultation and specialized resources such as:

- MotherToBaby (teratology information service),
- LactMed (lactation pharmacology database),
- ACOG guidelines,
- primary literature, and
- specialist pharmacy consultation.

Evidence-based interpretation rather than alphabetical classification is critical, as pregnant patients may receive misleading or overly cautious recommendations when

BIOS

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older systems are applied uncritically.

Systemic corticosteroids in pregnancy

Systemic corticosteroids remain foundational in managing moderate-to-severe uveitis, including in pregnancy. The guiding principle is clear: If steroids are clinically necessary to preserve vision or control dangerous inflammation, they shouldn't be withheld.[2-5]

There are a few key considerations to mention:

• First trimester risks: Some data suggest a small increase in the risk of orofacial clefts, though evidence is mixed and the absolute risk is low.

• Maternal side effects: Hyperglycemia is common but manageable through routine prenatal care.

• Short courses vs. chronic use: Prolonged high-dose steroid therapy is undesirable in all patients, including pregnant individuals, and warrants consideration of steroid-sparing agents.

Ultimately, uncontrolled inflammation poses a far greater risk than judicious corticosteroid use.

Antimetabolites: Contraindicated vs. acceptable options

Steroid-sparing immunomodulatory therapy is frequently necessary in chronic uveitis and requires careful reproductive planning.

The following agents are teratogenic and shouldn't be used in pregnancy:

- Methotrexate
- Mycophenolate mofetil

Both require washout periods prior to conception. Typical recommendations include:

- Methotrexate: three to four months (some clinicians extend to six months)
- MMF: Similar guidance; transition to safer therapy as early as possible.

Azathioprine is widely considered one of the safest systemic immunosuppressants for use in pregnancy when required. While some studies associate it with low birth weight or preterm birth, these outcomes often reflect underlying disease severity rather than drug effect. For patients requiring systemic IMT, azathioprine is a strong first-line choice. Use and considerations of conventional immunosuppressives for uveitis in pregnancy is summarized in Table 1.[1-8]

Biologic therapy during pregnancy

Biologic agents, particularly TNF-α inhibitors, play an increasingly prominent role in managing refractory uveitis. Their safety in pregnancy continues to be clarified, with growing data suggesting a more permissive approach.[5,6]

• ***TNF-α Inhibitors.*** Traditional practice has been to discontinue TNF inhibitors at the start of the third trimester due to placental transfer of IgG-based therapies. However, updated evidence suggests TNF inhibitors can be continued throughout pregnancy without increasing the infant's risk of severe infections. Continuation may reduce postpartum flare and maintain better maternal disease control. Certolizumab is a uniquely attractive option during pregnancy because it lacks an Fc region, resulting in minimal placental transfer. It's often preferred by patients concerned about fetal exposure[5] and can replace other anti-TNF agents before con-

Table 1: Conventional immunosuppressants in pregnancy and lactation.

Medication	Pregnancy Safety	Notes in Pregnancy	Lactation Safety
Methotrexate	Contraindicated	Teratogen; stop three to six months before conception.	Avoid
Mycophenolate mofetil (MMF)	Contraindicated	Major birth defect risk; switch pre-conception.	Avoid
Azathioprine	Acceptable when needed	Preferred steroid-sparing IMT in pregnancy.	Compatible
Cyclosporine	Use with caution	Acceptable if necessary; monitor BP and kidneys.	Compatible with monitoring
Tacrolimus	Use with caution	Some systemic use in pregnancy (transplant); monitor levels.	Compatible with monitoring

ception if desired, although switching isn't mandatory when disease control is excellent.

• ***Rituximab***. Data is limited but reassuring with the major concern being theoretical neonatal B-cell depletion.

• ***Tocilizumab***. Early data suggest limited placental transfer and cautious use with MFM collaboration is advised.

Biologic therapy selection should incorporate disease severity, response history, patient values and obstetric consultation. Considerations for use of biologics for uveitis in pregnancy is summarized in Table 2.[5,6]

Local therapy during pregnancy

Local corticosteroid therapy—topical, periocular or intravitreal—is often preferred for unilateral or moderate inflammation, especially when systemic medication exposure is undesirable. Local therapy offers advantages such as minimal systemic absorption, rapid control of inflammation and avoidance of systemic teratogenic risk.

However, steroid-induced intraocular pressure elevation remains a concern, especially in patients known to be "steroid responders." Still, during pregnancy—when timelines are finite—clinicians typically favor local therapy over systemic treatment for unilateral disease.

Systemic therapy for bilateral or severe disease

When uveitis is bilateral, vision-threatening or rapidly progressive, systemic therapy is necessary. High-dose systemic corticosteroids are an appropriate initial therapy even in pregnancy, followed by a slow taper. If high doses can't be safely maintained, azathioprine or a biologic therapy may be added.

The decision to introduce a TNF inhibitor early is influenced by these factors:

- Trimester of pregnancy,
- Anticipated steroid taper response,
- Disease chronicity and severity, and
- Potential for postpartum exacerbation.

Avoiding undertreatment is essential. Irreversible damage from poorly controlled inflammation carries lifelong consequences.

Anti-VEGF therapy during pregnancy

Anti-VEGF injections pose a unique challenge during pregnancy, particularly in managing choroidal neovascular membranes. Systemic absorption of intravitreal agents is low but not negligible, and VEGF plays a role in placental function.[9]

Important guidance:

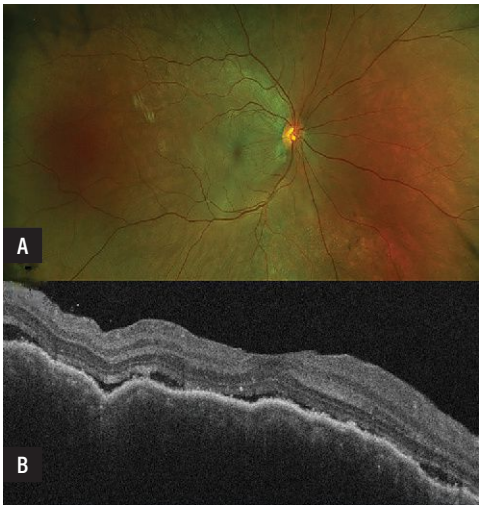
- If CNVM is active, treatment shouldn't be delayed. Vision loss from untreated CNVM is often permanent.
- The first trimester requires the most caution due to baseline miscarriage risk and organogenesis.
- When anti-VEGF therapy is necessary, ranibizumab may be preferred because it results in the lowest systemic VEGF suppression.
- Local steroid therapy may be attempted for inflammatory lesions but is generally insufficient for a true CNVM.

In all cases, shared decision-making is crucial, balancing fetal risk perception with the danger of permanent maternal vision loss.

Monitoring pregnant patients on immunosuppression

Pregnant patients on IMT generally don't require specialized maternal monitoring solely due to immunosuppression. Standard prenatal care applies with a few adjustments:

- Gestational diabetes screening earlier than usual for chronic steroid users.
- Close coordination with pediatrics for infants



A 32-year-old patient presented during the first trimester of pregnancy with bilateral serous retinal detachment (A) secondary to acute Vogt-Koyanagi-Harada disease. OCT revealed choroidal thickening and subretinal fluid (B). She required high-dose oral steroids as well as initiation of adalimumab during the pregnancy to control the inflammation.

Table 2: Biologics in pregnancy and lactation.

Medication	Pregnancy Safety	Notes in Pregnancy	Lactation Safety
Adalimumab	Acceptable	Placental transfer increase in third trimester; continuation acceptable.	Compatible
Infliximab	Acceptable	Similar to adalimumab; may continue through pregnancy.	Compatible
Certolizumab pegol	Acceptable	Minimal placental transfer; ideal option.	Compatible
Rituximab	Use with caution	Theoretical neonatal B-cell suppression; limited data.	Compatible; minimal milk transfer
Tocilizumab	Use with caution	Emerging data; limited pregnancy experience.	Likely compatible, limited data
Interferon-α	Acceptable in selected cases	Historically used in pregnancy; limited fetal risk.	Compatible

exposed to biologics, as timing of live vaccines may need modification.

- Maintenance of routine maternal immunizations: influenza; Tdap; and COVID boosters.

Collaboration with MFM specialists improves patient confidence and ensures comprehensive care.

Postpartum flares and breastfeeding considerations

The postpartum period, sometimes called the "fourth trimester," is a high-risk window for uveitis flare due to immune rebound. Management goals include rapid control of inflammation and safe reinstitution of pre-pregnancy therapy.

For mothers who choose to breastfeed, the general principles include:

- Corticosteroids: Safe during lactation.
- Biologics: Transfer into breast milk occurs but absorption is extremely low due to GI breakdown; generally considered safe.
- Methotrexate: Contraindicated; shouldn't be used during breastfeeding.
- Intravitreal anti-VEGF: Very low systemic levels; breastfeeding likely safe, though some patients may prefer "pump and dump" after injections for reassurance.

Conclusion

Management of uveitis in pregnancy requires an individualized, multidisciplinary approach that balances maternal visual function and fetal safety. Most patients experience a natural improvement in inflammation during mid-to-late pregnancy, yet postpartum flares are common and require vigilance. Safe and effective treatment options exist across all trimesters when guided by disease severity, pharmacologic understanding and shared decision-making.

By integrating obstetric input, proactively planning medication transitions for reproductive-age patients and applying thoughtful treatment strategies—ranging from local therapy to biologics—clinicians can successfully navigate uveitis management through pregnancy, delivery and the postpartum period while preserving maternal vision and supporting healthy pregnancy outcomes. RS

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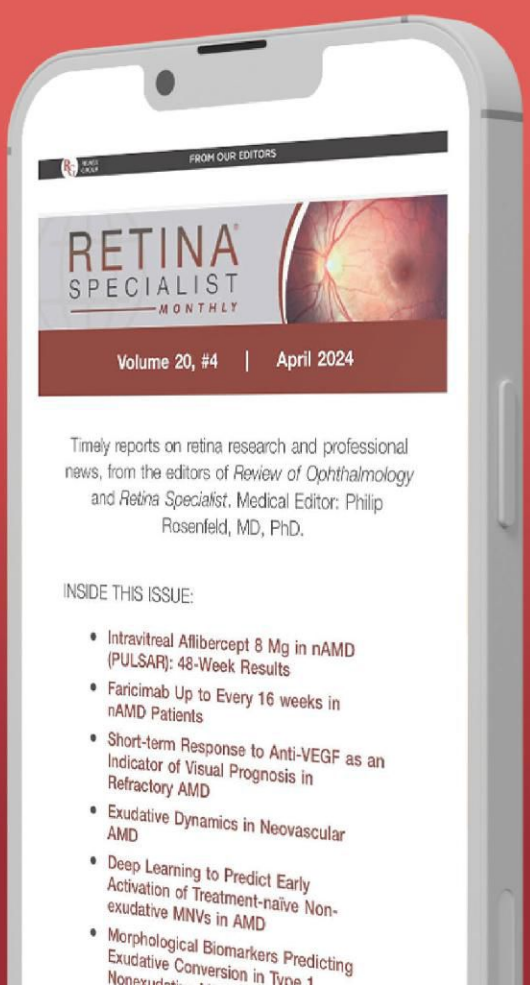
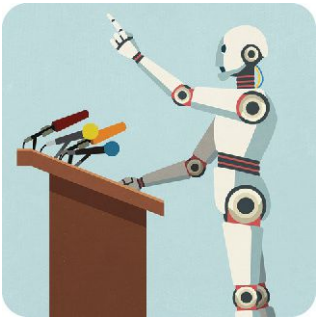


The rise of AI influencers

We'll soon need to critically evaluate who—or what—is speaking online.

By Jayanth Sridhar, MD

Artificial intelligence is no longer a distant abstraction reserved for research labs or speculative headlines. In 2025, AI quietly embedded itself into daily life: drafting emails; summarizing articles; editing images; and increasingly shaping what we see on social media. The result is a digital ecosystem where not all voices belong to humans and the line between authored content and algorithmic output is increasingly difficult to detect.



One of the most visible manifestations of this shift is the rise of AI influencers. These are entirely synthetic personas with computer-generated faces. While the first versions of AI influencers were obviously flawed and non-human, newer models have improved with increasing attention to consistent aesthetics, curated personalities and carefully optimized engagement strategies. Outside of medicine, examples already abound: virtual fashion models partnering with luxury brands; AI lifestyle influencers offering wellness advice; and synthetic "experts" explaining finance, travel or productivity. While some disclose their artificial nature openly, others don't. Regardless, many attract large followings, generate revenue and shape opinions just as effectively as human creators. In some ways, AI influencers have a higher "ceiling" of influence, given their ability to post constantly, adapt instantly and avoid reputational damage.

Medicine, including ophthalmology, will not remain insulated from this trend. The idea of an AI medical influencer is both tempting and troubling. On the positive side, AI-driven accounts could disseminate high-quality educational content at scale, counter misinformation and improve baseline health literacy while reducing human workload. On the other hand, they risk flattening nuance, obscuring uncertainty and blurring accountability. Unlike a physician, an AI influencer can't truly disclose conflicts, accept liability or contextualize advice within the messiness of real-world patient care. For a field as visually driven and technically complex as ophthalmology, polished explanations may paradoxically increase misunderstanding by appearing more certain than the science allows.

The ethical challenges are therefore substantial. Transparency becomes paramount: Audiences should know when content is AI-generated, who built it and whose interests it serves. There is also the question of detectability. While AI-generated images and text are becoming more difficult to identify, subtle cues remain, such as an overly consistent tone, implausible posting frequency, absence of lived experience or a lack of engagement with genuine clinical uncertainty. Physicians and trainees will need a new form of digital literacy, understanding not only how to post responsibly, but how to critically evaluate who or what is speaking. Being "AI-aware" may soon be as important as being evidence-aware.

AI influencers aren't inherently good or bad; rather, they are tools that reflect the incentives and values embedded in their design. They will exist regardless of our feelings about them; thus, the challenge ahead is not to reject them outright, but to recognize their limitations, anticipate their impact and ensure that human judgment remains central to medical discourse. In a landscape increasingly populated by synthetic voices, authenticity, transparency and professional accountability may become the most valuable signals we have.

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.

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BRIEF SUMMARY – PLEASE SEE THE TRIESENCE® PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

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TRIESENCE® is a synthetic corticosteroid indicated for:

- Treatment of the following ophthalmic diseases: sympathetic ophthalmia, temporal arteritis, uveitis, and ocular inflammatory conditions unresponsive to topical corticosteroids.
- Visualization during vitrectomy.

CONTRAINDICATIONS

- Patients with systemic fungal infections.
- Hypersensitivity to triamcinolone or any component of this product.

DOSAGE AND ADMINISTRATION:

- 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.
- Recommended dose for visualization: 1 to 4 mg (25 to 100 microliters of 40 mg/mL suspension) administered intravitreally.

WARNINGS AND PRECAUTIONS

- TRIESENCE® is a suspension; it should not be administered intravenously.
- Ophthalmic effects: May include cataracts, infections, and glaucoma. Monitor intraocular pressure.
- Hypothalamic-pituitary-adrenal (HPA) axis suppression, Cushing's syndrome, and hyperglycemia: Monitor patients for these conditions and taper doses gradually.
- 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, and 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.

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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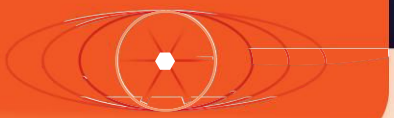

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†There is a general risk of infectious endophthalmitis development from intravitreal injection procedures.

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- Visualization during vitrectomy.

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- TRIESENCE® Suspension is contraindicated in patients with systemic fungal infections.
- TRIESENCE® Suspension is also contraindicated in patients with hypersensitivity to corticosteroids or any component of TRIESENCE® Suspension. Rare instances of anaphylactoid reactions have occurred in patients receiving corticosteroid therapy.

IMPORTANT SAFETY INFORMATION

Warnings & Precautions

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Please see Important Safety Information, as well as Full Prescribing Information at www.triesencehcp.com.

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