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Retina Today

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RARE AND INHERITED RETINAL DISEASE

A guide to diagnosing and managing rare conditions in your clinic.

INHERITED RETINAL DISEASE PIPELINE

TOP IRDS TO WATCH: RP, LCA, STARGARDT, AND MORE

NUTRITIONAL SUPPLEMENTS FOR IRDS

NOW APPROVED

The **first and only** FDA-approved treatment for adults with idiopathic macular telangiectasia type 2 (MacTel)

ENCELTO™

(revakinagene taroretcel-lwey)

implant, for intravitreal use

Harness the tech with the survival effect ON PHOTORECEPTORS[1]

See the data behind ENCELTO

Scan the QR code or visit ENCELTO.com/ecp

INDICATIONS AND USAGE

ENCELTO is an allogeneic encapsulated cell-based gene therapy indicated for the treatment of adults with idiopathic macular telangiectasia type 2 (MacTel).

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

ENCELTO is contraindicated in patients with active or suspected ocular or periocular infections, and in patients with known hypersensitivity to Endothelial Serum Free Media (Endo-SFM).

WARNINGS AND PRECAUTIONS

ENCELTO implantation surgery and/or implantation related procedures have been associated with the following:

Severe Vision Loss

Severe vision loss defined as three or more lines of visual acuity loss [≥15 Early Treatment Diabetic Retinopathy Study (ETDRS) letters] has occurred following ENCELTO implantation. Monitor patients for signs and symptoms of vision loss and manage as clinically indicated.

Infectious Endophthalmitis

Infectious endophthalmitis may occur following ENCELTO implantation. Signs and symptoms of infectious endophthalmitis include progressively worsening eye pain, vision loss, or scleral and conjunctival injection. To mitigate the risk of endophthalmitis, use proper aseptic surgical technique for ENCELTO implantation. Monitor patients for signs or symptoms of infectious endophthalmitis. Remove ENCELTO implant if infectious endophthalmitis occurs and manage symptoms according to clinical practice.

Retinal Tear and Detachment

Retinal tears and retinal detachment may occur following ENCELTO implantation. Signs and symptoms of retinal tears include acute onset of flashing lights, floaters, and/or loss of visual acuity. Signs and symptoms of retinal detachment may include progressive visual field loss and/or loss of visual acuity. Use standard vitreoretinal surgical techniques during ENCELTO implantation to minimize the risk of retinal tears and retinal detachment. Monitor for any signs or symptoms of retinal tear and/or retinal detachment. Treat rhegmatogenous retinal detachment and retinal tears promptly. Remove ENCELTO implant, if vitrectomy with a complete gas fill or silicone oil fill is required.

Vitreous Hemorrhage

Vitreous hemorrhage, which may result in temporary vision loss, has occurred following ENCELTO implantation. Patients receiving antithrombotic medication (e.g., oral anticoagulants, aspirin, nonsteroidal anti-inflammatory drugs) may be at increased risk of vitreous hemorrhage. To reduce the risk of vitreous hemorrhage, interrupt antithrombotic medications prior to the ENCELTO implantation. Vitrectomy surgery may be necessary to clear severe, recurrent, or non-clearing vitreous hemorrhage. If the patient has a late onset vitreous hemorrhage (greater than one year following ENCELTO implantation surgery), examine the ENCELTO implantation site for possible implant extrusion. If implant extrusion has occurred, surgically reposition ENCELTO.

Implant Extrusion

Implant extrusion through the initial scleral wound has occurred following ENCELTO implantation. Signs and symptoms of implant extrusion include recurrent uveitis, vitreous hemorrhage, eye pain more than one year after implantation, or visibility of titanium fixation loop under the conjunctiva. To reduce the risk of implant extrusion, carefully follow the specific surgical steps for ENCELTO implantation.

Evaluate patients after 6 months to confirm proper positioning of ENCELTO and then annually. If ENCELTO begins to extrude, surgically reposition ENCELTO to a proper scleral wound depth either in the same site or in the opposing inferior quadrant of the vitreous cavity.

Cataract Formation

Cataract formation, including cataract cortical, cataract nuclear, cataract subcapsular, cataract traumatic, and lenticular opacities, has occurred following ENCELTO implantation. To reduce the risk of ENCELTO-related cataract formation or progression, carefully follow the specific surgical steps for ENCELTO implantation.

Suture Related Complications

Suture related complications, including conjunctival erosions due to suture tips and suture knots, have occurred following ENCELTO implantation.

To mitigate the risk of suture related complications, carefully follow the specific surgical steps for ENCELTO implantation and manage suture-related complications as clinically indicated.

Delayed Dark Adaptation

Delayed Dark Adaptation, a delay in the ability to adjust vision from a bright lighting condition to a dim lighting, has occurred following ENCELTO administration which remained unchanged for the duration of study follow up. Advise patients to take caution while driving and navigating in the dark.

ADVERSE REACTIONS

The most common adverse reactions (≥2%) reported with ENCELTO were conjunctival hemorrhage, delayed dark adaptation, foreign body sensation, eye pain, suture related complications, miosis, conjunctival hyperemia, eye pruritus, ocular discomfort, vitreous hemorrhage, blurred vision, headache, dry eye, eye irritation, cataract progression or formation, vitreous floaters, severe vision loss, eye discharge, anterior chamber cell, iridocyclitis.

Please see Brief Summary of full Prescribing Information on following pages.

Reference: ENCELTO [prescribing information]. Cumberland, RI. Neurotech Pharmaceuticals, Inc.

neurotech

BRIEF SUMMARY OF PRESCRIBING INFORMATION

This Brief Summary does not include all of the information needed to use ENCELTO™ safely and effectively.

See full Prescribing Information for ENCELTO.

ENCELTO (revakinagene taroretcel-lwey) implant, for intravitreal use

Initial U.S. Approval: 2025

INDICATIONS AND USAGE

ENCELTO is indicated for the treatment of adults with idiopathic macular telangiectasia type 2 (MacTel).

DOSAGE AND ADMINISTRATION

Recommended Dose

For intravitreal implantation only

- ENCELTO is administered by a single surgical intravitreal procedure performed by a qualified ophthalmologist.
- The recommended dose is one ENCELTO implant per affected eye. Each ENCELTO implant contains 200,000 to 440,000 allogeneic retinal pigment epithelial cells expressing recombinant human ciliary neurotrophic factor (rhCNTF) (NTC-201-6A cell line), a neurotrophic factor.

CONTRAINDICATIONS

ENCELTO is contraindicated in patients with:

- Active or suspected ocular or periocular infections.
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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.

ADVERSE REACTIONS (cont'd)

Clinical Trials Experience (cont'd)

The safety data described in this section reflects exposure to ENCELTO in two clinical trials, Study 1 (NTMT-03-A) and Study 2 (NTMT-03-B) and are pooled for analysis. A total of 117 patients received ENCELTO, and 111 patients underwent a sham procedure and were followed for a duration of 24 months.

Serious adverse reactions occurred in six patients (5%) including suture related complications (n=5) and implant extrusion (n=1).

Table 1 lists the most common adverse reactions that occurred in ≥2% patients and with higher frequency in ENCELTO group compared to Sham group in Study 1 and Study 2.

Table 1. Adverse Reactions occurring in ≥2% of Patients and with higher frequency in ENCELTO group compared to Sham group in ENCELTO studies*

Adverse Reactions	ENCELTO (N=117) n (%)	Sham (N=111) n (%)
Conjunctival hemorrhage	36 (31)	29 (26)
Delayed dark adaptation	27 (23.1)	1 (1)
Foreign body sensation in eyes	18 (15)	15 (13.5)
Eye pain	18 (15)	10 (9)
Suture related complication**	18 (15.4)	3 (2.7)
Miosis	18 (15.4)	0 (0.0)
Conjunctival hyperemia	13 (11)	9 (8)
Eye pruritus	10 (9)	4 (3.6)
Ocular discomfort	10 (9)	1 (1)
Vitreous hemorrhage	10 (8.5)	0 (0.0)
Vision blurred	8 (7)	4 (4)
Headache	8 (7)	1 (1)
Dry eye	7 (6)	2 (2)
Eye irritation	6 (5.1)	2 (2)
Cumulative cataract incidence	6 (5)	0 (0)
Vitreous floaters	6 (5)	0 (0.0)
Severe visual loss>15 letters***	4 (3)	0 (0)
Eye discharge	4 (3.4)	1 (0.9)
Anterior chamber cell	4 (3.4)	0 (0.0)
Iridocyclitis	3 (2.6)	0 (0)

*Pooled data from Study 1 and Study 2; Adverse reaction rates were comparable between the two studies

**Suture related complications include exposed suture, foreign body sensation, conjunctival wound dehiscence, painful sutures, suture irritation, suture granuloma, scleral wound opening, and itchy suture

***Includes one case of visual loss due to cataract formation which remained unresolved at the end of the study

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

There are no data on the use of ENCELTO in pregnant women. Endogenous CNTF is naturally found in maternal plasma, placental cells, and umbilical cord blood. It is not known if the use of ENCELTO increases CNTF above naturally occurring levels in these tissues.

In animal reproduction studies, subcutaneous administration of rhCNTF to pregnant rats and rabbits demonstrated no evidence of teratogenic effects on the fetus. However, when administered to rabbits at a dose level of 10ug/kg/day, a decrease in implantations and live fetuses was observed. When administered to rats at a dose level of 100ug/kg/day a decrease in corpora lutea was observed.

The estimated background risk of major birth defects and miscarriage in the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects is 2% to 4% and of miscarriage is 15% to 20% of clinically recognized pregnancies.

Data

Animal Data

See *Risk Summary* for details on data.

Lactation

Risk Summary

There is no data on the presence of ENCELTO in human milk, its effects on the breastfed infant, or its impact on milk production.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ENCELTO and any potential adverse effects on the breastfed infant from rhCNTF or from the underlying maternal condition.

Pediatric Use

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

Geriatric Use

There were 38 patients (32%) 65 years of age and older and two patients (1%) 75 years of age and older in Study 1 and Study 2 who received ENCELTO. Clinical studies of ENCELTO did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently than younger patients.

Manufactured for:
Neurotech Pharmaceuticals, Inc.
Cumberland, RI 02864

ENCELTO™ (revakinagene taroretcel-lwey) implant, for intravitreal use | neurotech

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RT Retina Today

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TABLE OF CONTENTS

FEATURED ARTICLES

22 **Gene Therapy for Inherited Retinal Disease: The Pipeline**
By *Retina Today* Staff

24 **Top IRDs to Watch: Retinitis Pigmentosa**
By Aidan Lee, MD, and Hossein Ameri, MD, PhD, FRCSI, MRCOphth

27 **Top IRDs to Watch: Leber Congenital Amaurosis**
By Benjamin Bakall, MD, PhD, and Shyamanga Borooah, PhD, MBBS, FRCP, FRCSEd, FRCOphth

33 **Top IRDs to Watch: Stargardt Disease**
By Maria Ludovica Ruggeri, MD, and Ishrat Ahmed, MD, PhD

36 **Top IRDs to Watch: Cone and Cone-Rod Dystrophies**
By Dallin Milner, MD, and Marc Mathias, MD

40 **Top IRDs to Watch: Achromatopsia**
By Landon J. Rohowetz, MD; Byron L. Lam, MD; and Jesse D. Sengillo, MD

44 **Nutritional Supplementation for IRDs: Preservation or Placebo?**
By Paula C. Morales, MD; Cesar Estrada-Puente, MD; and Ramiro Maldonado, MD

ONLINE FEATURES

Top IRDs to Watch: Choroideremia
By Maria Ludovica Ruggeri, MD, and Ishrat Ahmed, MD, PhD

Top IRDs to Watch: Usher Syndrome
By Maria Ludovica Ruggeri, MD, and Ishrat Ahmed, MD, PhD

DEPARTMENTS

UP FRONT

8 **Guest Editor's Page**

9 **Retina News**

MEETING MINUTES

10 **ARDS 2025: Surgical Pearls**
By Frank Ma, MD, PhD

12 **Fellows and FOCUS at VBS 2025**
By Saumya Shah, MD; David Fell, MD; Kevin C. Allan, MD, PhD; Joana E. Andoh, MD; and Ethan A. Osias, MD

ONE TO WATCH

15 **David Xu, MD**

35 **Nikisha Kothari, MD**

SURGICAL PEARLS

16 **Doubling Down on Traumatic Macular Hole Management**
By Jose Luis Montiel Zamora, MD; Carlos Andres Valdes Lara, MD, FICO; and Abril Itandehui Miranda Lopez

MEDICAL RETINA

18 **A Series of Rare Events in Geographic Atrophy Therapy**
By Tina Tang, MD, and Nauman Chaudhry, MD

RISING STARS IN RETINA

47 **Rachel Downes, MD**

PEDIATRICS

48 **Pediatric Hemorrhage: The Answer Is in the Fellow Eye**
By Srujay Pandiri, BA; Celine Chaaya, MD; and Nimesh A. Patel, MD

OCULAR ONCOLOGY

50 **Surgical Management of Retinal Detachment in Uveal Melanoma**
By Rodrigo Anguita, MBBS, MD, FEBO, FICO, and Lyndon da Cruz, MA, MBBS, PhD, FRCOphth, FRACO

GLOBAL PERSPECTIVES

53 **Creative Positioning in Vitreoretinal Surgery**
By Alicia Alcuaz Alcalaya, MD; Eduardo Pérez-Salvador García, MD, PhD; and María Jesús López Peña, MD, PhD

CODING ADVISOR

55 **How to Create Clean Claims**
By Joy Woodke, COE, OCS, OCSR

VISUALLY SPEAKING

57 **Features of Choroidal Tuberculoma**
By Soulaymane Rachda, MD; Yassine Elkhalifa, MD; Selma Ouazzani Touhami, MD; Niima Elfahli, MD; Younes Tlemçani, MD, PhD; Sarah Belghmaidi, MD, PhD; Ibtissam Hajji, MD, PhD; and Abdeljalil Moutaouakil, MD, PhD

IN THE BACK

58 **Ad Index**

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Refer to the Valeda User Manual for indications for use and important safety information.

A HOPEFUL FUTURE FOR PATIENTS WITH IRDS

BY BEN SHABERMAN, VICE PRESIDENT, SCIENCE COMMUNICATIONS, FOUNDATION FIGHTING BLINDNESS

When I joined Foundation Fighting Blindness in 2004, the research underway for inherited retinal diseases (IRDs) was compelling. Our community was particularly encouraged by the dramatic vision restoration for dogs born blind from Leber congenital amaurosis (biallelic *RPE65* mutations) made possible by a groundbreaking gene augmentation therapy.[1]

However, with virtually all IRD research in animals at the time, I wondered if and when these cutting-edge therapies would move into clinical trials. Could we halt or reverse blindness in humans as well? Did retina specialists have a better message for IRD patients other than to go home, get a cane, and learn Braille? "Sorry, there's nothing we can do," was the common, hopeless refrain.

Fast forward to today, and the progress in IRD treatment development has been remarkable. More than 30 clinical trials are now underway for vision-saving and vision-restoring therapies (see *Gene Therapy for Inherited Retina Disease: The Pipeline* on page 22). Even more impressive is the commercial investment in the IRD space; at least 40 companies are now investing in the development of IRD treatments.

With these advances, my early concerns have turned into excitement. When I present the latest IRD research, I never have enough time to cover all the studies, and most of my research articles now cover developments in clinical trials in human (as opposed to mouse) studies.

Today, when most patients with IRDs visit their retina specialist, the message is one of hope and promise. There's a path forward. While we have only one approved therapy—the *RPE65* gene therapy that worked so well in dogs—several treatments in late-stage clinical trials are showing promising safety and efficacy.

I am particularly excited about gene-agnostic approaches, which are designed to work regardless of the patient's genetic profile. One such approach, optogenetics, is restoring vision for patients who have lost virtually all their photoreceptors. Four companies are now in clinical trials for this approach.

In addition to communicating hope, eye care professionals should also be ordering genetic testing for their patients with IRDs. By identifying the mutated gene, which occurs in about 60% to 70% of cases,[2] doctors can confirm the diagnosis, better understand familial risk, and guide patients toward relevant clinical trials. Foundation Fighting Blindness offers no-cost genetic testing, which has been ordered for more than 27,000 patients since 2017. Once tested, patients are put into the My Retina Tracker Registry, which can notify them of relevant clinical trials. (A registrant's privacy is always protected, and personal information is never divulged to companies or researchers.) More than 40,000 people are currently in the registry.[3]

Certainly, there are headwinds for IRD research. To gain more approvals, we need more sensitive and precise outcome measures for evaluating therapeutic efficacy in clinical trials. Also, the investment climate for biomedical research, especially for startups, has been challenging since the COVID-19 pandemic. Finally, potential changes in federal policy and research funding could have detrimental effects on our progress.

Nonetheless, when I think about the progress we've made over the last 2 decades, I can't help but be optimistic. Our momentum remains strong despite myriad challenges. More treatments for IRDs will cross the finish line. And that's a hopeful message to deliver to patients and their families. ■

1. UF Health. In gene therapy first, scientists restore vision to dogs born blind. April 25, 2001. Accessed April 21, 2025. bit.ly/451Xq4K
2. Weisschuh N, Mayer AK, Strom TM, et al. Mutation detection in patients with retinal dystrophies using targeted next generation sequencing. *PLoS One*. 2016;11(1):e0145951.
3. Foundation Fighting Blindness. Clinical Enrollment join forces to launch patient-centric trial matching initiative [press release]. Foundation Fighting Blindness. April 10, 2025. Accessed April 21, 2025. bit.ly/43RbixA

BEN SHABERMAN
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- Financial disclosure: Employee (Foundation Fighting Blindness)

MORE RESOURCES

FOUNDATION FIGHTING BLINDNESS

Foundation Fighting Blindness provides important educational resources for you and your patients, including disease state education, genetic testing, and clinical trials. Check it out at www.fightingblindness.org or follow the QR code.

HIV DRUG MAY HELP IMPROVE VISION IN DME

The results of a recent clinical trial suggest lamivudine, an inexpensive, long-approved drug for human immunodeficiency virus, can improve vision in patients with diabetic macular edema (DME) more effectively and at a lower cost than many existing treatments.[1]

Researchers at the University of Virginia collaborated with a team at Brazil's Universidade Federal de São Paulo to enroll 24 adults with center-involving DME and a BCVA of less than 69 letters in a small, randomized, clinical trial. Participants were assigned to receive either twice-daily oral lamivudine or placebo for 8 weeks, in addition to an intravitreal injection of bevacizumab (Avastin, Genentech/Roche) at week 4.[1,2]

Participants with DME who received lamivudine showed significant vision improvements, even before their first bevacizumab injection. Their vision improved by 9.8 letters at week 4, while the participants receiving placebo had a decrease in BCVA by 1.8 letters. At 8 weeks, the lamivudine recipients had improved BCVA by 16.9 letters, while the placebo group had improved by only 5.3 letters.[1,2]

These results suggest lamivudine may work both alone and in conjunction with anti-VEGF therapy, although larger studies are necessary, the researchers note.[1]

1. Study: long-approved HIV drug may improve vision in patients with DME [press release]. May 30, 2025. Accessed June 27, 2025. eyewire.news/news/study-long-approved-hiv-drug-may-improve-vision-in-patients-diabetic-macular-edema-patients
2. Pereira F, Magagnoli J, Ambati M, et al. Oral lamivudine in diabetic macular edema: A randomized, double-blind, placebo-controlled clinical trial [published online ahead of print May 23, 2025]. *Med.*

OUTCOMES OF PATIENTS LOST TO FOLLOW-UP AFTER PDR TREATMENT

A retrospective cohort study examined the visual outcomes of patients in the United States with proliferative diabetic retinopathy (PDR) who returned for care after being lost to follow up (LTFU) for more than 1 year following treatment with anti-VEGF therapy, panretinal photocoagulation (PRP), or both.[1]

The average time between the patients' visit prior to LTFU and their return visit was 679 days. The study authors found that visual acuity had significantly worsened at the return visit (logMAR VA: 0.485 or 20/60) compared with the visit prior to LTFU (logMAR VA: 0.436 or 20/55). However, visual acuity returned to baseline at 1 year after the return visit (logMAR VA: 0.437 or 20/54). Newly diagnosed complications that arose during the period of LTFU included DME (29.0%), vitreous hemorrhage (18.5%), tractional retinal detachment (5.7%), and neovascular glaucoma (1.5%). They also found that monotherapy with PRP was associated with a lower risk of these complications and lower risk of a final VA worse than 20/200.[1]

The authors concluded that patients with PDR who are LTFU are at a significant risk for complications and vision loss, underscoring the importance of efforts to promote adherence to treatment in this patient population.[1]

1. Khurana RN, Wang JC, Zhang S, Li C, Lum F. Outcomes of patients with proliferative diabetic retinopathy treated with anti-VEGF therapy and/or PRP in the United States who were lost to follow up [published online ahead of print June 3, 2025]. *Ophthalmol Retina.*

GLP-1 RA USE IN DIABETES MAY INCREASE RISK OF WET AMD

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are commonly used to treat diabetes and obesity, yet little is known about the long-term ocular effects of prolonged systemic exposure. A recent study found that the use of GLP-1 RAs among patients with diabetes was associated with a two-fold higher risk of wet AMD development.[1]

This retrospective cohort study followed 139,002 patients (46,334 were exposed to GLP-1 RAs, and 92,668 were not) for 3 years. The incidence of wet AMD was higher among the exposed cohort than among the unexposed cohort. Cox proportional hazard models, both unadjusted and adjusted, estimated the hazard ratio for wet AMD development to be greater than 2.0 among patients exposed to GLP-1 RAs.[1]

Further research is needed to elucidate the exact pathophysiological mechanisms involved and to understand the trade-offs between the benefits and risks of GLP-1 RAs, the authors noted in their paper.[1]

1. Shor R, Mihalache A, Noori A, et al. Glucagon-like peptide-1 receptor agonists and risk of neovascular age-related macular degeneration [published online ahead of print June 5, 2025]. *JAMA Ophthalmol.*

COMPANIES UNITE TO PROVIDE RESOURCES ON VISION LOSS IN AMD

Hadley and Notal Vision recently announced a strategic partnership to bridge the gap between early

(Continued on page 14)

ARDS 2025: SURGICAL PEARLS

At this year's meeting, top surgeons discussed how to handle epiretinal membranes and macular holes.

BY FRANK MA, MD, PHD

The 53rd annual Aspen Retinal Detachment Society (ARDS) meeting, held March 1 – 5, 2025, in Snowmass Village, Colorado, included several wonderful talks that focused on the management of complex surgical cases. Here, one of our top-notch fellows summarizes five key lectures on epiretinal membranes (ERMs) and macular holes. I hope you enjoy this recap and join us February 28 – March 4, 2026, for the 54th ARDS meeting for more education and mountaintop views.

– Timothy G. Murray, MD, MBA

During the 53rd annual ARDS meeting, experts from around the world discussed the pathophysiology and management of ERMs and macular holes. Mrinali P. Gupta, MD; Lejla Vajzovic, MD; Mario R. Romano, MD, PhD; and John T. Thompson, MD, each shared their unique insights (Figure).

EPIRETINAL MEMBRANES

ERMs exert tractional forces when attached to the retina, leading to gliosis and a decline in visual function. Dr. Romano discussed the management of ERMs and focused on the importance of early detection because a decline in visual function precedes overt structural damage, and the surgical challenges only increase as the ERMs become more advanced.

Dr. Romano described the intraretinal damage from internal limiting membrane (ILM) peeling, and emphasized its importance in using a centripetal peeling technique to minimize this damage. On lamellar holes, his studies revealed that epiretinal proliferation is present in 70% of the cases and results from intraretinal glial activation rather than tractional forces. These membranes do not exhibit significant traction and rarely progress to full-thickness macular holes, he said.

Dr. Gupta's talk on ERMs focused on those that form after retinal detachment (RD) repair. Although recurrent RD and proliferative vitreoretinopathy are often the primary concerns for surgeons, ERM and cystoid macular edema are frequent complications that can severely affect postoperative visual outcomes. The incidence of ERMs after RD repair, which varies widely with rates ranging from 8% to 58%, depends on the methodology and follow-up duration. She noted that while mild ERMs are common, significant ERMs that require surgical intervention occur in only a small percentage of cases, typically ranging from 1% to 8%.[1]

Dr. Gupta also explored the surgical factors that influence ERM formation, including the number of laser spots used during the procedure. Studies show that more than 750 laser spots increases the risk of ERM development, even after adjusting for baseline factors such as detachment severity.[2]

Dr. Gupta reviewed studies on drainage retinotomies and PFO, highlighting their effect on ERM rates. In some studies, drainage retinotomies were associated with increased risk of ERMs, particularly in cases that required larger retinotomies. Interestingly, the PRO study found no significant difference in ERM rates between drainage retinotomy and PFO, suggesting the surgical technique itself may not be as important as other factors such as retinal health.[3]

MACULAR HOLES

In a second talk, Dr. Gupta reviewed complex macular holes, focusing on cases that failed previous repairs. While traditional macular hole surgery techniques remain effective for most cases, more advanced strategies are required for refractory and recurrent holes. She recognized the growing role of medical management of these holes. Dr. Gupta explained that the first step in managing complex macular holes is to categorize them by size, with smaller holes typically requiring different approaches than larger ones. The presence or absence of the ILM also plays a crucial role in determining the surgical strategy.

Dr. Gupta mentioned several ILM flap techniques, amniotic membrane graft (AMG), and autologous retinal transplantation (ART) before focusing on the "viscostretch" technique, developed by Donald J. D'Amico, MD, in 2020.

This technique involves using cohesive viscoelastic to release retinal pigment epithelium adhesions and increase retinal elasticity; early data showed a 65% closure rate from a multicenter retrospective study of 20 eyes. Dr. Gupta recommended ILM peeling as an effective approach for holes under 500 µm and additional techniques for those up to 650 µm, after which ILM flaps, AMG, or ART should be considered.

Dr. Vajzovic's presentation focused on additional techniques for refractory or recurrent macular holes. She outlined her technique for smaller holes, emphasizing the benefits of platelet rich plasma (PRP), which serves as a biological adhesive to stabilize the ILM flaps and prevent displacement. She noted that PRP is particularly useful for optic pit macular holes, where the adhesive properties offer enhanced stability during the procedure. Subretinal balanced salt solution injections are also part of her approach to macular hole closure. Her approach is highly individualized, with the goal of closing the hole the first time to avoid the need for subsequent surgeries.

Dr. Vajzovic then discussed larger macular holes, which often require ART and AMG. ART has shown promise in promoting anatomic closure, although functional outcomes remain unpredictable.[4] She addressed the technical challenges of ART, particularly the difficulty in harvesting the retinal tissue and ensuring proper graft orientation. Despite these challenges, ART can be effective in some cases, particularly when there is no residual ILM. In cases where the hole is too large for ART, she recommends AMG as an alternative.

Dr. Vajzovic's approach emphasizes an aggressive first-time repair strategy, especially for larger macular holes, with the goal of maximizing anatomic closure and visual recovery.

Finally, Dr. Thompson delivered the 43rd annual Taylor Smith & Victor Curtin lecture on the natural history and treatment of lamellar macular holes and pseudoholes. He began by acknowledging the confusion in the literature surrounding classification. He discussed the publication of a consensus definition that categorized lamellar macular holes and pseudoholes into three distinct types based on OCT findings.[5] The classifications include the following:

- lamellar macular holes, characterized by foveal cavitation with undermined edges;
- macular pseudoholes, marked by a center-sparing ERM and a steepened foveal profile; and
- ERM foveoschisis, defined by contractile ERMs and foveoschisis at the Henle fiber layer.

Dr. Thompson emphasized that many lamellar macular holes remain stable and do not require treatment, as visual acuity typically remains stable. However, some patients experience progressive visual acuity loss, necessitating vitrectomy. He reviewed studies that demonstrated postoperative visual improvements in these patients, with VA improvements ranging from 20/63 to 20/43 in one study.[6] Dr. Thompson recommended vitrectomy for symptomatic patients with significant vision loss, noting that OCT findings play a crucial role in determining which patients are most likely to benefit from surgery. For foveoschisis cases, sparing the ILM around the fovea and short-term tamponade can reduce macular hole formation. Although surgical outcomes are often positive, visual acuity improvements tend to be modest.

Images courtesy of Kevin Caldwell Photography

Figure. Drs. Romano (A), Gupta (B), Vajzovic (C), and Thompson (D) each added their expertise to the discussion of ERMs and macular holes during the ARDS meeting.

COMPREHENSIVE EDUCATION

These presentations provided a comprehensive exploration of complex macular holes, ERMs, and lamellar macular holes. The speakers emphasized the importance of tailored, patient-specific approaches, using advanced surgical techniques, and careful postoperative management to optimize anatomic and visual outcomes. ■

1. Popovic MM, Berinstein JM, Franco J, et al. Epiretinal membrane formation following rhegmatogenous retinal detachment repair: a retrospective cohort study. *Ophthalmologica*. 2024:1-9.
2. Cakir B, Peacker BL, Zeng R, et al. Extensive endolaser during vitrectomy for primary rhegmatogenous retinal detachment is associated with epiretinal membrane formation. *Ophthalmic Surg Lasers Imaging Retina*. 2024;55(6):326-333.
3. Starr MR, Ryan EH, Yonekawa Y. Primary retinal detachment outcomes study: summary of reports number 1 to number 18. *Curr Opin Ophthalmol*. 2023;34(3):211-217.
4. Moysidis SN, Koulisis N, Adrean SD, et al. Autologous retinal transplantation for primary and refractory macular holes and macular hole retinal detachments: the global consortium. *Ophthalmology*. 2021;128(5):672-685.
5. Hubschman JP, Govetto A, Spaide RF, et al. Optical coherence tomography-based consensus definition for lamellar macular hole. *Br J Ophthalmol*. 2020;104(12):1741-1747.
6. Chehaibou I, Tadayoni R, Hubschman J-P, et al. natural history and surgical outcomes of lamellar macular holes. *Ophthalmol Retina*. 2024;8(3):210-222.

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FELLOWS AND FOCUS AT VBS 2025

This year's program was packed with pearls on mentorship, career advice, diversity and inclusion, and more.

BY SAUMYA SHAH, MD; DAVID FELL, MD; KEVIN C. ALLAN, MD, PHD; JOANA E. ANDOH, MD; AND ETHAN A. OSIAS, MD

The 13th annual Vit-Buckle Society (VBS) meeting, held March 20 – 22, 2025, in Austin, kicked off with a day for fellows, medical students, and residents. Here, we share some of the highlights from the programming filled with education and networking (Figure).

MORNING EDUCATION

Before breaking into the Fellows' Program and the FOstering Careers for Underrepresented Stars (FOCUS) Program in the afternoon, all attendees gathered for a few sessions. An important and consistent theme throughout the day was mentorship to help trainees advance their careers. Financial literacy, often overlooked within the medical field, took center stage with Nikisha Kothari, MD, who offered wisdom on managing personal finances at all levels of training. This session provided useful real-world insights such as how to tackle debt, save money as an early attending, and navigate various retirement plans.

Another panel discussed collaborating with federal and industry partners to advance research. Experts shared the timeline for applying for K-grants and gave advice on constructing budgets; they even provided a list of funding organizations beyond the federal government.

Next, Grant Justin, MD, led an engaging global health panel discussion. Panelists shared international and domestic experiences, showcasing the creativity and innovation required to tackle problems facing ophthalmology worldwide. For example, limited access to surgical devices in West Africa meant Dr. Justin's team had to rig an air compressor to work with a Constellation vitrectomy platform (Alcon) and ask patients to sing to monitor for bradycardia during scleral buckle placement, due to the lack of intraoperative heart monitoring.

Moreover, around the world, the aging population requires increased access to screening and follow-up, especially considering many patients with diabetic retinopathy are unaware of their diagnosis. Grayson W. Armstrong, MD, MPH, shared his experience with a global AI diabetic retinopathy screening program in India that he hopes could help patients at Mass Eye and Ear as well. Nurses at 150 community centers across India were trained to capture fundus imaging that was interpreted by AI, which dramatically expanded high-sensitivity screening to more than one million patients per year. Similar studies are underway in Boston with the goal of expanding access to ophthalmic care through AI-assisted screening programs.

FOCUS PROGRAM SHINES

In the afternoon, the FOCUS sessions emphasized leadership, resilience, and the power of inclusive innovation.

One of the FOCUS Program's greatest strengths is the culture of vulnerability and sense of belonging. Small group panels opened the floor for intimate conversations about the challenges faced by trainees, with a particular emphasis on the current political climate. Leaders in private practice and academia, including Hong-Uyen Hua, MD; Matthew A. Cunningham, MD; Roberto Diaz-Rohena, MD; and Mercy Kibe, MD, shared their journeys within the field of retina as underrepresented minorities. The rawness and familiarity of the stories resonated with many, inspiring hope that, regardless of the obstacles that arise, resilience within the ophthalmology community will keep the mission of inclusivity alive.

This conversation segued into a panel discussion on resilience, led by Jessica D. Randolph, MD. Difficult topics such as imposter syndrome, setbacks, and feelings of failure were tackled with openness and honesty. The panel

Image courtesy of Kevin Caldwell Photography

Figure. The Fellows and FOCUS Program participants gathered to network after a full day of education ranging from financial pearls to building resilience—and everything in between.

discussed the saying, "You can't be what you can't see," which highlights the importance of representation and believing you can be what you see. At times, it can be difficult to imagine yourself filling the shoes of mentors who are nothing short of powerhouses. Hearing about their struggles that led to triumph was inspiring.

In the closing session, Alexis K. Warren, MD, hosted a Q&A with Kgao Legodi, MD, about his career path in South Africa. Dr. Legodi became one of only a few retina specialists in apartheid South Africa and, for a time, the only Black one. Enduring discrimination and prejudice, he became one of the foremost experts in his field. What especially stood out about Dr. Legodi was his humility and humanism. Much of his talk consisted of advice on how to treat people, build community, and be the best physicians we can be.

FELLOWS AT VBS

The Fellows Program kicked off with an honest discussion about finding your first job out of fellowship and the reality of early career pivots. Moderated by Jayanth Sridhar, MD, and featuring Nika Bagheri, MD; Nicholas Farber, MD; Geeta Lalwani, MD; and Safa Rahmani, MD, the panel discussed the pros and cons of working within academic institutions, government-funded organizations, and private practices, as well as their early experiences in practice. Only two of the five speakers were still at the same practice at which they started. While priorities such as access to research, working with trainees, autonomy, and financial compensation heavily influence the kind of environment you should target, factors such as family and job availability ultimately tend to drive most people's initial decisions.

More challenging is recognizing when a situation may not be right and finding the courage to change course. Dr. Lalwani discussed her decision to move from academic medicine to private practice to prioritize her autonomy and family. When she found out she was pregnant soon after starting and alerted the practice, her contract was terminated. Rather than negotiating with her new employers (who had revealed their true colors), Dr. Lalwani started a solo practice in a new city, where she has now been thriving for more than a decade. Plan as best you can but roll with the punches and trust your intuition, the panel agreed.

The second session, moderated by Mrinali P. Gupta, MD, focused on practice building. According to the panel, which included Dr. Cunningham; Brian K. Do, MD; and Katherine E. Talcott, MD, a strong start involves strategic outreach and thoughtful integration into the referral network and surgical environment. As a new surgeon, work with your practice's public relations team, visit referring optometrists (bring donuts and coffee!), and consistently communicate with referring providers after seeing their patients. The panel also suggested giving talks at local CME events and ophthalmology societies. In the OR, they advised gaining consistent OR block time by gradually filling gaps and being precise when scheduling cases. They recommended bringing your preferred equipment settings and surgical tools to your new OR to optimize success and confidence.

The panel also discussed coping with complications and mentoring trainees. When cases do not go as planned, it is essential to trust your training, talk to colleagues, and take responsibility for all patient outcomes. Recording and reviewing cases, tracking results, and clearly discussing risks during the preoperative consent can help improve care and manage expectations. For those involved in teaching, set expectations with trainees at the beginning of the day, rotate roles often, and avoid giving away control during critical moments. Finally, the panelists emphasized that professionalism is key: Never speak poorly about colleagues, and always inform referring physicians if their patient is considering another provider to maintain transparency and trust.

The afternoon closed with a short panel on finding your niche outside of clinical medicine, which was moderated by Royce W. S. Chen, MD, and featured Avni P. Finn, MD, MBA; James Lin, MD; Phoebe Lin, MD, PhD; and

VIT-BUCKLE SOCIETY

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Meeting Coverage: Trainee Programming at VBS

Edward H. Wood, MD, who talked about their paths in research and medical education. While academic positions offer more time and resources, large private practices have become an important locus for clinical trial research and fellowship training. The lines are more blurred than ever before, and there are many different opportunities to train future generations of retina specialists and participate in cutting-edge research. ■

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SAVE THE DATE: April 9 – 11, 2026
14th Annual Vit-Buckle Society Meeting
Las Vegas

(Continued from page 9)
detection, treatment monitoring, and adaptive living for patients with AMD. The collaboration connects users of Notal Vision's ForeseeHome and SCANLY Home OCT monitoring programs with Hadley's specialized content and programming, including the company's "Living with Macular Degeneration" workshop series.[1]

A coproduced podcast features experts discussing early detection of eye diseases and the role of at-home monitoring. The accompanying email campaigns and social media efforts are designed highlight the synergy between home monitoring and the supportive programming.[1]

"AMD management requires both technological and behavioral interventions," explained Kester Nahen, CEO of Notal Vision, in a press release. "By referring our patients to Hadley's programs in our patient outreach, we empower individuals to proactively address vision changes—reducing anxiety and improving adherence to clinical follow-ups."[1] ■

1. Hadley and Notal Vision partner to empower patients with vision loss through education and leading technology [press release]. Eyewire+. June 24, 2025. Accessed June 27, 2025. eyewire.news/news/hadley-and-notal-vision-partner-to-empower-patients-with-vision-loss-through-education-and-leading-technology

Eyewire+ Pharma Update

- **Klinge Biopharma,** in partnership with Formycon, entered into an exclusive license agreement with Valorum Biologics for the commercialization of aflibercept-mrbb (FYB203/Ahzantive), a biosimilar to 2 mg aflibercept (Eylea, Regeneron), in the United States and Canada.
- **Alcon** announced its intention to acquire LumiThera and its photobiomodulation device for the treatment of early and intermediate dry AMD.
- **The European Medicines Agency's Pharmacovigilance Risk Assessment Committee** recommended that nonarteritic anterior ischemic optic neuropathy be listed as a rare side effect of semaglutide drugs used in the treatment of type 2 diabetes.
- **W. L. Gore & Associates** launched a silicone-free 0.5 mL syringe plunger designed for prefilled syringes. The silicone-free quality of the new plunger avoids problems such as elevated subvisible particulate levels, floaters, protein aggregation resulting in immunological responses, ocular inflammation, and increased IOP.
- **VeonGen Therapeutics,** formerly ViGeneron, announced that its lead program, VG801, in development for the treatment of *ABCA4* mutation-associated retinal dystrophies such as Stargardt disease, received Rare Pediatric Disease Designation from the FDA.

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ONE TO WATCH

RT Retina Today

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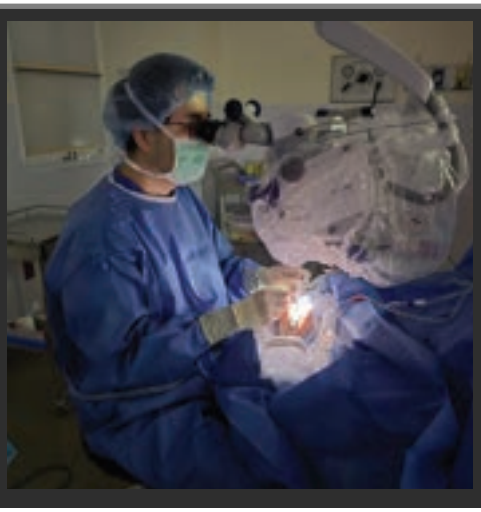
David Xu, MD



Dr. Xu's advice: Read textbooks and stay current in the literature to become a sharp diagnostician. Watch your own surgical videos and be your toughest critic!

WHERE IT ALL BEGAN

I grew up in Rockville, Maryland, and I was always interested in computers and engineering; it was no surprise that I pursued a Biomedical Engineering degree at Duke University. While at Duke, I picked up several hobbies, including building speakers, designing audio amplifiers, and computer programming. In a small way, I credit my fine dexterity for retina surgery to these hobbies that required soldering and assembling microelectronics.

MY PATH TO RETINA

My medical schooling at the Cleveland Clinic Lerner College of Medicine started with a summer research block. The program emphasized that becoming a physician-scientist was a journey, and I chose to start that journey with William J. Dupps Jr, MD, PhD, MS, a cornea specialist at Cole Eye Institute, because he was researching corneal biomechanics. Thus, I initially picked the field of ophthalmology based on my undergraduate degree in engineering. During my second year, I chose to work in the field of retina with Peter K. Kaiser, MD, where we conducted retrospective research on macular degeneration. From then on, I was hooked on retina.

SUPPORT ALONG THE WAY

I still work closely with many of the amazing mentors who helped me throughout medical school, residency, and fellowship, of which there are too many to name. I'm lucky to continue working with my mentors at Wills Eye Hospital after staying on after fellowship. I'm indebted to all of them for teaching me how to be a good retina diagnostician and a competent surgeon and for showing me how to empathically and professionally interact with patients.

AN EXPERIENCE TO REMEMBER

It's very rewarding for me as a retina surgeon to plan for a surgery and have that plan go smoothly from start to finish. Challenging surgical cases such as an IOL exchange, diabetic tractional detachment, and proliferative vitreoretinopathy require advanced planning. It is incredibly rewarding to hone my surgical skills, culimating in an elegant and efficient surgery that manifests good vision for the patient. I greatly enjoy this process of challenge and growth. Likewise, being able to share this process of discovery with retina fellows has been equally rewarding. ■

David Xu, MD, is a vitreoretinal surgeon at Wills Eye Hospital/Mid Atlantic Retina and an assistant professor of Ophthalmology at Thomas Jefferson University Hospital in Philadelphia. He is a consultant for Abbvie, Apellis Pharmaceuticals, Basuch + Lomb, Carl Zeiss Meditec/DORC, and Gyroscope Therapeutics. He can be reached at **davidxu64@gmail.com.**

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DOUBLING DOWN ON TRAUMATIC MACULAR HOLE MANAGEMENT

The double inverted internal limiting membrane flap technique may offer another treatment option for these patients.

BY JOSE LUIS MONTIEL ZAMORA, MD; CARLOS ANDRES VALDES LARA, MD, FICO; AND ABRIL ITANDEHUI MIRANDA LOPEZ

Traumatic macular hole (TMH) usually occurs secondary to blunt trauma in young patients. Its pathophysiology includes vitreoretinal disruption, tangential traction, and structural retinal damage.[1] In up to 39% of patients, spontaneous closure may occur; however, in persistent cases, the standard treatment is vitrectomy with internal limiting membrane (ILM) peeling.[2,3]

For large or persistent holes, techniques such as the inverted ILM flap have shown higher anatomic closure rates by facilitating glial cell migration over the defect.[4] In complex situations, the double inverted flap technique has been proposed, which involves inserting two ILM flaps into the hole and creating a double scaffold that promotes cell proliferation and tissue reorganization to achieve closure.

The following case describes the use of this technique in a patient with refractory TMH.

CASE REPORT

A 36-year-old woman presented with TMH in the left eye following a car accident. Initial treatment included vitrectomy with ILM peeling 1 month after the event; however, the hole closure was incomplete with poor anatomic and functional outcomes (Figure 1A). Her initial VA was 20/100, and a full-thickness MH (FTMH) with elevated edges and intraretinal cysts was documented via OCT, with a basal diameter of 1,152 µm (Figure 1B).

During the second procedure, triamcinolone was injected to visualize residual vitreous and complete the vitrectomy. Brilliant blue staining revealed a small area of previously peeled ILM and residual ILM tissue. ILM peeling was extended, leaving two long peripheral remnants to serve as scaffolding. The edges of the FTMH were stimulated using a Charles cannula, and heavy liquid was used to help insert both ILM remnants into the hole. This was followed by fluid-air exchange and SF_6 gas injection (Figure 2).

One month later, the patient's VA improved to 20/50, and complete hole closure was documented (Figure 3).

DISCUSSION

The double inverted flap technique may offer a new solution for large persistent TMH. Unlike conventional ILM peeling (which relies on passive approximation of the hole

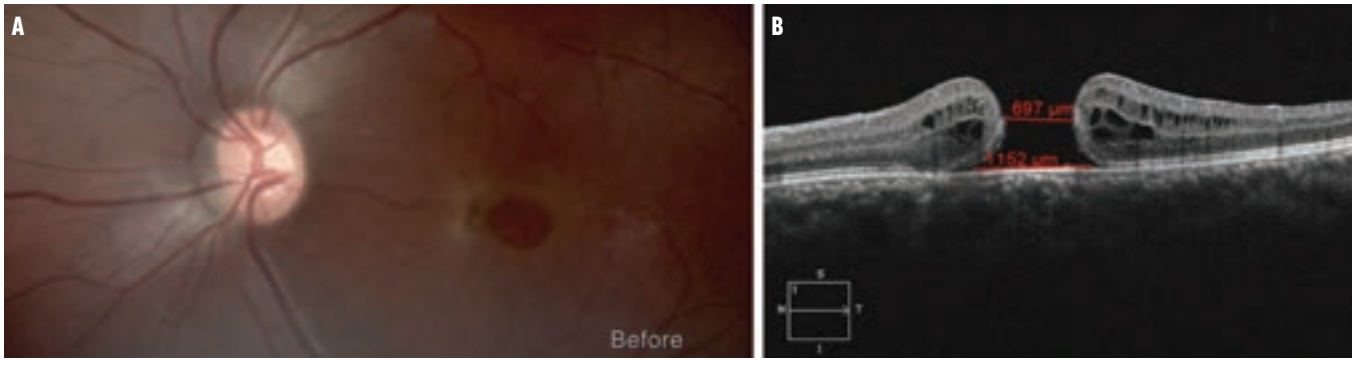

Figure 1. The FTMH is still evident after the first procedure with vitrectomy and ILM peeling (A). OCT shows the FTMH, elevated edges, and intraretinal cysts (B).

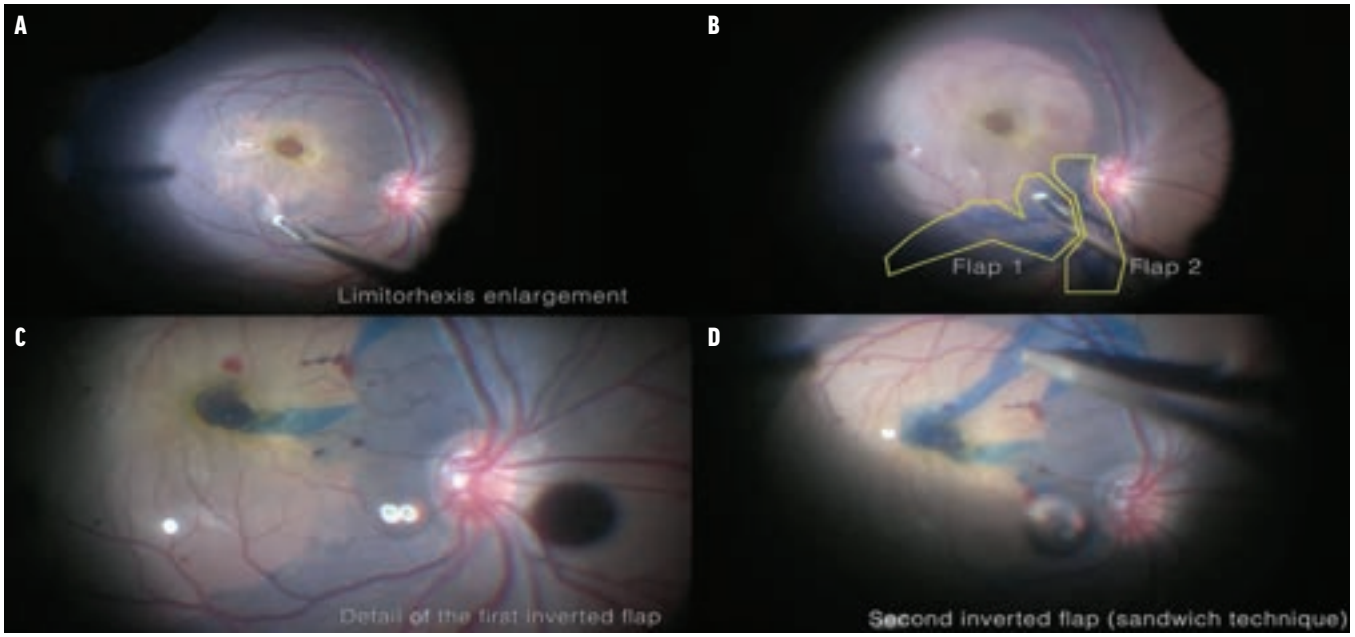

Figure 2. The initial ILM peeling area is enlarged using retinal forceps, creating two ILM remnants to serve as a scaffold for hole closure (A, B). The edges of the MH are stimulated with a Charles cannula, liquid is injected, and the first inverted flap is placed inside the hole (C). The second flap is placed over the first, followed by a fluid-air exchange and injection of SF_6 gas (D).

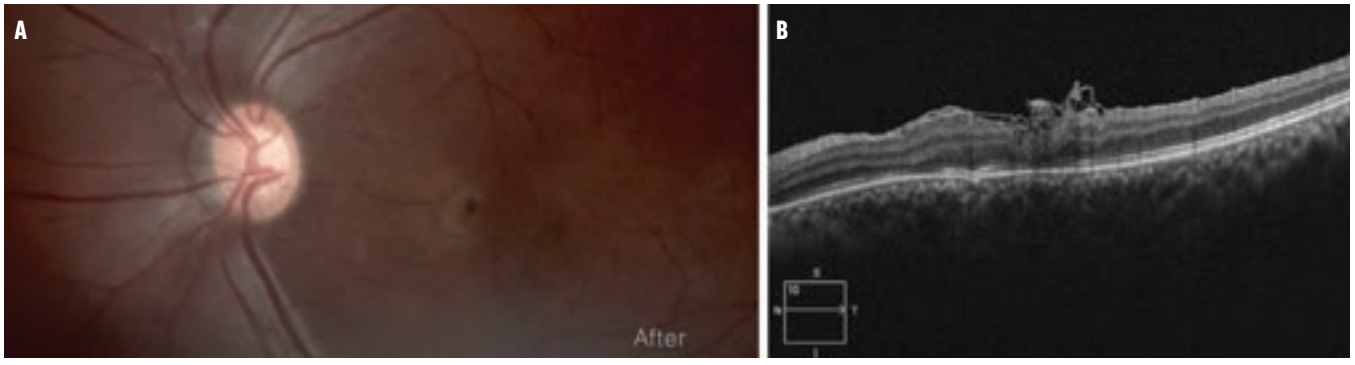

Figure 3. Complete hole closure is noted after the second surgery with a double ILM flap and fluid-air exchange (A). OCT confirms closure of the TMH with ellipsoid zone restoration (B).

edges) and the traditional inverted flap technique (which covers the hole with a single ILM flap), this method inserts two flaps into the defect to provide dual support for cell proliferation and neurosensory tissue regeneration.

From a pathophysiological standpoint, TMH involves vitreoretinal traction, ILM rupture, and loss of neurosensory retinal structure.[1] In this context, successful closure and functional recovery depend on the elimination of tractional forces on the macula, glial cell proliferation (particularly Müller cells) into the hole, and the release of neurotrophic factors such as basic fibroblast growth factor (bFGF), which helps inhibit neuronal and photoreceptor cell apoptosis.[5]

With ILM peeling, the membrane is removed to reduce retinal traction, but in large or persistent holes, this strategy may not achieve anatomic closure. With the inverted flap technique, a single ILM fragment is placed over the hole to serve as a substrate for gliosis. The double inverted flap technique builds on the mechanism described by Michalewska et al in 2010 and involves the insertion of two ILM flaps into the defect to create a double-layer structure that provides a more robust scaffold for cell proliferation.[4] This promotes Müller cell migration into the hole, facilitates retinal fiber reorganization and neurosensory layer regeneration, and induces greater bFGF release.[6] Combined with edge stimulation using a Charles cannula to remove adhesions, this technique supports retinal repair and creates a favorable environment for photoreceptor reorganization, improving the foveal contour and enhancing retinal remodeling.

Alternatively, the use of human amniotic membrane grafts has been proposed for persistent hole closure. This technique has shown an anatomic closure rate of 94%, but its effectiveness in restoring visual acuity is limited, at 66%.[7] This is due to the non-neurosensory nature of the graft, which

(Continued on page 20)

A SERIES OF RARE EVENTS IN GEOGRAPHIC ATROPHY THERAPY


These cases highlight screening and follow-up considerations with anti-complement therapy.

BY TINA TANG, MD, AND NAUMAN CHAUDHRY, MD

In recent years, significant advances in the treatment of geographic atrophy (GA) have been made with the FDA approval of pegcetacoplan (Syfovre, Apellis) and avacincaptad pegol (Izervay, Astellas). While these therapies—both of which target the complement system to slow GA progression—offer promising benefits, they also carry risks, including the potential development of wet AMD.

The decision to treat patients remains complex, requiring careful consideration of individual patient factors and an in-depth patient discussion of potential risks and benefits. The following cases depict patients who developed wet AMD within 10 months of commencing anti-complement therapy for GA, highlighting the need for careful screening and monitoring of patients being started on these therapies.

CASE 1

An 83-year-old man presented with a 3-year history of progressive visual decline in his left eye. His past ocular history was notable for longstanding poor vision in the right eye with BCVA of counting fingers secondary to macular neovascularization (MNV). The left eye, historically with a BCVA of 20/30, had deteriorated to 20/70 at presentation. The anterior segment examination was unremarkable. Indirect ophthalmoscopy revealed retinal pigment epithelium (RPE) changes in each eye. Imaging studies, including red-free imaging, OCT, and fundus autofluorescence (FAF), demonstrated significant GA progression in the left eye (Figure 1). Given the progression, intravitreal pegcetacoplan therapy was initiated in the left eye and administered every 8 weeks. Eight weeks after the fourth injection, the patient's VA worsened to 20/200 OS with findings of subretinal hemorrhage and pigment epithelial detachment (PED; Figure 2). There was no evidence of exudative changes at the previous visit.

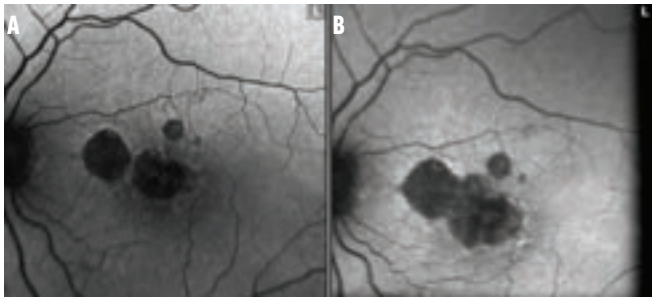

Figure 1. FAF shows significant progression of the GA lesion in the left eye from baseline (A) to 9 months (B). Note the large area of RPE loss leading to hypoautofluorescence with sickened RPE along the edge of the atrophic area seen as hyperautofluorescence.

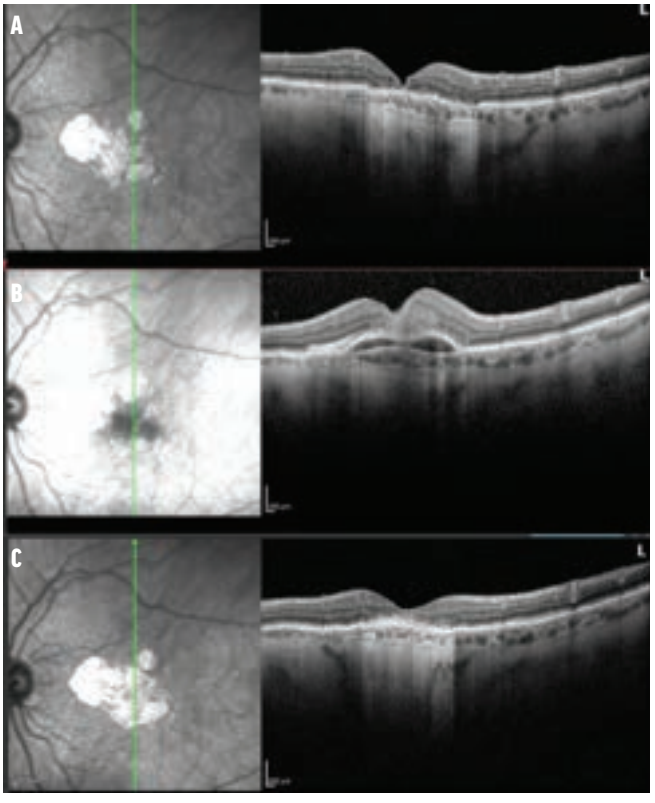

Figure 2. OCT imaging documents the transformation from dry (A) to wet (B) AMD 8 weeks after the fourth injection of pegcetacoplan. Note the fibrovascular PED with associated subretinal hemorrhage. After anti-VEGF therapy, OCT imaging shows resolution of the hemorrhage and PED (C).

Pegcetacoplan was discontinued, and anti-VEGF therapy was started. While the PED and hemorrhage resolved, the BCVA remained at 20/200 with GA. The patient declined further anti-complement therapy.

CASE 2

A 78-year-old woman presented with a history of dry AMD and a gradual decline in visual acuity due to GA progression in the left eye. Intravitreal avacincaptad pegol was initiated. After the fourth injection, the patient's VA declined from 20/50 to 20/100. Clinical examination and OCT revealed new intraretinal fluid and subretinal hyperreflective material, indicating conversion to wet AMD (Figure 3). Intravitreal bevacizumab (Avastin, Genentech/Roche) was administered; however, subsequent follow-up showed worsening fluid. The treatment was then switched to 8 mg aflibercept (Eylea HD, Regeneron), which led to a reduction in intraretinal fluid. At the 4-month follow-up, VA had improved to 20/60. The plan is to continue both anti-VEGF and anti-complement treatment.

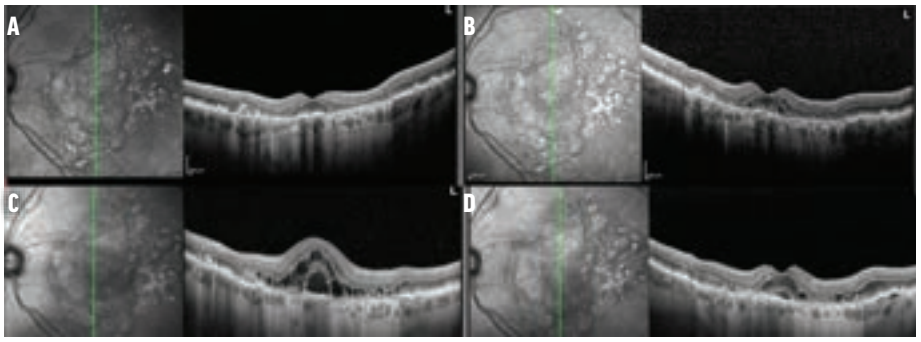

Figure 3. This patient with GA and new-onset wet AMD (A) experienced progression of intraretinal fluid despite treatment with intravitreal bevacizumab (B). OCT imaging shows improvement of the intraretinal fluid compared with baseline (C) after switching to intravitreal 8 mg aflibercept (D).

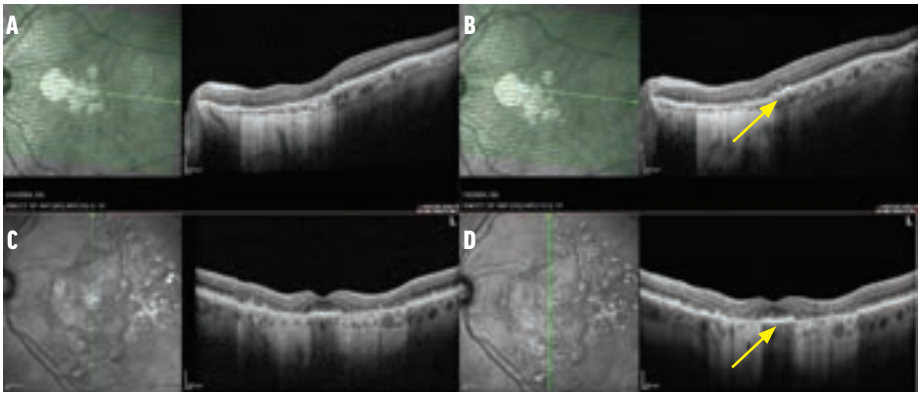

Figure 4. OCT imaging of the left eye of the patient in case 1 (A) shows early development of a double-layer sign with increasing subretinal hyperreflectivity (B, arrow) during the injections with complement inhibition therapy prior to wet AMD conversion. Similarly, the left eye of case 2 (C) shows early development of a double-layer sign with increasing subretinal hyperreflectivity (D, arrow) during the injections with complement inhibition therapy prior to wet AMD conversion.

DISCUSSION

The emergence of complement inhibition therapy has introduced new tools for managing GA.[1,2] However, these treatments carry a risk of conversion to wet AMD.[1-6] These cases highlight the potential risk of conversion and the importance of monitoring and prompt intervention in patients undergoing GA therapy. They also emphasize the potential risk of irreversible vision loss following conversion to wet AMD.

In the OAKS and DERBY trials evaluating pegcetacoplan, the incidence of new-onset wet AMD over 24 months was 12.2% in monthly dosing, 6.7% in every-other-month dosing, and 3.1% in the pooled sham arms.[6] The majority of the MNV cases identified on fluorescein angiography were occult. Similarly, 24-month data from the GATHER2 trial assessing monthly 2 mg avacincaptad pegol reported choroidal neovascularization rates of 12% compared with 9% in the sham arm.[5]

Data from OAKS and DERBY showed that when pegcetacoplan was administered with anti-VEGF treatment, no unexpected outcomes were observed (the median change in BCVA from the study visit preceding wet AMD conversion to month 24 was -5.0 letters in those receiving pegcetacoplan monthly, -6.0 letters in those receiving pegcetacoplan every other month, and -5.0 letters in those receiving sham).[1] These findings appear consistent with real-world data presented at the 2025 Macula Society meeting, in which patients maintained good vision despite wet AMD conversion.[3]

Data from GATHER1 and GATHER2 also demonstrated no significant difference in BCVA change from baseline to months 12 and 18 between patients treated with avacincaptad pegol and those receiving sham with the development of MNV. Among patients who developed MNV, the mean change in BCVA from baseline to month 12 was -4.2 letters in both the avacincaptad pegol and sham groups. At month 18, the mean change was -9.6 letters in the avacincaptad pegol group and -10.3 letters in the sham group.[5]

The cases reported here were associated with rare events. In case 1, the patient's vision remained at 20/200 despite resolution and treatment of exudative changes. It is important to counsel patients that, although rare, conversion to wet AMD during anti-complement therapy for GA can lead to irreversible vision loss, even with prompt treatment. In

case 2, the patient's vision improved from 20/100 to 20/60 after the treatment of MNV, highlighting the importance of early detection and treatment of MNV conversion.

Certain baseline characteristics have been associated with an increased likelihood of developing wet AMD during complement inhibition therapy. In the phase 2 FILLY trial, the presence of MNV in the fellow eye and the double-layer sign on OCT were identified as significant risk factors.[4] Case 1 had a history of MNV in the fellow eye and, thus, had a high risk of conversion. In both cases, the patients developed a subtle double-layer sign during the initial injections prior to the conversion to wet AMD (Figure 4).

DOCUMENT AND SHARE

As the use of complement inhibition for GA increases, it is imperative to document and share clinical outcomes to enhance our understanding of their efficacy and safety profiles. Regularly monitoring patients for early signs of conversion to wet AMD is critical. During the trials, imaging with OCT angiography was not the standard protocol; however, given the risks of MNV conversion, we now include OCT imaging for new patients. In our practice, we carefully review all raster lines of OCT scans every visit and perform OCT angiography at the initiation of therapy, every 6 months, and earlier if new symptoms are reported or if there is any suggestion of new clinical changes. Looking to the future, ongoing research into alternative treatments for GA may one day broaden our therapeutic options. ■

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(Continued from page 17)
does not foster a suitable environment for gliosis or efficient photoreceptor reorganization. Fortunately, the double inverted flap technique offers advantages in accessibility and cost and minimizes the risks associated with external graft rejection or complications. As a whole, it creates a better environment for complete anatomic closure of TMH due to the presence of more cells within the hole and the dual scaffolding that facilitates cell migration. This active repair process enables significant functional recovery, allowing patients to experience visual improvements.

TIME WILL TELL

The double inverted ILM flap technique represents a potential alternative for the treatment of refractory TMH. Inserting two ILM flaps into the defect creates a double scaffold structure that promotes cell proliferation, particularly of Müller cells, and neurosensory tissue reorganization. This mechanism enhances anatomic hole closure and facilitates functional recovery by providing an optimal environment for retinal repair and photoreceptor reorganization.

Furthermore, by using autologous tissue, the technique offers benefits in terms of accessibility and cost. While the initial outcomes in this case suggest the technique may be effective, prospective studies are needed to evaluate its long-term effectiveness and its potential inclusion among therapeutic options for complex cases. ■

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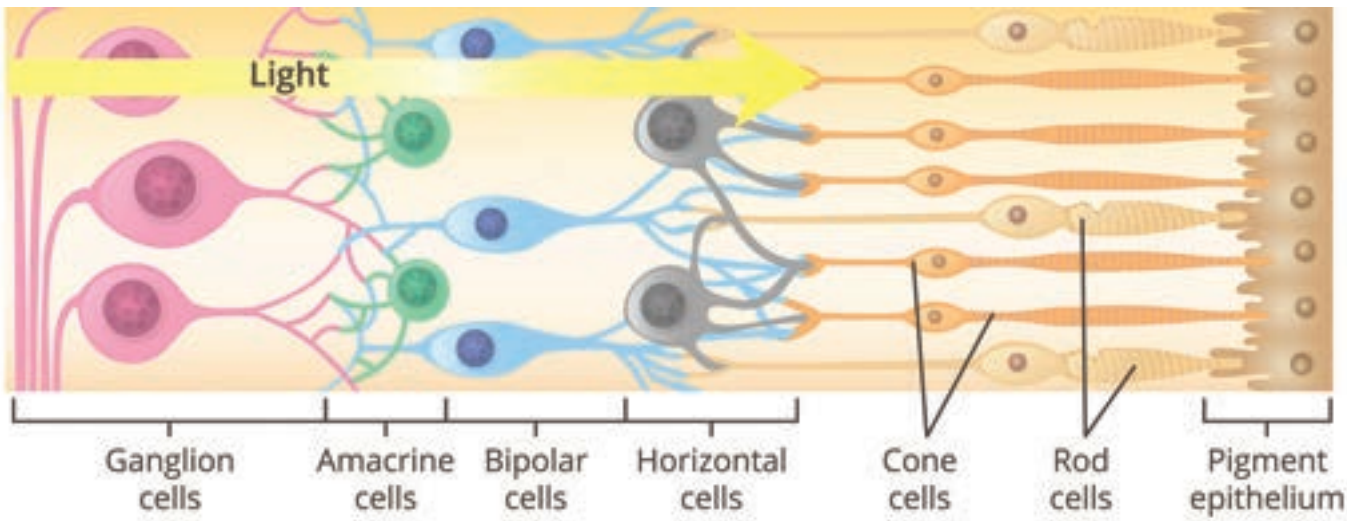
GENE THERAPY FOR INHERITED RETINAL DISEASE: THE PIPELINE

The field of inherited retinal disease research is exploding with more than 30 therapies under investigation for Leber congenital amaurosis, retinitis pigmentosa, Stargardt disease, cone and cone-rod dystrophies, achromatopsia, choroideremia, Usher syndrome, and others. Although many still rely on traditional AAV vectors, several novel mechanisms of action and delivery methods hold promise for improved efficacy and safety and, potentially, gene agnostic treatment. Here, we provide a snapshot of the pipeline to help you educate patients—and foster hope that therapies may soon be within reach for some conditions.

- The Staff of *Retina Today*



Ganglion Cells

Retinitis Pigmentosa
RTx-015 (Ray Therapeutics)
BS01 (Bionic Sight)
GS030-DP/GS030-MD (GenSight Biologics)
KIO-301 (Kiora Pharmaceuticals)

Bipolar Cells

Stargardt Disease/Retinitis Pigmentosa
MCO-010 (Nanoscope)

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The staff of *Retina Today* would like to thank Jesse D. Sengillo, MD, for reviewing this article and offering his insights into the pipeline.

Cone/Rod Cells

Achromatopsia
AAV8.hCNGA3 (STZ Eyetrial)

Batten Disease
NGN-101 (Neurogene)
TTX-381 (Tern Therapeutics)

Leber Congenital Amaurosis
ATSN-101 (Atsena Therapeutics)
OPGx-001 (Opus Genetics)
Sepofarsen (Sepul Bio)
rAAV8.hRKp.AIPL1 (MeiraGTx)

Stargardt Disease
OCU410ST (Ocugen)
ACDN-01 (Ascidian Therapeutics)
VG801 (VeonGen)
SB-007 (Splice Bio)

Retinitis Pigmentosa
Iaru-zova (Beacon Therapeutics)
rAAV.hPDE6A (STZ Eyetrial)
AAV2/5-hPDE6B (eyeDNA Therapeutics/Coave Therapeutics)
SPVN06 (SparingVision)
VP-001 (PYC Therapeutics)
VG901 (VeonGen)
OCU400 (Ocugen)
AAV5-hRKp.RPGR (Janssen/Johnson & Johnson)

Usher Syndrome
AAVB-081 (AAVantgarde Bio)
Ultevursen (Sepul Bio)

X-Linked Retinoschisis
ATSN-201 (Atsena Therapeutics)

GENE	TREATMENT AGENT (SPONSOR)	TREATMENT STRATEGY	DELIVERY METHOD	TRIAL ID	PHASE	STATUS	PRIMARY COMPLETION
Leber Congenital Amaurosis							
CEP290	QR-110 (Sepofarsen, Sepul Bio)	Alter splicing error; antisense oligonucleotides	Intravitreal	NCT06891443	3	Recruiting	November 2027
GUCY2D	AAV8-GRK1-GUCY2D (ATSN-101, Atsena Therapeutics)	Gene replacement	Subretinal	NCT03920007	1/2	Active, not recruiting	May 2023
LCA5	AAV8-hLCA5 (OPGx-001, Opus Genetics)	Gene replacement	Subretinal	NCT05616793	1/2	Recruiting	December 2024
AIPL1	rAAV8.hRKp.AIPL1 (MeiraGTx)	Gene replacement	Subretinal	Under investigation in the United Kingdom			
Retinitis Pigmentosa/Rod-Cone Dystrophy							
RPGR	AAV5-hRKp.RPGR (Janssen/Johnson & Johnson)	Gene replacement	Subretinal	NCT04671433	3	Complete	
				NCT04794101	3	Active, not recruiting	September 2029
Gene agnostic	OCU400 (Ocugen)	Overexpression of NR2E3	Subretinal	NCT06388200	3	Recruiting	June 2025
Gene agnostic	MCO-010 (Nanoscope)	Optogenetics	Intravitreal	NCT04945772	2b	Complete	
Gene agnostic	KIO-301 (Kiora Pharmaceuticals)	Photoswitch	Intravitreal	NCT06628947	2	Not yet recruiting	March 2026
RPGR	rAAV2tYF-GRK1-RPGR (Iaru-zova; AGTC-501, Beacon Therapeutics)	Gene replacement	Subretinal	NCT04850118	2/3	Recruiting	August 2025
				NCT03316560	1/2	Active, not recruiting	November 2023
				NCT06333249	1/2	Active, not recruiting	April 2023
PDE6A	rAAV.hPDE6A (STZ Eyetrial)	Gene replacement	Subretinal	NCT04611503	1/2a	Active, not recruiting	July 2027
PDE6B	AAV2/5-hPDE6B (eyeDNA Therapeutics/Coave Therapeutics)	Gene replacement	Subretinal	NCT03328130	1/2	Recruiting	December 2029
Gene agnostic; *RHO, PDE*	AAV-RdCVF-RdCVFL (SPVN06, SparingVision)	Overexpression of rod-derived cone viability factor; a cone neurotrophic factor	Subretinal	NCT05748873	1/2	Recruiting	March 2025
Gene agnostic	rAAV2.7m8-CAG-ChrimsonR-tdTomato (GS030-DP, GS030-MD, GenSight Biologics)	Optogenetics and visual interface stimulating glasses	Intravitreal	NCT03326336	1/2a	Recruiting	December 2022
Gene agnostic	AAV2-CAG-ChronosFP (BS01, Bionic Sight)	Optogenetics	Intravitreal	NCT04278131	1/2	Recruiting	December 2024
CNGA1	AAV2.NN-CNGA1 (VG901, VeonGen)	Gene replacement	Intravitreal	NCT06291935	1b	Recruiting	April 2026
Gene agnostic	RTx-015 (Ray Therapeutics)	Optogenetics	Intravitreal	NCT06460844	1	Recruiting	May 2026
PRPF31	VP-001 (PYC Therapeutics)	Gene replacement	Intravitreal	NCT06455826	1	Recruiting	November 2025
				NCT06852963	1/2	Not yet recruiting	June 2027
Stargardt Disease							
Gene agnostic	MCO-010 (Nanoscope)	Optogenetics	Intravitreal	NCT05417126	2	Complete	
ABCA4	AAV5-hRORA (OCU410ST, Ocugen)	Regulates pathways in oxidative stress and lipofuscin formation	Subretinal	NCT05956626	1/2	Recruiting	October 2025
ABCA4	VG801 (VeonGen)	Gene replacement	Subretinal	NCT07002398	1/2	Recruiting	May 2026
ABCA4	SB-007 (Splice Bio)	Gene replacement	Subretinal	NCT06942572	1/2	Recruiting	October 2028
ABCA4	ACDN-01 (Ascidian Therapeutics)	Exon-editing RNA	Subretinal	NCT06467344	1/2	Recruiting	August 2030
X-Linked Retinoschisis							
RS1	AAV.SPR-hGRK1-hRS1syn (ATSN-201, Atsena Therapeutics)	Gene replacement	Subretinal	NCT05878860	1/2	Recruiting	October 2025
Usher Syndrome							
USH2A	Ultevursen (Sepul Bio)	Antisense oligonucleotide; induces exon 13 skipping	Intravitreal	NCT06627179	2b	Recruiting	December 2027
MYO7A	AAVB-081 (AAVantgarde Bio)	Gene replacement	Subretinal	NCT06591793	1/2	Recruiting	July 2025
Achromatopsia							
CNGA3	AAV8.hCNGA3 (STZ Eyetrial)	Gene replacement	Subretinal	NCT02610582	1/2	Active, not recruiting	June 2027
Batten Disease							
CLN2	TTX-381 (Tern Therapeutics)	Gene replacement	Subretinal	NCT05791864	1/2	Recruiting	July 2026
CLN5	NGN-101 (Neurogene)	Gene replacement	Intracerebroventricular and intravitreal	NCT05228145	1/2	Active, not recruiting	November 2028

TOP IRDS TO WATCH:
RETINITIS PIGMENTOSA

Here's what you need to diagnose, counsel, and follow patients with the most common inherited retinal disease.

By Aidan Lee, MD, and Hossein Ameri, MD, PhD, FRCSI, MRCOphth


Retinitis pigmentosa (RP) is the most common form of inherited retinal disease (IRD), affecting approximately one in 4,000 individuals worldwide.[1]

RP is inherited in autosomal dominant, autosomal recessive, or X-linked patterns, with onset typically occurring in adolescence or early adulthood. It presents with nyctalopia, followed by progressive constriction of the field of vision and then, in severe cases, complete blindness. Classic fundoscopic findings include bone-spicule pigmentation, attenuated retinal vessels, and waxy pallor of the optic disc (Figure 1). As the disease progresses, posterior subcapsular cataract, cystoid macular edema (CME), and epiretinal membranes (ERM) may develop, contributing to further vision loss.

DIAGNOSTIC PEARLS

The diagnosis of RP involves history, fundus examination, imaging, functional testing, and molecular genetics.

Spectral-domain OCT assists in evaluating ellipsoid zone (EZ) integrity and detecting complications such as CME and ERM (Figure 2). Full-field electroretinography remains the standard for functional testing, often revealing severely diminished or absent rod and cone responses.

Fundus autofluorescence (FAF) is a critical noninvasive tool that often reveals a hyperautofluorescent ring in the macula that represents the transition zone between the healthy and the degenerating retina (Figure 3).

After analyzing FAF images across 11 genotypes of RP, we identified eight distinct autofluorescence patterns—four within the macula (eg, central foveal hyperautofluorescence, bull's-eye patterns) and four in the extramacular retina (eg, midperipheral rings, patchy or diffuse hypoautofluorescence).[2] While certain features such as double concentric hyperautofluorescent rings were once considered pathognomonic (eg, *NR2E3*), this study found them in other genotypes as well, including *RHO*, *RPGR*, and *USH2A*-linked RP. These findings suggest FAF is valuable for

AT A GLANCE

- Retinitis pigmentosa (RP) is the most common form of inherited retinal disease, affecting approximately one in 4,000 individuals worldwide.
- Classic fundoscopic findings in RP include bone-spicule pigmentation, attenuated retinal vessels, and waxy pallor of the optic disc.
- Although there is no cure for most forms of RP, management focuses on visual rehabilitation, monitoring for treatable complications, and preserving quality of life.
- The therapeutic landscape for RP is rapidly evolving, and several clinical trials show promise.

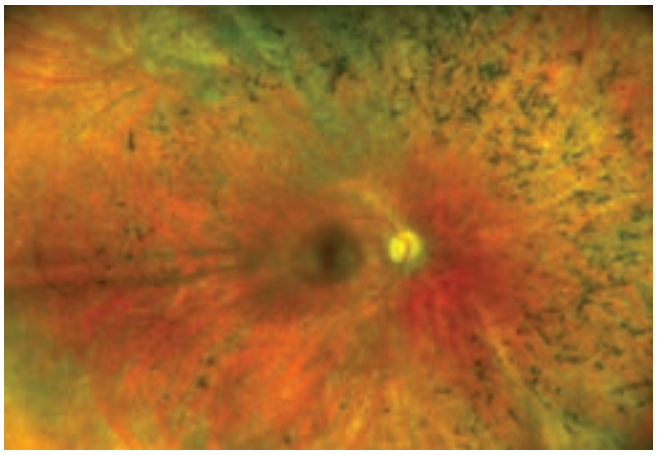

Figure 1. Patients with RP often present with bone-spicule pigmentation, loss of peripheral retinal vessels, and vascular attenuation.

documenting disease severity and progression but is not reliable for distinguishing specific genotypes.

Ultra-widefield (UWF) fundus photography and autofluorescence are becoming important tools in the diagnosis and follow-up of RP. In a study using UWF fundus imaging, we found that RP patients had significantly fewer peripheral retinal vessels compared with controls, with 22% of eyes completely lacking vessels in the far periphery. These findings highlight that symmetrical peripheral vessel dropout is a relatively constant feature of RP, which—after retinal bone-spicule pigmentation—may be the most recognizable characteristic on UWF imaging, surpassing more subjective signs such as vascular attenuation and waxy disc pallor.[3]

GENETIC TESTING

RP has been associated with mutations in more than 100 genes.[4] Identifying the causative mutation provides valuable prognostic information, clarifies inheritance patterns, and is increasingly necessary for clinical trial eligibility and consideration of investigational gene therapy treatments.

MORE RESOURCES

FOUNDATION FIGHTING BLINDNESS

Foundation Fighting Blindness provides important educational resources for you and your patients, including disease state education, genetic testing, and clinical trial updates.

About Retinitis Pigmentosa

Low Vision Resources

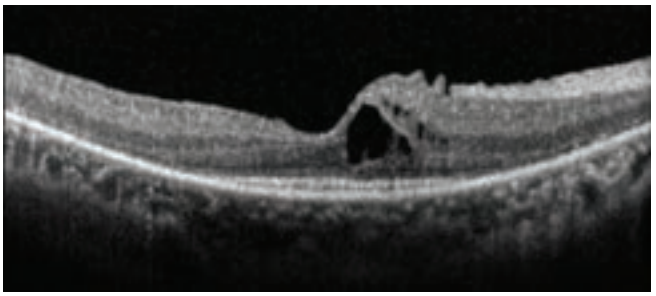

Figure 2. OCT imaging of a patient with RP reveals the loss of the EZ and outer nuclear layer outside the fovea, as well as CME and ERM.

The gene panels vary among laboratories. Our recent study compared the genetic testing reports of Invitae and Blueprint Genetics in 216 patients with IRD, including RP, and found major differences between the two labs.[5] Interestingly, among the seven patients tested by both laboratories, none had identical reported gene variants, even when the mutations were in genes present on both testing panels. These findings highlight the importance of carefully interpreting genetic testing results and considering the variability between testing platforms.

LONG-TERM MANAGEMENT AND COMPLICATIONS

Management focuses on visual rehabilitation, monitoring for treatable complications, and preserving quality of life. CME occurs in 18% to 50% of RP patients and can often be managed with topical and/or systemic carbonic anhydrase inhibitors.[6,7] Other cases may respond to topical NSAIDs or topical, periocular, or intravitreal steroids. Cataract, especially posterior subcapsular opacities, is common and may require surgical intervention in visually significant cases.

Currently, no vitamin or supplement clearly benefits patients with RP. While high-dose vitamin A supplementation was previously reported to slow disease progression in RP based on a large clinical trial,[8] a recent reanalysis of the same trial concluded that vitamin A supplementation does not slow the progression of RP.[9] Furthermore, vitamin A may pose risks to patients with liver disease, renal transplant history, or osteopenia.[10,11]

A phase 1 study showed that oral N-acetylcysteine (NAC), a compound that reduces oxidative stress, administered for 6 months was well-tolerated and resulted in small but statistically significant improvements in visual acuity and light sensitivity.[12] Currently, a phase 3 multicenter, randomized clinical trial evaluating the efficacy and safety of oral NAC in RP patients is underway.[13] If successful, NAC may become a viable therapy option for patients with RP.

Finally, low vision services, orientation and mobility training, and psychosocial support are essential for patients coping with vision loss.

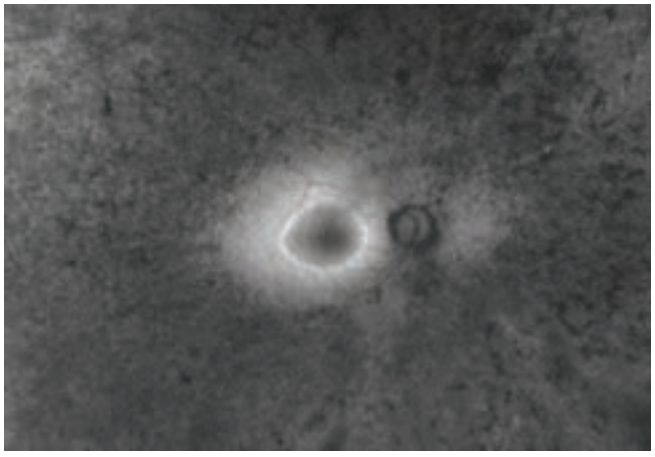

Figure 3. FAF of a patient with RP shows a macular hyperautofluorescent ring and peripheral hypoautofluorescence.

MONITORING PROGRESSION AND TREATMENT RESPONSE

Monitoring RP involves both functional and structural modalities. While visual field testing, particularly kinetic perimetry, has been a valuable tool in evaluating peripheral vision loss and disease trajectory, it is prone to operator variability and is difficult to compare.[14,15]

Microperimetry enables precise mapping of retinal sensitivity and can detect progression even when visual acuity remains stable.[16] EZ length, visualized on OCT, reflects photoreceptor integrity and correlates well with visual function, making it a useful biomarker of progression.[17] Full-field stimulus threshold testing provides a global sensitivity measure, making it feasible to measure treatment response even in advanced disease without fixation and severely limited visual fields.[18] The multi-luminance mobility test evaluates navigational ability under different lighting conditions and is used as a meaningful outcome measure in gene therapy trials.[19]

Low-luminance visual acuity detects central visual deficits not captured by standard acuity testing and is increasingly recognized as a sensitive endpoint in early-stage disease.[20]

CLINICAL PIPELINE

The therapeutic landscape for RP is rapidly evolving. Voretigene neparvovec-ryzl (Luxturna, Spark Therapeutics), the first FDA-approved gene therapy for *RPE65*-associated retinal dystrophy, represents a major breakthrough.[21] A 2022 analysis of 101 gene therapy clinical trials targeting IRDs showed RP as the most studied condition with 39 trials.[22] Common targets include *RPE65*, *ND4*, and *REP1*, with 77 trials using gene augmentation strategies and adeno-associated viral vectors in 90% of cases.

On the horizon, two phase 3 trials show promise: the LUMEOS trial of AAV5-hRKp.RPGR (Janssen) targeting *RPGR* and the gene agnostic liMeliGhT trial of OCU400-301 (Ocugen), which targets *NR2E3*.[23,24] If successful, these therapies could bring viable treatment options to the market in the near future, representing the next generation of mutation-specific and mutation-agnostic gene therapies.

RP remains a leading cause of inherited blindness. With advances in diagnostics and emerging treatment on the horizon, there is real hope for improving the outlook of patients living with this condition. ■

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TOP IRDS TO WATCH:
LEBER CONGENITAL AMAUROSIS

An update on management and approved and emerging treatments.

By Benjamin Bakall, MD, PhD, and Shyamanga Borooah, PhD, MBBS, FRCP, FRCSEd, FRCOphth


Leber congenital amaurosis (LCA) comprises a heterogenous group of inherited retinal diseases (IRDs) characterized by severely reduced vison in the first few months of life. LCA has a prevalence of one in 50,000 to 100,000 people and is currently known to be caused by 29 different genes.[1,2] The diagnosis and treatment of LCA have come to prominence since the 2017 FDA approval of voretigene neparvovec-ryzl (Luxturna, Spark Therapeutics) to treat LCA caused by mutations in the *RPE65* gene (Figure 1).[3]

CLINICAL FEATURES

LCA classically manifests before 6 months of age, and patients develop congenital nystagmus, poor pupillary light response, severely reduced vision, high hyperopia, and oculodigital reflex. Electroretinography is typically extinguished. However, there is significant functional variability; some patients have a visual acuity at light perception only, while others have more preserved vision, termed *severe early childhood-onset retinal dystrophy*. Some cases resemble retinitis pigmentosa with more preserved central vision.

Fundus examination is also variable and can be normal in early disease but commonly progresses with varying macular and peripheral atrophy and pigmentation. *CRB1*-related LCA can show extensive retinal dystrophy but with periarteriolar preservation of the retinal pigment epithelium, observed on both fundus imaging and autofluorescence (Figure 2). Other genes, including *RDH12*, can be associated with extensive retinal dystrophy and pigment clumping (Figure 3). OCT can be normal in early disease and demonstrate varying degrees of outer retinal degeneration.

LCA can be associated with renal disease, developmental delay, and Joubert syndrome, with underdevelopment of the cerebellar vermis identified by a "molar tooth" sign on brain MRI.[4]

AT A GLANCE

- Leber congenital amaurosis (LCA) has a prevalence of one in 50,000 to 100,000 people.
- LCA typically appears in early childhood, requiring the patient and family to consult a low vision specialist for evaluation and to learn about tools and adaptive technologies.
- In 2017, the FDA approved voretigene neparvovec-ryzl (Luxturna, Spark Therapeutics) to treat LCA caused by mutations in *RPE65*.

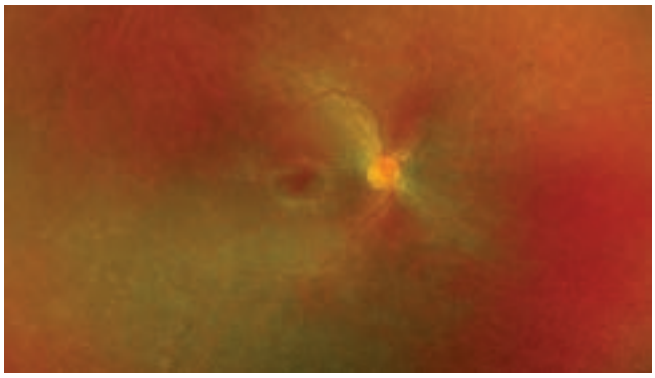

Figure 1. *RPE65*-associated LCA in the right eye of a 15-year-old girl presents with diffuse mild pigment mottling and multiple small white dots.

Supportive Care

LCA typically appears in early childhood, requiring the patient and family to consult a low vision specialist for evaluation and to learn about tools and adaptive technologies. For children, assistance from local education or other programs for sight impairment are suggested to provide early mobility and Braille training. Children with developmental delay may also require further generalized supportive care.

GENETICS

Genetic testing provides the definitive molecular diagnosis of LCA. Most cases are autosomal recessive, where individuals carry two abnormal copies of an LCA gene. The proteins expressed by these genes have varied functions, including visual cycle (*RPE65, RDH12, LRAT*), phototransduction (*AIPL1, GUCY2D, RD3*), signal transduction (*CABP4, KCNJ13*), protein folding (*CCT2*), ciliary transport (*CEP290, IQCB1, LCA5, RPGRIP1, SPATA7, TULP1, IFT140, CLUAP1*), photoreceptor morphogenesis (*CRB1, GDF6, PRPH2*), regulation of retinal differentiation (*CRX, OTX2*), NAD biosynthesis (*NMNAT1*), and nucleotide synthesis (*IMPDH1*).[5]

There are currently 25 genes associated with autosomal recessive LCA: *AIPL1, CABP4, CCT2, CEP290, CLUAP1, CRB1, CRX, DTHD1, GDF6, GUCY2D, IDH3A, IFT140, IQCB1, KCNJ13, LCA5, LRAT, NMNAT1, PRPH2, RD3, RDH12, RPE65, RPGRIP1, SPATA7, TULP1*, and *USP45*. Four genes (*CRX, IMPDH1, OTX2*, and *TUBB4B*) are associated with autosomal dominant transmission, where one abnormal copy of the gene is sufficient to cause disease.[5]

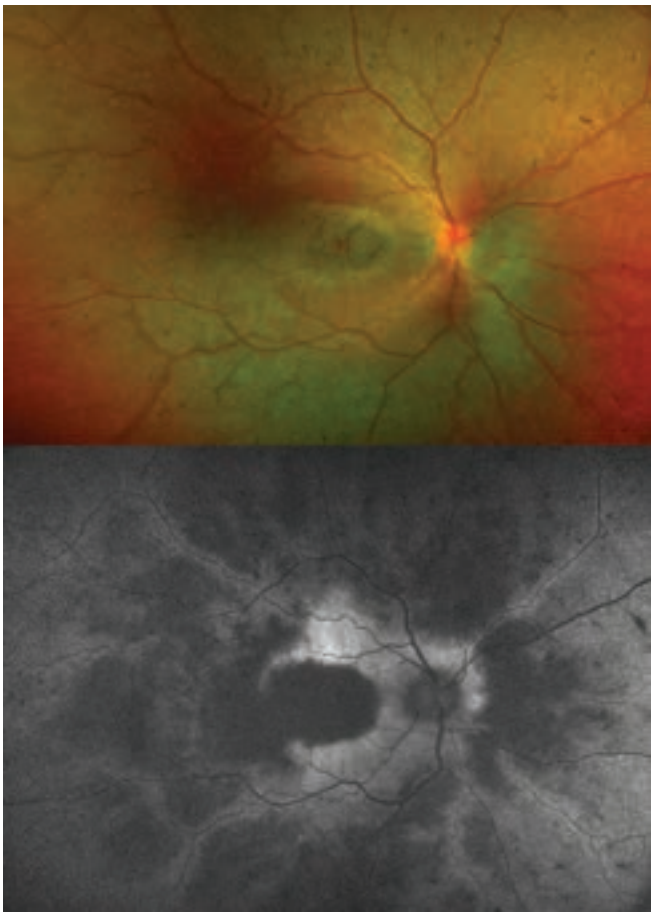

Figure 2. The fundus photograph (top) of the eye of a 10-year-old girl with *CRB1*-associated LCA presents with periarteriolar preservation of the retinal pigment epithelium. The fundus autofluorescence (bottom) shows loss of central macular autofluorescence.

The rationale for gene therapy is that replacing the abnormal gene with a functional copy will restore visual function in areas of preserved retinal structure. An ongoing trial of QR-110 (Sepofarsen, Splice Bio) uses antisense oligonucleotides targeting an intronic splice site in messenger RNA aiming to restore normal splicing. These approaches have been attempted for autosomal recessive LCA associated with better preserved retinal anatomy, including LCA associated with *RPE65, CEP290, GUCY2D, LCA5*, and *AIPL1*.

APPROVED THERAPY

Voretigene neparvovec-rzyl, the first gene therapy for a human IRD for *RPE65*-associated retinal dystrophy,[3] is a subretinal AAV2 vector expressing the *RPE65* gene in the retinal pigment epithelium to restore *RPE65* enzyme levels and help generate 11-cis-retinol protein from all-trans

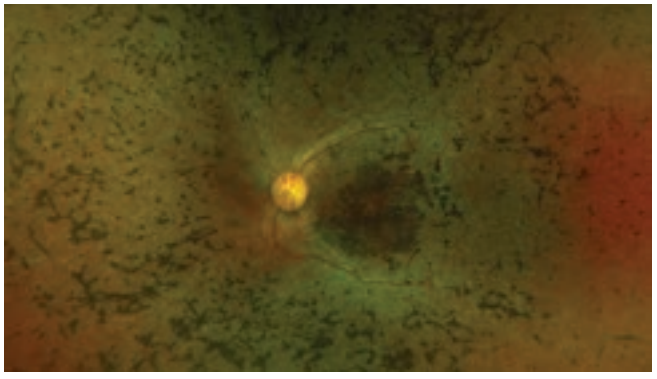

Figure 3. The fundus photograph of the left eye of a 29-year-old woman with *RDH12*-associated LCA demonstrates extensive pigment clumping throughout the fundus.

retinyl esters. The primary outcome of the phase 3 study was change in performance using a multiluminance mobility test (MLMT) that showed significantly improved scores at 1 year.[3] There was also significant improvement on full-field stimulus threshold (FST) testing and improvement in kinetic visual field testing. Four-year follow-up data confirmed the sustained benefit of the MLMT improvement. There were no reports of severe immune response.[6] However, development of chorioretinal atrophy in a subset of the treated patients has been reported after treatment.[7]

SELECT ONGOING AND EMERGING LCA TRIALS

EDIT-101 (Editas) is an AAV5-CRISPR-Cas9 construct that removes a splice site created in intron 26 of the *CEP290* gene. In the phase 1/2 study (NCT03872479), there was clinically meaningful improvement in visual acuity, FST testing, or mobility testing for nine (64%) of the treated participants.[8]

QR-110 is an RNA antisense oligonucleotide targeting the IVS26 mutation in the *CEP290* gene. Significant improvement in visual acuity and retinal sensitivity has been reported.[9] Although the phase 2/3 study did not meet the primary endpoint of improved visual acuity,[10] the company is pursuing a phase 3 trial (NCT06891443).

A phase 1/2 study of rAAV8.hRKp.AIPL1 (MeiraGTx) was conducted in the United Kingdom using an AAV8-AIPL1 construct delivered to the subretinal space in children with *AIPL1*-associated retinal dystrophy. Subjects had improvement in visual acuity and visual evoked potentials in the treated eye, with reduced function in the untreated eye.[11]

A phase 1/2 study (NCT03920007) is evaluating AAV5-GUCY2D (Atsena Therapeutics), which targets guanylate cyclase mutations to restore phototransduction. The 12-month data showed that some patients had improvement on the MLMT, and there was significant improvement on FST testing.[12]

A phase 1/2 dose-escalation study (NCT0561679) of AAV8-hLCA5 (OPGx-001, Opus Genetics) is investigating subretinal delivery in *LCA5*-associated retinal dystrophy. The LCA5 protein, lebercilin, is involved in the formation and function of the connecting cilia in photoreceptors, which is essential for protein transportation within the cell.[13]

Opus Genetics is also planning a phase 1/2 retinal gene therapy for *RDH12*-associated retinal dystrophy in 2025.[14]

TEST THE GENES

Although there are limited treatment options for LCA, we are approaching a paradigm shift where the causative gene can be identified in more than 75% of cases.[15] Additionally, there is an approved treatment for one form of LCA and ongoing clinical trials for other types of LCA. As a result, it is important for patients with suspected LCA to have genetic testing. This is ideally performed by IRD specialists who can manage patients and guide them to relevant clinical trials or treatments and low vision specialists at an early age. ■

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Moments this precious deserve protection

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.

izervay™
(avacincaptad pegol intravitreal solution) 2 mg

The #1 PRESCRIBED FDA-approved treatment for new GA patients*

*Based on Symphony data from 3/24-4/25. May not represent entire patient population.

When you see GA, start IZERVAY

Learn more at **IZERVAYecp.com.**

IMPORTANT SAFETY INFORMATION (CONT'D)

WARNINGS AND PRECAUTIONS (CONT'D)

Increase in Intraocular Pressure

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

ADVERSE REACTIONS

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

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

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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TOP IRDS TO WATCH: STARGARDT DISEASE

An overview of the most common juvenile macular dystrophy.

By Maria Ludovica Ruggeri, MD, and Ishrat Ahmed, MD, PhD


Stargardt disease, the most common juvenile inherited macular dystrophy, has an estimated prevalence of one in 10,000 people.[1] It is most frequently caused by mutations in the *ABCA4* gene and is inherited in an autosomal recessive pattern. Dysfunction of *ABCA4* leads to the accumulation of toxic byproducts, including lipofuscin, which contributes to the classic phenotype of juvenile-onset bilateral macular flecks and atrophy.[1] More than 900 pathogenic mutations have been identified in the *ABCA4* gene, explaining the wide phenotypic heterogeneity observed in Stargardt disease. Several cases of Stargardt-like dystrophy have been linked to autosomal dominant mutations, most notably in *ELOVL4*.[2]

CLINICAL PRESENTATION

Patients with Stargardt disease usually present in childhood or early adulthood with blurry vision or central scotomas. Photophobia is common, as is dyschromatopsia. Visual acuity can range from 20/20 to 20/200 or worse. Ophthalmoscopic findings also vary with disease severity and range from mild retinal pigment epithelium (RPE) abnormalities and yellow-white pisciform flecks to, in more advance cases, chorioretinal atrophy (Figure A).[3] The pisciform flecks, which are pathognomonic for Stargardt disease, are present at the level of the RPE and result from the accumulation of lipofuscin. These flecks are more readily visualized during fundus examination with green light illumination. The macula can also have a "beaten bronze" appearance due to lipofuscin accumulation. The disease typically affects the macula and extends to the midperiphery, while the far peripheral retina remains mostly unaffected.

MULTIMODAL IMAGING

Although the clinical presentation is often indicative of the diagnosis, multimodal imaging provides additional insights into the structural changes associated with Stargardt disease.

OCT is particularly useful for demonstrating ellipsoid zone disruption, photoreceptor layer disorganization, and outer retinal loss in the macula, which is useful for monitoring progression (Figure B). OCT facilitates the early detection of foveal outer retinal degeneration, and central foveal

AT A GLANCE

- Stargardt disease is the most common juvenile inherited macular dystrophy with an estimated prevalence of one in 10,000 people.
- Patients with Stargardt disease usually present in childhood or early adulthood with blurry vision or central scotomas.
- Vision rehabilitation is strongly recommended to help patients with Stargardt disease adapt to their visual impairment and maintain their quality of life.

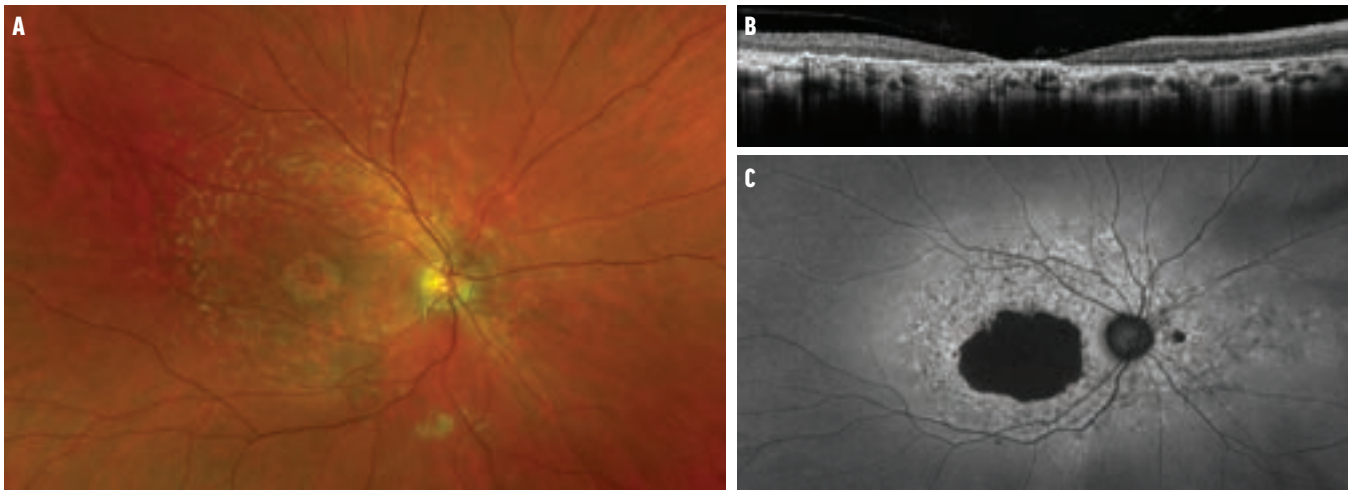

Figure. A color fundus photograph of the eye of a patient with Stargardt disease demonstrates the presence of yellow-white pisciform flecks in the perifoveal region, along with central foveal atrophy (A). OCT shows significant outer retinal loss centrally (B). FAF reveals foveal hypoautofluorescence with surrounding flecks and peripapillary sparing (C).

thickness has been found to correlate with visual acuity loss. Furthermore, early thickening of the outer limiting membrane may precede the onset of atrophy.[4]

Fundus autofluorescence (FAF) is a valuable imaging modality in staging Stargardt disease.[5,6] It typically reveals a central reduction in autofluorescence, often surrounded by a ring of hyperautofluorescence, resulting in a bull's eye maculopathy-like appearance (Figure C).[7]

The presence of a dark choroid on fluorescein angiography is also pathognomonic for Stargardt disease and can be seen in up to 80% of cases. Lipofuscin-laden RPE cells block choroidal fluorescence and enhance the contrast of retinal vessels.[8] However, with the increasing availability and accuracy of genetic testing, fluorescein angiography is used less often as a primary diagnostic imaging modality.

Microperimetry provides detailed topographical mapping of macular function, although results can be affected by media opacities such as cataracts. Despite its limitation, microperimetry remains a valuable tool for monitoring disease progression and is a reliable and sensitive functional outcome measure in clinical trials.[9]

Full-field electroretinography (ffERG) may demonstrate normal to subnormal scotopic and photopic responses, particularly in early stages. However, a wide range of ffERG abnormalities have been reported.[1] ffERG findings may also have prognostic value, with studies showing that early photoreceptor dysfunction is associated with increased risk of developing more severe visual impairment over time.[10]

MANAGEMENT

Regular follow-up to monitor disease progression is important for patients with Stargardt disease. During these visits, OCT and microperimetry are useful for evaluating structural and functional changes. Genetic testing is crucial for patients who may qualify for and are interested in clinical trials. Patients should avoid excessive vitamin A intake, including supplements and topical retinoids, which may exacerbate the accumulation of lipofuscin and potentially accelerate retinal degeneration.[11] Patients should use ultraviolet light-blocking sunglasses to reduce light toxicity. Vision rehabilitation is strongly recommended to help patients adapt to their visual impairment and maintain their quality of life.

Although uncommon, macular neovascularization has been reported in association with Stargardt disease and should be considered in cases of sudden vision changes.[12,13] Rare cases of subretinal fibrosis and RPE hypertrophy following minor ocular trauma have been described.[14] Lastly, the management of age-related cataracts requires thorough discussion, as postoperative light sensitivity can be bothersome for patients with Stargardt disease and should be carefully weighed against potential benefits of improved clarity.

CLINICAL TRIALS

Several ongoing clinical trials are investigating emerging therapeutic strategies, including the following:

(Continued on page 52)

ONE TO WATCH

RT Retina Today

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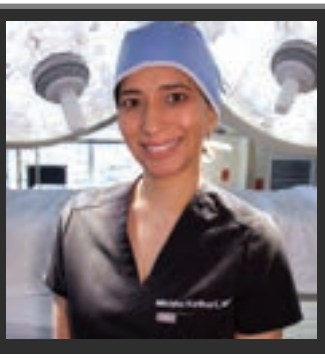
Nikisha Kothari, MD



Dr. Kothari's advice: Find joy in the privilege of being entrusted with someone's vision. It's why we chose this career—remember that, especially when times get tough.

WHERE IT ALL BEGAN

My childhood in Voorhees, New Jersey, was filled with a big family and amazing memories. From an early age, I had a strong interest in both medicine and political science, and in the end, I chose to pursue medicine. My mother, a physician and a major influence in my life, undoubtedly shaped that decision—after all, as they say, "The apple doesn't fall far from the tree." Surprisingly, my parents supported my bold choice to move to Miami for a combined undergraduate and medical school program at the University of Miami. That decision was a turning point in my education, propelling me toward a career in ophthalmology.

MY PATH TO RETINA

As a medical student, my exposure to Bascom Palmer Eye Institute and the relationships I developed with the residents quickly convinced me to apply for ophthalmology. By my second year of residency at Bascom Palmer, it was clear that retina was my true calling. While my interest in the field and the surgeries played a significant role in my decision, so did the strong connections I formed with the retina team. My training at both Bascom Palmer and the University of California, Los Angeles, gave me the confidence to enter practice as a retina specialist, equipped to manage busy clinic days, handle challenging cases, maintain a high surgical volume, and contribute to research.

SUPPORT ALONG THE WAY

I have had many mentors throughout my journey who have shaped my path in meaningful ways. I learned so much about ophthalmology from my senior and co-residents and co-fellows. Some of my fondest memories and moments of growth came from time spent in the resident and fellow rooms. Audina M. Berrocal, MD, is one of those rare mentors who continues to guide me through all phases of life. She has witnessed my growth from an eager medical student to an accomplished vitreoretinal surgeon and mother. Her approach to both retina and life continues to resonate with many of us who trained at Bascom Palmer, and her influence remains a guiding force for me.

During fellowship at the Stein Eye Institute, Jean-Pierre Hubschman, MD, became an invaluable role model. His logical, precise, and efficient approach to surgery, coupled with his exceptional technical skills, demonstrated what surgical excellence looks like. To this day, his advice echoes in my mind while I operate. And, of course, the late Allen E. "Buzz" Krieger, MD, taught me two very different, yet equally important, lessons: how to buckle practically anything and how to lead a spiritually fulfilling life.

AN EXPERIENCE TO REMEMBER

While I've had many incredible surgical experiences and profound patient interactions that are memorable, recently I've been deeply touched by the insights shared by my oldest patients. They often see life as a series of incredible experiences that come together to form beautiful memories. In the hustle of a busy practice, it's a wonderful reminder to pause and appreciate this life. ■

Nikisha Kothari, MD, is a partner at Texas Retina Associates in Dallas, practicing medical and surgical retina. She participates in numerous clinical trials for retinal diseases, and she is a consultant for Apellis and Regenxbio. She can be reached at **nkothari@texasretina.com.**

TOP IRDS TO WATCH:
CONE AND CONE-ROD DYSTROPHIES

A look at the prevalence, symptoms, and long-term management of a rare set of inherited retinal diseases.

By Dallin Milner, MD, and Marc Mathias, MD


Cone dystrophies (COD) and cone-rod dystrophies (CORD) are a subset of inherited retinal diseases (IRDs) characterized by primary cone degeneration with variable secondary rod involvement.[1] Due to the high concentration of cones in the macula, central vision can be affected early and severely.

While clinical presentation is a spectrum, low vision is often present in the second decade in COD and as early as the first decade in CORD with progression to legal blindness early in the third decade for half of patients.[2] It is important to recognize these rare IRDs early to connect patients with low vision programs and possible clinical trials.

PRESENTING SIGNS AND SYMPTOMS

Generally, patients with COD/CORD present with reduced central vision, photophobia, hemeralopia, and generalized dyschromatopsia.[3] Depending on the degree of rod involvement, they may also complain of varying degrees of nyctalopia. This is in contrast to retinitis pigmentosa, or rod-cone dystrophy, where the earliest symptoms are typically nyctalopia and peripheral vision loss (Table).

The physical examination is often variable. The macula may appear normal, particularly early in the disease course, or patients may present with subtle macular retinal pigment epithelium (RPE) mottling or a classic bull's eye maculopathy. The optic disc may be normal or present with temporal pallor. With CORD and more significant rod involvement, patients may demonstrate peripheral RPE changes such as mottling, pigment clumping, or frank bone-spicules.

DIAGNOSTIC PEARLS

The standard for the diagnosis of COD/CORD is full-field electroretinography (ffERG). COD is characterized by reduced photopic amplitudes with overall preserved scotopic amplitudes, while CORD demonstrates both

AT A GLANCE

- Typically, patients with cone dystrophies (COD) and cone-rod dystrophies (CORD) present with reduced central vision, photophobia, hemeralopia, and generalized dyschromatopsia.
- The standard for clinical diagnosis of COD and CORD is full-field electroretinography.
- Most novel interventions in COD/CORD are focused on mutations in the *ABCA4* gene.

TABLE. COMPARISON OF CONE DYSTROPHY, CONE-ROD DYSTROPHY, AND RETINITIS PIGMENTOSA

	Cone Dystrophy	Cone-Rod Dystrophy	Retinitis Pigmentosa
Prevalence	~1/40,000	~1/40,000	~1/4,000
Symptoms	Central vision loss, photophobia, hemeralopia, color vision disturbance	Similar symptoms as cone dystrophy with varying nyctalopia and peripheral vision loss later	Nyctalopia and peripheral vision loss early, central vision loss late
Examination	Bull's eye maculopathy, macular RPE mottling and atrophy	Bull's eye maculopathy, macular RPE mottling and atrophy, variable peripheral RPE changes and atrophy	Peripheral bone-spicules and RPE changes, retinal vessel attenuation, waxy disc pallor, macular RPE changes later; PSC more common
Full-Field ERG	Reduced photopic A- and B-wave amplitudes with relative preservation of scotopic amplitudes	Reduced photopic and scotopic A- and B-wave amplitudes with more severe reduction in photopic amplitudes	Reduced photopic and scotopic A- and B-wave amplitudes with more severe reduction in scotopic amplitudes

Abbreviations: RPE, retinal pigment epithelium; PSC, posterior subcapsular cataract; ERG, electroretinogram

photopic and scotopic reduction with the photopic amplitudes more severely depressed.[4] Delayed 30 Hz flicker ERG implicit time may be the earliest finding. With more progressive cone degeneration, photopic responses demonstrate a reduction in A- and B-wave amplitudes.[1,5] While most ffERG findings are not specific to a particular gene, a specific pattern with generalized cone dysfunction and supranormal rod function can be pathognomonic of *KCNV2*-associated retinopathy.[6]

Fundus autofluorescence (FAF) may reveal hypo- and hyperautofluorescent changes in the macula and periphery and can be used to follow disease progression (Figure).[7] Ultra-widefield FAF can be important for identifying any peripheral retinal changes.

Macular OCT will typically demonstrate outer retinal abnormalities, particularly in the central macula where cones have the highest concentration. The interdigitation zone is typically absent, the ellipsoid zone may be attenuated or absent, and more severe RPE atrophy can be seen.[8-10]

Color vision testing can be important to detect early dyschromatopsia. Kinetic visual field testing typically demonstates a central scotoma with relative preservation of peripheral isopters in COD and varying levels of peripheral field loss in CORD.

Adaptive optics, where available, allow visualization of photoreceptors and demonstrate decreased cone density in COD and decreased cone and rod density in CORD.[11]

GENETIC TESTING

More than 30 genes—involved in phototransduction, outer segment morphogenesis, and intraflagellar transport—can cause COD/CORD.[12-15] The causative gene can be identified in up to 80% of cases.[3] Most COD/CORD is autosomal recessive but can be autosomal dominant or X-linked as well. In autosomal dominant and X-linked disease, the most common genetic mutations involve *GUCY2D* and *RPGR*, respectively.[1] The most common causative gene for autosomal recessive COD/CORD is *ABCA4*.

LONG-TERM MANAGEMENT

While an understanding of current clinical trials is important, clinicians must offer low vision services and social resources to patients with COD/CORD. Given the high risk of depression, anxiety, and feelings of social isolation, these resources should be offered early and at follow-up visits.[16]

CLINICAL PIPELINE

Few clinical trials specifically target COD/CORD, although some patients may be eligible for gene-specific trials. Most interventions in COD/CORD are focused on mutations in *ABCA4*. When this gene is dysfunctional, bis-retinoids accumulate as lipofuscin deposits in the RPE, leading to RPE dysfunction and death, and, eventually, photoreceptor loss.[17]

Splice Bio and AAVantgarde aim to replace the defective *ABCA4* gene. Splice Bio is currently recruiting for a phase 1/2 clinical trial (NCT06435000), while AAVantgarde is recruiting for an observational study (NCT06591806). Ascidian Therapeutics, which has developed RNA exon-editing technology, is recruiting for a phase 1/2 trial (NCT06467344).[18]

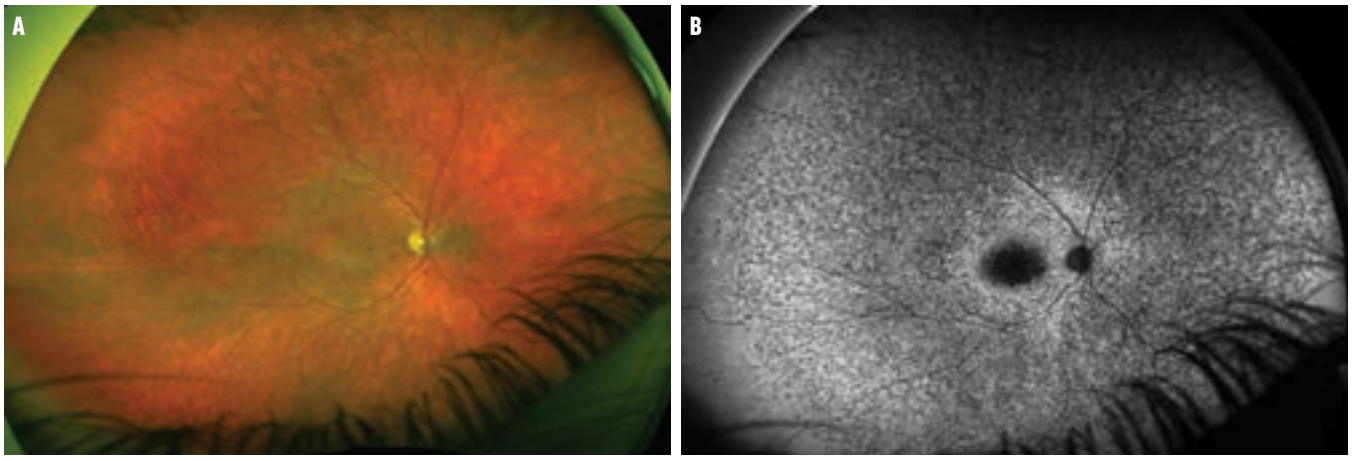


Figure. Ultra-widefield fundus imaging of a 22-year-old woman with *ABCA4*-associated CORD demonstrates granular RPE mottling with poorly delineated subretinal flecks (A). Ultra-widefield FAF better demonstrates the widespread RPE abnormality with granular hypoautofluorescence and hyperautofluorescence in the macula and periphery (B).

OCU410ST (Ocugen) uses an AAV vector to deliver human retinoic acid-related orphan receptor alpha—a nuclear hormone receptor involved in controlling inflammation and lipogenesis.[19] Preliminary data from the phase 1 trial (NCT05956626) is promising, with decreased lesion growth and improved visual function.[20]

Optogenetics use a viral vector to transfect bipolar ganglion cells with a light sensitive opsin, thereby giving them photosensitive properties.[21] Nanoscope Therapeutics is evaluating a single intravitreal injection of a multi-characteristic opsin (MCO-010) delivered via an AAV vector (NCT05417126).[22] Some patients with COD/CORD phenotypes may be eligible for these trials.

Pharmacologic interventions aim to reduce the production of harmful components of the retinoid cycle.[22] Belite Bio is recruiting for a phase 2/3 study (NCT04489511) evaluating tinlarebant, an oral therapy that reduces retinal binding protein 4, the major transport protein for vitamin A in the bloodstream.[23] Alkeus Pharmaceuticals is in late-stage clinical trials (NCT04239625) for gildeuretinol (ALK-001), a modified form of vitamin A designed to reduce the acculmuation of toxic vitamin A dimers in the retina. Other therapeutic targets include C5 inhibition (avacincaptad pegol, Astellas; NCT03364153) and visual cycle modulators (Emixustat, Kubota Vision; NCT03772665).[22]

RARE, BUT BLINDING

While COD/CORD is rare, advances in genetic testing, imaging, and potential therapies offer improved counseling, earlier diagnosis, and possible eligibility for clinical trials for these young patients with blinding disease. ■

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TOP IRDS TO WATCH:
ACHROMATOPSIA

Pearls for diagnosing and managing a rare inherited disease with significant variability.

By Landon J. Rohowetz, MD; Byron L. Lam, MD; and Jesse D. Sengillo, MD



Achromatopisa, an inherited retinal disease characterized by loss of cone function, is inherited in an autosomal recessive pattern and occurs in about one in 30,000 to 50,000 births.[1] Common symptoms include color blindness, decreased visual acuity, pendular nystagmus, central scotoma, eccentric fixation, and photophobia.[2,3] Hyperopia is common among patients with achromatopsia.[3]

This condition is characterized by variable expressivity depending on the amount of residual cone function.[1] Patients with complete (typical) achromatopsia have a more severe phenotype due to a total lack of function of all three types of cones and typically present at around 6 months of age with nystagmus and photophobia.[3] VA is generally worse than 20/200. Patients with incomplete (atypical) achromatopsia have a less severe phenotype due to the presence of varying degrees of functioning cones, with VA as good as 20/80, mild or absent photophobia and nystagmus, and partially intact color discrimination.[3]

Signs of disease on fundoscopic examination are frequently absent, although possible findings include vessel attenuation, alteration of the foveal reflex, and retinal pigment epithelium (RPE) mottling. RPE atrophy may develop in early to late adulthood (Figure).[3] Although historically thought to be a stationary disease, recent long-term data has illustrated a progressive decline in visual function and macular integrity in many patients with achromatopsia.[2]

DIAGNOSTIC PEARLS

Important components in the diagnosis of achromatopsia include family history, nystagmus examination, color vision assessment, and visual acuity testing. Additional diagnostic tests include OCT, electroretinography (ERG), visual fields, and microperimetry.

Full-field ERG classically demonstrates diminished or absent photopic responses with normal or only slightly reduced scotopic responses. However, due to the limited number of photoreceptors within the fovea, full-field ERG may be normal in up to 75% of patients. Therefore, multifocal ERG, which allows for isolated evaluation of macular function, is generally more accurate.[4,5]

Typical findings on OCT include macular thinning, disruption of the ellipsoid zone, and macular RPE atrophy.[6]

AT A GLANCE

- Achromatopisa, inherited in an autosomal recessive pattern, occurs in approximately one in 30,000 to 50,000 births.
- The most common genetic mutations responsible for achromatopisa are in the *CNGB3* and *CNGA3* genes.
- Care aims to reduce symptom burden, such as reduce photophobia; accurate refraction can optimize visual acuity, and low vision aids are necessary.

Of patients with achromatopsia, 85% have some degree of photoreceptor disruption.[4] Foveal hypoplasia, another common finding, has been hypothesized to represent a gene-specific feature in patients with *CNGA3*, *CNGB3*, or *ATF6* mutations, although this association is not well-established.[2,3,7] Fundus autofluorescence demonstrates varying degrees of macular hypoautofluorescence or ring-shaped hyperautofluorescence.[8]

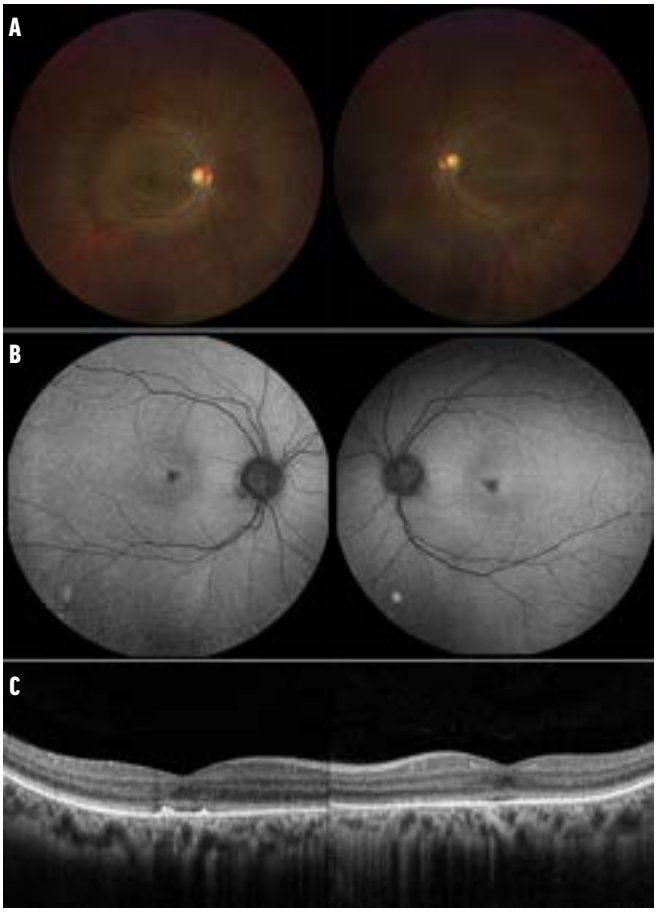
Color vision testing may be helpful in identifying patients' specific phenotypes, and patients demonstrate abnormalities in all axes. Note that testing may be unreliable if patients use color-object associations or differentiate colors based on their brightness using undamaged photoreceptors.[1]

Visual field testing may demonstrate small central scotomas with careful testing, although poor fixation can limit reliability.[3] Microperimetry generally demonstrates reduced macular sensitivity and may be more sensitive than standard visual field testing.[2]

GENETIC TESTING

Achromatopsia is an autosomal recessive condition exhibiting genetic heterogeneity. The most common mutations are in the *CNGB3* (50% to 70%) and *CNGA3* (approximately 25%) genes. *CNGB3* mutations are the most frequent disease-causing mutations in patients of European descent, while *CNGA3* mutations are more common in those of Asian and middle Eastern descent.[9,10] Other reported disease-causing mutations include those in *ATF6* (2%), *GNAT2* (less than 2%), *PDE6C* (less than 2%), and *PDE6H* (0.3%).[2,11]

There do not appear to be direct associations between specific gene mutations and phenotype. Mutations on the same gene can cause either incomplete or complete forms of the disease. Genetic testing can be useful for prognostic information, identifying carriers, and establishing a prenatal diagnosis. Testing is highly sensitive and specific when the aforementioned genes are included and can be used to confirm the disease, as it demonstrates 100% penetrance.[12] Given the small number of causative genes and the clear phenotype associated with the disease, targeted genetic testing rather than whole exome or whole genome sequencing may be appropriate. A small minority of patients (less than 10%) demonstrate no known genetic mutation in the presence of a clear clinical diagnosis.[13]



Images courtesy of Byron L. Lam, MD

Figure. A 37-year-old man presented with progressive vision loss in each eye since early childhood due to achromatopsia. Fundus photography (A) was unremarkable other than macular RPE mottling in each eye. Fundus autofluorescence (B) demonstrated mild foveal hypoautofluorescence, and OCT (C) demonstrated mild subfoveal RPE atrophy in each eye.

MANAGEMENT AND COMPLICATIONS

Management for patients with achromatopsia aims to reduce symptom burden. Accurate refraction is important to optimize visual acuity, and low vision aids are necessary to assist patients at home and in public. Due to the debilitating photophobia characteristic of the disease, patients may prefer to avoid light exposure using dark or special filter glasses, tinted contact lenses, and visors.[3]

Low vision aids such as magnifiers, occupational assistance, and preferential seating at the front of the classroom and away from windows should be provided, as appropriate.[3] Because the limitations imposed by the disease can cause significant psychological and social distress, patients and families should have access to resources to cope.

MORE RESOURCES

FOUNDATION FIGHTING BLINDNESS

Foundation Fighting Blindness provides important educational resources for you and your patients, including disease state education, genetic testing, and clinical trial updates.

About Achromatopsia

Low Vision Resources

ACHROMATOPSIA REPRESENTS AN IDEAL TARGET DISEASE FOR GENE THERAPY GIVEN THE WELL-DEFINED GENETIC ASSOCIATIONS AND THE PRESENCE OF RESIDUAL NON-FUNCTIONING CONE PHOTORECEPTORS, AND SEVERAL TRIALS ARE UNDERWAY.

CLINICAL PIPELINE

Achromatopsia represents an ideal target disease for gene therapy given the well-defined genetic associations and the presence of residual non-functioning cone photoreceptors, and several trials are underway.[13]

In 2007, an AAV vector was used to transduce a mouse model with *GNAT2* with a resultant increase in ERG responses to 80% of the normal range, serving as proof of principle for AAV-mediated gene therapy in achromatopsia.[14] Since then, gene therapy has been successfully used in animals with achromatopsia caused by other genetic mutations including *CNGA3* and *CNGB3*, leading to a Fast Track designation by the FDA.[15,16]

AAV-CNGB3 (MeiraGTx UK) was studied in a phase 1/2 trial (NCT03001310) that involved the subretinal delivery of an AAV8 vector with *CNGB3* in 23 participants. In the trial, favorable responses were recorded in several efficacy assessments including photo-aversion (11 of 20 patients), color vision (six of 23), and vision-related quality-of-life questionnaires (21 of 23).[17] The program has stalled since being acquired by Janssen in 2023.[18]

An ongoing phase 1/2 trial investigating subretinal delivery of AAV8.hCNGA3 (STZ Eyetrial) for achromatopsia in 13 patients has shown good interim safety and efficacy outcomes.[19] In an early phase 1 trial (NCT04041232), investigators are also evaluating the potential role of supplementing glycerol phenylbutyrate, a fatty acid compound that facilitates protein folding, in patients with achromatopsia caused by mutations in *ATF6*.[13]

FOCUS ON THE FUTURE

Achromatopsia, a rare, debilitating ocular condition, is characterized by decreased visual acuity, photophobia, nystagmus, and diminished or absent color vision. Diagnosis can be established by family history, clinical examination, multimodal imaging, and genetic testing. Management is currently limited to symptom management, although early clinical trials involving subretinal gene therapy have demonstrated some promise. ■

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BRIDGING THE VISUAL DISCONNECT IN GEOGRAPHIC ATROPHY

Educating asymptomatic and early-stage patients on risks drives adherence to therapy.

By: Caesar K. Luo, MD, FASRS

One of the salient lessons we are learning as more patients are treated with complement inhibition therapy for geographic atrophy (GA) is that earlier treatment translates into a better chance of slowing down disease progression and extending patients' quality of life with the vision they still have. However, there is often a disconnect between patients' visual acuity and when they begin treatment. Here, I will discuss how I bridge this gap through patient education, various visual assessment methods, and setting patient expectations regarding treatment.

Early Functional Impact of GA

GA can appear asymptomatic in its earliest stages, yet still subtly impair everyday activities and ultimately limit patients' independence. In early stages, patients often report difficulty with reading or seeing in dim light before any change appears on a Snellen chart, which highlights the importance of patient-reported symptoms for early detection. In fact, Snellen visual acuity is an imperfect measure of our patients' actual functioning at home, and so I rely on what patients are telling me about what they are experiencing with their vision. By listening closely to what patients are saying, I can guide the conversation around the benefits of treatment. After all, we're not treating optical coherence tomographies (OCTs), and we're not treating photos; we're treating the patients sitting in front of us, and I believe they are exceptionally attuned to what they are experiencing.

Vision Assessment Methods

Despite its limitations, I still perform Snellen visual acuity tests on each patient, as it remains our primary tool due to its speed and workflow integration. However, for high-risk GA patients, I also rely on low luminance visual acuity (LLVA) testing, which offers a quick, objective measure to validate patient concerns about night vision. More detailed assessments, such as contrast sensitivity and microperimetry, are highly informative but are typically reserved for our clinical trials due to their increased time and staffing demands.

Educating Early-Stage Patients

To help bridge the knowledge gap between patients and early-stage disease progression, I rely on available data through imaging and published research. For example, I will show patients their fundus autofluorescence (FAF) and OCT images to highlight early biomarkers like incomplete retinal pigment epithelial and outer retinal atrophy (iRORA) and subretinal drusenoid deposits, which is helpful for them to understand their disease progression and any high-risk features they possess.

I also reference published literature and discuss available FDA-approved complement inhibitor treatments such as pegcetacoplan (Syfovre, Apellis) and avacincaptad pegol (Izervay, Astellas), which we know from experience work best in earlier stages of GA. I remind patients while they might be asymptomatic while in my office, it's important to begin considering these treatment options sooner rather than later to preserve their functional vision and quality of life for as long as possible. Being able to provide patients with the knowledge and tools for them to see the global picture of their disease is the most important thing.

Setting Treatment Expectations

As I discuss treatment options with my patients who are experiencing early-stage GA, I inform them once the disease enters the fovea, the utility of these complement inhibitors decreases significantly, and I don't really recommend them at that point. My goal is to prevent their disease from reaching that point for as long as possible. Once these patients agree to begin treatment, I remind them while complement inhibitors slow GA progression, these treatments do not restore vision and require fixed intravitreal injections to help maintain efficacy. I also like to engage patients' support system during this time. I find that once family and friends are engaged, these are the patients who are most able to continue treatment and make it a priority to keep up with their appointments. Ultimately, I like to give my patients hope and advocate for their success. I discuss our groundbreaking FDA-approved therapies and all the incredible work coming down the pipeline in the GA space that may offer even more treatment options. I reiterate that early-stage disease is the time to begin saving vision while there is still something to save. ■

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NUTRITIONAL SUPPLEMENTATION FOR IRDS: PRESERVATION OR PLACEBO?

Recent evidence suggests some benefits, but more work is needed.

By Paula C. Morales, MD; Cesar Estrada-Puente, MD; and Ramiro Maldonado, MD



Inherited retinal diseases (IRDs) are characterized by degeneration of photoreceptors, leading to irreversible vision loss starting from birth to even late middle age.[1] Nutritional supplementation has been used to potentially diminish progression of many IRDs. In this article, we provide an overview of the current evidence supporting various nutritional supplementation for IRDs.

VITAMIN A SUPPLEMENTATION IN RP

Vitamin A is crucial for the visual cycle, serving as an essential component of the visual pigment rhodopsin. In its active form as 11-cis retinal, vitamin A is integral for phototransduction. It also supports the structural integrity of photoreceptors and the retinal pigment epithelium (Figure).[2] Given vitamin A's fundamental role in vision, a randomized controlled trial involving 601 patients with retinitis pigmentosa (RP) demonstrated that 15,000 IU/day of vitamin A palmitate led to a slower annual decline in 30-Hz cone flicker electroretinography (ERG) amplitude loss. The vitamin A group experienced a 6.2% loss compared with 7.5% in the control group (P = .01), without significant differences in visual field or acuity outcomes.[3]

A more recent analysis found no evidence that high-dose vitamin A slowed overall disease progression, highlighting methodological limitations in previous studies. Importantly, a subgroup analysis revealed a potential benefit for patients with *RHO*-related RP, with an approximately 6.1% slower progression per year. However, after correction for multiple comparisons, this effect did not reach statistical significance.

AT A GLANCE

- Nutritional supplementation represents a potential adjunctive approach to treating inherited retinal disease, although limitations in bioavailability, study design, and long-term clinical validation remain.
- Vitamin A, docosahexaenoic acid, lutein, zeaxanthin, N-acetylcysteine, tauroursodeoxycholic acid, curcumin, and saffron have all been studied for their potential therapeutic effect.
- Precision medicine tailored to specific genetic profiles could help identify candidates more likely to benefit from specific supplements.

This suggests that the effects of vitamin A supplementation may depend on specific genetic subtypes, highlighting the need for personalized approaches. Furthermore, clinicians must carefully consider the potential toxicity risks associated with high-dose vitamin A, such as hepatotoxicity and teratogenicity. Its use should be approached cautiously, especially among women of childbearing age.[4]

THE NEUROPROTECTIVE ROLE OF OMEGA-3 FATTY ACIDS

Docosahexaenoic acid (DHA) is a long-chain polyunsaturated fatty acid of the omega-3 family that is vital for the maintenance of retinal photoreceptor outer segment membranes. This structural role facilitates phototransduction. The results of DHA supplementation trials in RP have been inconsistent.[5-7] For instance, the 4-year randomized controlled DHAX trial did not show statistically significant results, although it demonstrated a trend, suggesting slightly delayed progression in X-linked RP. While DHA did not reduce rod or cone decline in ERG, a subsequent DHAX analysis demonstrated it may slow progression in final dark-adapted thresholds and visual field sensitivity parameters.[8,9]

DECREASING THE OXIDATIVE PROCESS IN IRDS

Oxidative stress is a widely recognized contributor to retinal degeneration, with the accumulation of reactive oxygen species leading to photoreceptor damage and progressive vision loss. Considering this, antioxidant therapies have been investigated extensively as potential means to mitigate oxidative injury and preserve retinal function.[10]

Carotenoid: Natural Blue Light Filter

Carotenoids such as lutein and zeaxanthin have received considerable attention due to their propensity to accumulate in the macula, where they filter high-energy blue light and neutralize reactive oxygen species.[11] In a 4-year randomized controlled trial, 240 patients with RP were assigned to receive either 12 mg lutein plus 15,000 IU/day vitamin A or placebo plus 15,000 IU/day vitamin A. The primary outcome, measured by the Humphrey visual field 30-2 test, showed no significant difference between the groups. However, a secondary measure using the 60-4 grid revealed a significantly slower decline in the lutein group (26.6 dB/year) compared with controls (34.1 dB/year; $P = .05$), with a greater effect in patients with higher serum lutein and increased macular pigment optical density. No significant differences were observed in ERG or visual acuity outcomes.[12]

Another trial focused solely on lutein supplementation. This crossover study randomly assigned 45 patients to receive either placebo then lutein or lutein then placebo over 48 weeks. Results showed a small but statistically significant improvement in log retinal area of visual field (0.018 [95% CI, 0.001-0.036], $P = .04$). However, the study was limited by a small sample size.[13]

Glutathione Precursors and Oxidative Stress Modulation

N-acetylcysteine (NAC) functions as a free radical scavenger and is metabolized into cysteine, which is essential for producing glutathione, a critical element of the body's intrinsic antioxidant defense system.[14]

The FIGHT-RP1 trial evaluated the safety and efficacy of oral NAC at escalating doses (600 mg to 1,800 mg twice a day) over 24 weeks. Supplementation resulted in statistically significant improvements in BCVA across all dose groups, with the 1,800 mg cohort also showing significant gains in macular sensitivity. However, no significant structural preservation was observed in ellipsoid zone width, suggesting that NAC did not halt anatomic photoreceptor loss over the study period.[15] Given these promising findings, a phase 3 study is enrolling 438 patients. If the preliminary analyses at 21 months indicate benefit in the NAC group, placebo patients will be transitioned to active treatment.[16]

The Role of TUDCA

In addition to conventional antioxidants, emerging nutraceuticals are being studied for their neuroprotective potential. Tauroursodeoxycholic acid (TUDCA) has shown promise in experimental studies by inhibiting apoptosis, reducing oxidative stress, suppressing endoplasmic reticulum stress, and exerting antiinflammatory and antiangiogenic effects. Animal models receiving TUDCA demonstrated structural and functional preservation of the retina. Despite promising findings, no clinical trials are being conducted to validate TUDCA's therapeutic potential.[17]

Promising Plant-Based Compounds

Curcumin, a compound derived from turmeric, has demonstrated potent antiinflammatory and antioxidant properties in preclinical retina models. It acts as a free radical scavenger and enhances the activity of antioxidant enzymes. Curcumin's antiinflammatory effects are mediated through the downregulation of proinflammatory cytokines, as well as the inhibition of the NF-κB signaling pathway. Despite

these promising effects, its clinical utility is limited by challenges related to its low bioavailability.[18]

Fernandez-Sanchez et al demonstrated that saffron and its active compounds, safranal and crocetin, slow photoreceptor cell degeneration and improve ERG responses in *P23H* retina models.[19] Furthermore, when combined with photobiomodulation, saffron was initially thought to show synergistic effects that reduced photoreceptor apoptosis and mitigated the upregulation of Müller cells gliosis.[20] However, a recent analysis suggests photobiomodulation and saffron may not enhance their individual neuroprotective properties and could potentially have antagonistic interactions. This combined treatment showed only limited benefits in reducing early neuroinflammation in retina models.[21]

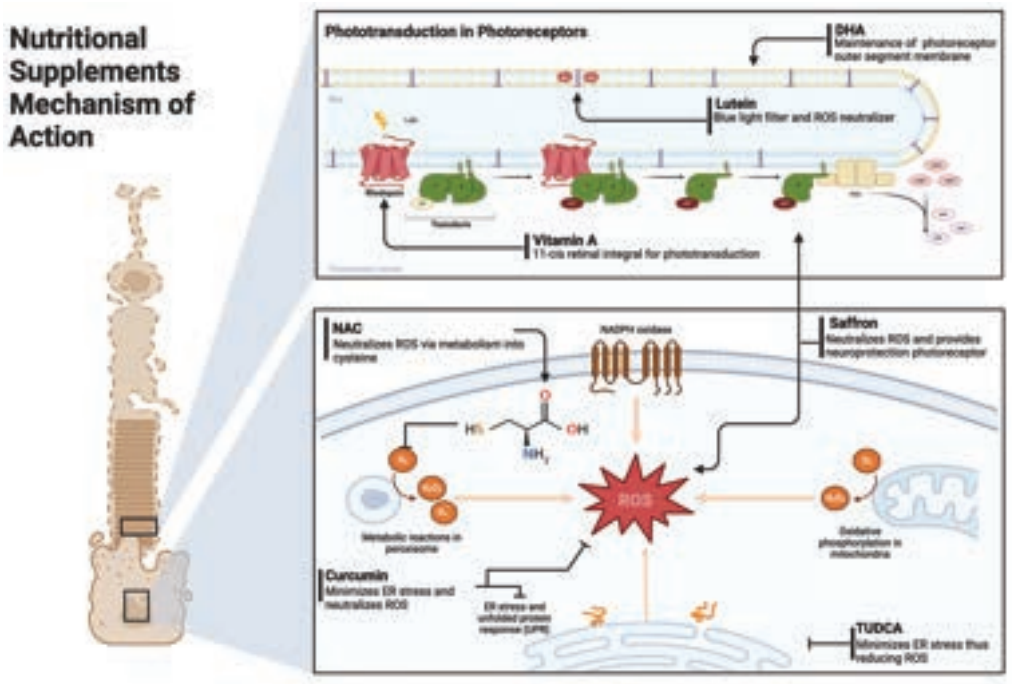

Figure. This image summarizes the proposed mechanisms by which vitamin A, omega-3 fatty acids, and other nutraceuticals may exert neuroprotective and antioxidant effects in IRDs. ***Image created in BioRender. Morales P. 2025. https://BioRender.com/muapy0p***

CLINICAL TAKEAWAYS

Nutritional supplementation is a potential adjunctive approach, although limitations in bioavailability, study design, and long-term clinical validation remain key challenges. Until robust evidence demonstrates clear benefits, nutritional supplementation continues to function as a placebo rather than an established therapeutic co-adjuvant. ■

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RISING STARS IN RETINA

Retina Today

YoungMD > Connect

Get to know outstanding retina fellows from the class of 2025.

Rachel Downes, MD

***Retina Today (RT):* When did you know that you wanted to become a retina specialist?**

Like many residents before me, I was captivated by the excitement around retina at Cleveland Clinic's Cole Eye Institute. Our retina faculty are not only exemplary physicians and surgeons but also dynamic and engaging people. Their enthusiasm for the profession is contagious. Although I entered residency open to a number of different subspecialties or a career in comprehensive ophthalmology, the intricacies of retinal diseases and the complex problem-solving inherent to vitreoretinal surgery ultimately drew me to this field.

***RT:* Who do you look to as mentors?**

Luck has played a huge role in my career by bringing the right mentors into my life at the right times. So many inspiring people have shaped my path, but two in particular have been most influential in my residency and fellowship training. My program director, Sunil K. Srivastava, MD, has taught me not only about retina but also about creating a workplace culture of respect, excellence, and fun. I am fortunate to have trained with him, and I know I will hear his advice in my mind when I am operating as an attending next year. Katherine E. Talcott, MD, has been an important role model for me as a woman in retina. She is among the most skilled surgeons I have had the privilege to work with and is a clear rising star in our field, yet she is humble and generous with her time.

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

A satisfying full-circle moment came the first time I taught a resident during a combined cataract surgery and vitrectomy under the guidance of Alex Yuan, MD, PhD. In fellowship, it can feel like you are treading water. During that case, I realized how far I had progressed in my skills and knowledge since residency and how much I have to offer to patients and trainees.

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

I am joining my mentors as a vitreoretinal surgeon at Cole Eye Institute. I hope to provide exceptional care to my patients in the clinic and OR and create a welcoming and engaging environment for my trainees and staff. Through research, clinical trials, and teaching, I aspire to play my part in shaping the future of our field.

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

It is no secret that a career in retina requires significant commitment and effort. In training, it is easy to focus on the sacrifices you are making for this career, but don't lose sight of all the rewards you receive in return. Our work provides tangible benefits for patients, allows us to work with our hands, and presents at least one new challenge each day. This combination is unique to a career in medicine.

Stay humble and open to learning from everyone around you—not only your attendings but also the nurses, technicians, and patients. ■

FIRST CAREER MILESTONE

Dr. Downes is joining Cleveland Clinic's Cole Eye Institute as a vitreoretinal surgeon.

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REGENXBIO

PEDIATRIC HEMORRHAGE: THE ANSWER IS IN THE FELLOW EYE

Further analysis helped us decide how to proceed in this complex pediatric case.

BY SRUJAY PANDIRI, BA; CELINE CHAAYA, MD; AND NIMESH A. PATEL, MD

A 7-year-old boy was referred to our clinic for an incidental finding of vitreous hemorrhage in the left eye. His parents had noted a change in his iris color from blue to green, which prompted them to seek care. The patient's medical history included congenital bilateral hearing loss.

EXAMINATION

At presentation, the patient's BCVA was light perception OS and 20/60 OD. Slit-lamp examination of the left eye showed dense vitreous hemorrhage against the posterior of the lens with no fundoscopic view. B-scan ultrasound of the left eye showed dense opacities and membranes throughout the vitreous (Figure 1). A V-shaped membrane was attached at the disc, suggestive of a funnel retinal detachment (RD).

When faced with an abnormal presentation, a good look at the contralateral eye can help solve the mystery. A thorough fundus examination of the patient's right eye demonstrated temporal avascularity of the retina with exudates, overlying hemorrhage, and a fibrotic preretinal band (Figure 2). Fluorescein angiography (FA) of the right eye demonstrated temporal straightening of the vessels with significant supernumerary branching and leakage (Figure 3).

DIAGNOSIS AND MANAGEMENT

Given the age of the patient and the abnormal FA findings of the right eye, the leading diagnosis was familial exudative vitreoretinopathy (FEVR). When considering a diagnosis of FEVR, it is important to confirm your suspicion with genetic testing and ask about the patient's family ocular history. In our patient, genetic testing revealed a positive result of the *TSPAN12* pathogenic variant, confirming FEVR.

Similar to other proliferative conditions with bilateral involvement, maintaining the eye with the best prognosis is paramount. Although there is a tendency to jump straight to surgery for the RD in the left eye, stabilizing and providing prophylactic laser for the right eye must be prioritized. In pediatric patients, this is usually best performed under general anesthesia, as was the case for this patient. An important point regarding laser is to be judicious with the power; the avascular retina is often thin, and high-energy laser may create holes and trigger more membrane proliferation.

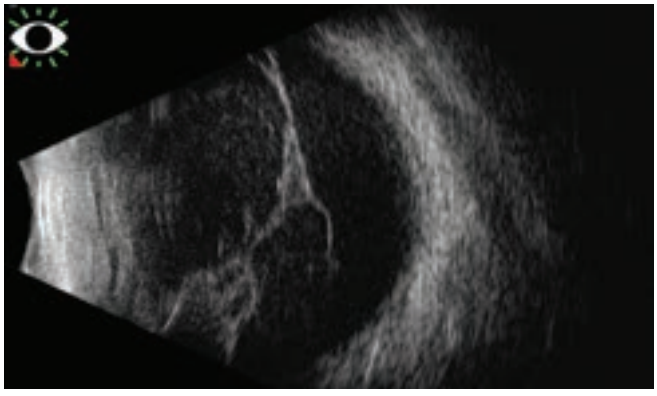


Figure 1. B-scan ultrasound of the patient's left eye showed a V-shaped membrane attached at the disc.

Examination under anesthesia was necessary to provide a more detailed assessment of the left eye for prognostication. With the limited ultrasound, it appeared that the retina was taut and likely inoperable. However, findings obtained under anesthesia were more consistent with a very dense, partially mobile vitreous hemorrhage with a low-lying tractional RD. A follow-up surgical procedure was subsequently scheduled. In cases when the need for surgery is unknown, we recommend avoiding performing the examination under anesthesia and surgery on the same day. This allows time for

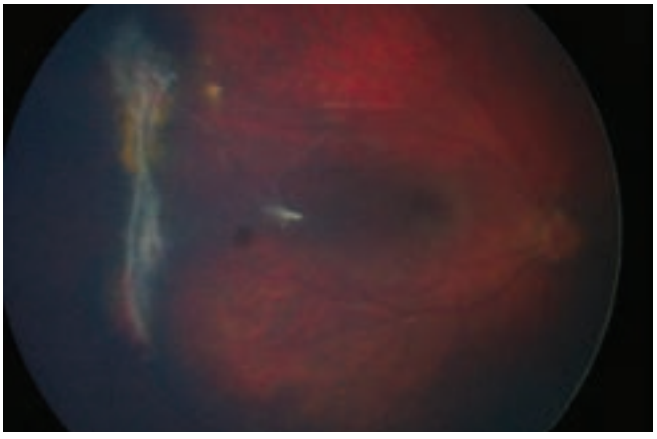
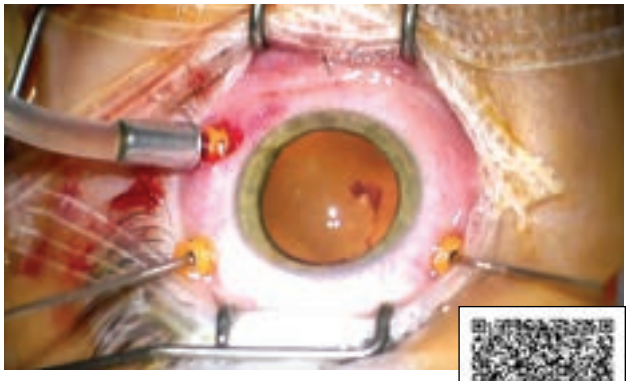


Figure 2. Fundus photography of the right eye showed temporal avascularity of the retina, exudates, overlying hemorrhage, and a fibrotic preretinal band.

proper consent, planning, and preparation for postoperative management. An added benefit is a predictable procedure time for the OR schedule.

Intraoperatively, there are a few important considerations. The first decision is whether to remove the lens. Generally, sparing the lens is helpful for promoting visual development, maintaining a posterior chamber for a tamponade, protecting the cornea, and preventing aphakic glaucoma.[1-3] Although there was some blood on the posterior surface of the lens, a vitrectomy was performed with limited visualization (Video). A temporal tractional RD was observed with two dense fibrous bands from the nerve to the temporal periphery. Surgeons should be as minimally invasive as possible to avoid retinal breaks. It is not necessary to lift the hyaloid or remove all of the hemorrhage. The primary aims are to clear the visual axis, relieve traction, and apply laser to prevent neovascular complications. Furthermore, adding a scleral buckle is important, as much of the traction is anterior to the equator. Laser was applied to the avascular retina, and because no breaks were created, air was used.

WATCH IT NOW



Video. Vitrectomy for Tractional Retinal Detachment Associated With FEVR.

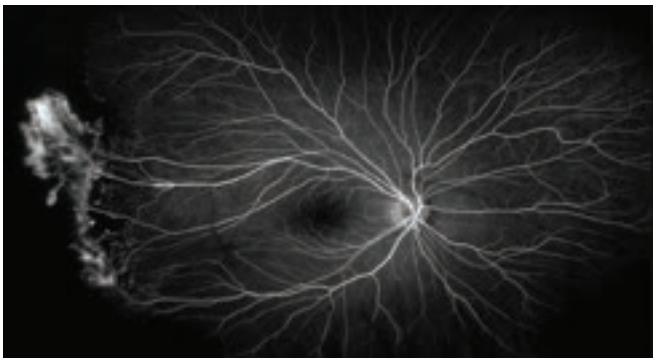


Figure 3. FA of the right eye showed temporal vessel straightening with branching and leakage.

OUTCOME

At the patient's final follow-up more than 2 years after presentation, his right eye remained stable following the laser treatment, with noted regression of the neovascularization. If traction worsens in the future, a prophylactic scleral buckle will be considered.

The left retina remained attached with improvement in vision from light perception to counting fingers at 3 ft. The patient developed a cataract in the left eye, so we conducted cataract surgery and placed an intraocular lens with a concurrent posterior capsulotomy, which prevents visual axis opacification.[4] Because FEVR can reactivate over time, continued follow-up is required. ■

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SURGICAL MANAGEMENT OF RETINAL DETACHMENT IN UVEAL MELANOMA


Addressing this complication requires careful planning and follow-up.

BY RODRIGO ANGUITA, MBBS, MD, FEBO, FICO, AND LYNDON DA CRUZ, MA, MBBS, PHD, FRCOPHTH, FRACO

Retinal detachment (RD) in the setting of uveal melanoma (UM) can occur as a direct consequence of the tumor itself, as a complication of its treatment, or as an unrelated event. RDs associated with UM can occur in a variety of forms, including exudative (ERD), tractional (TRD), or rhegmatogenous (RRD).[1]

The timing of the onset of RD significantly influences the diagnosis, urgency, and surgical approach (Table). It is essential to maintain a careful balance between tumor control, mitigation of spread, and preservation of visual function when selecting the surgical procedure. A multidisciplinary approach involving ocular oncologists and vitreoretinal surgeons is critical to achieve optimal patient outcomes. This article provides a broad overview of the various types of RDs in patients with UM, with a focus on surgical management.

DETACHMENT TYPES IN UM

ERD

ERD is the most common presentation in UM with the volume of fluid generally correlating with tumor size; thus, a large ERD is rare in small, untreated melanomas.[2,3] Medium or large tumors, especially metastatic lesions, can cause rapid progression of exudation and can be misdiagnosed as RRD without recognizing the underlying choroidal lesion. In these cases, a high index of suspicion for ERD is warranted, and ultrasound plays an important role (Figure 1).

After treatment, ERD can occur due to toxic tumor syndrome, which is characterized by intratumoral necrosis, ischemia, and vascular incompetence. This syndrome manifests with macular edema, hard exudates, ERD, iris neovascularization, and neovascular glaucoma.[4]

TRD and Combined TRD/RRD

TRD and combined TRD with RRD are typically late complications of radiation therapy for UM and fall under the broader complication of radiation retinopathy. Radiation retinopathy usually occurs 6 months to 3 years after treatment and is characterized by endothelial cell loss and capillary occlusion, which progresses to retinal ischemia and neovascularization.[5] In later stages, these can result in TRDs.[6]

Beykin et al reported a 1.48% incidence of TRD/RRD in 473 patients treated with ruthenium-106 brachytherapy. All patients underwent pars plana vitrectomy (PPV) with silicone oil tamponade; despite anatomic success, visual outcomes were limited.[7] No tumor growth or dissemination was observed during the follow-up period (average of 18.4 months) after PPV.

TABLE. TYPES OF UVEAL MELANOMA-ASSOCIATED RETINAL DETACHMENTS

Type of RD	Timing of Onset	Clinical Features
Exudative retinal detachment (ERD)	Present at diagnosis or after treatment	- Subretinal fluid resolves gradually after treatment - Massive ERD after treatment may suggest complications such as toxic shock syndrome
Rhegmatogenous retinal detachment (RRD)	Before (as complication of biopsy) or after treatment	- Linked to retinal breaks - Requires differentiation from ERD (the presence of hydration folds on OCT and/or proliferative vitreoretinopathy suggests RRD)
Tractional retinal detachment (TRD) and Combined TRD/RRD	Post-radiotherapy	- Fibrotic traction secondary to ischemia and neovascularization - Poor visual outcomes - Complex cases with both TRD and RRD components

RRD

The occurrence of RRD in patients with UM is rare (Figure 2). At Moorfields Eye Hospital, a large tertiary center in London that treats approximately 300 new cases

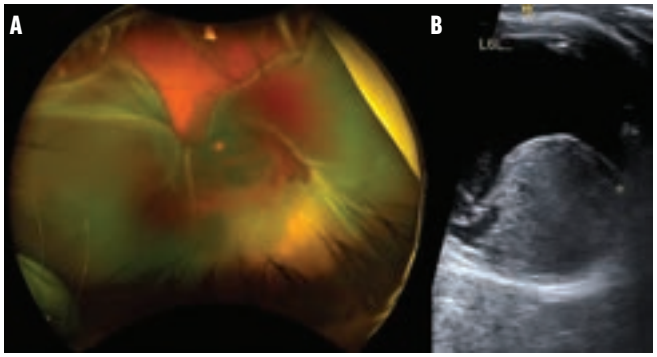

Figure 1. Color fundus photography demonstrates a subtotal ERD (A). B-scan ultrasonography reveals a choroidal melanoma underlying the ERD (B).

of UM and 1,800 new cases of RRD annually, the incidence is approximately one case per year.[8]

RRD may be identified in three contexts:

- concurrent with UM, where symptoms of RRD lead to incidental discovery of the tumor,
- as a rare complication of transvitreal retinochoroidal biopsies, particularly in the case of flat lesions, and
- post-treatment due to a normal posterior vitreous detachment or treatment complications (eg, globe perforation during plaque placement).

Anatomic success in RRD associated with UM is strongly influenced by the presence of proliferative vitreoretinopathy (PVR). Haimovici et al reported a small series without PVR and a primary success rate of 90% using scleral buckle and pneumatic retinopexy.[8] In contrast, our series showed 37% of patients with PVR at presentation and a 59% initial success rate, mainly repaired by PPV. With multiple surgeries, we were ultimately able to achieve retinal reattachment in 84% of cases.[9]

SURGICAL TECHNIQUE: FACTORS TO CONSIDER

Treatment Status

In cases of untreated UM, the safety of full PPV remains uncertain. Although transvitreal retinochoroidal biopsies are generally considered safe,[10] there is limited evidence to support full PPV in this context. Consequently, scleral buckling or pneumatic retinopexy is often preferred to minimize the risk of seeding. When PPV is essential (eg, in cases of PVR), it is advisable to perform the surgery at the time of plaque removal, if the detachment does not interfere with plaque placement.[1]

In the case of treated tumors, radiation therapy, conjunctival scarring, extraocular muscle fibrosis, and rare cases of scleral necrosis post-brachytherapy may complicate scleral buckle placement.[11] In such cases, PPV is the most appropriate technique, especially when managing concomitant RRD and vitreous hemorrhage, PVR-related RRD, TRD, or a combined TRD/RRD. In cases of treated UM, PPV has not been associated with an increased risk of metastasis.[12]

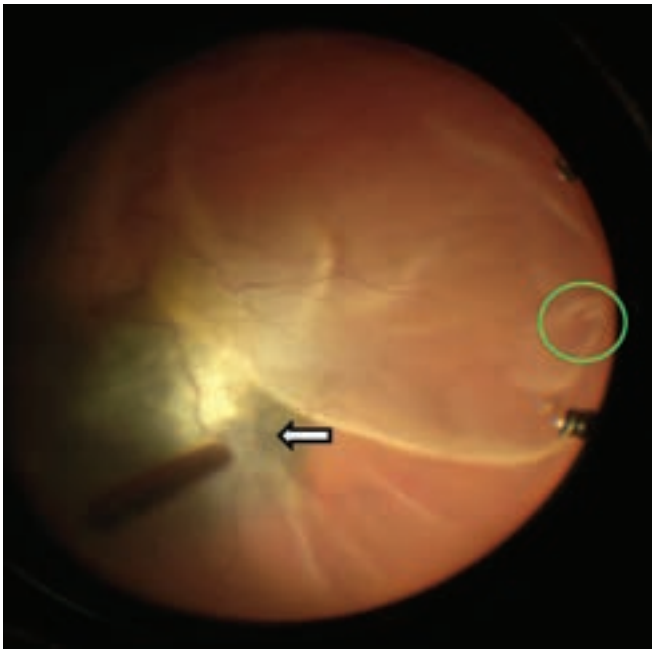

Figure 2. Intraoperative imaging during PPV for an RRD in a patient with a previously treated peripapillary choroidal melanoma shows a superotemporal horseshoe retinal tear (green circle). The white arrow indicates the treated melanoma.

Tumor Location

Small posterior pole melanomas are often suitable to all surgical techniques; medium to large tumors in the periphery may interfere with adequate tamponade, as the tumor affects how the gas or oil bubble conforms to the retina.[1]

Retinal Tear Location

Tears located near the tumor are particularly difficult to treat. Scleral buckling and pneumatic retinopexy are often unsuitable, as the gas bubble may not conform adequately to the retina around the tumor; therefore, it may not tamponade the break, and the scleral buckle may fail to create effective indentation. In such cases, PPV remains the most suitable option.[1]

Anesthesia

While vitreoretinal surgery is commonly performed under local anesthesia, the timing of RD repair in relation to tumor treatment affects the choice of anesthetic. Radiation-induced scarring often complicates the use of a sub-Tenon block, as anesthetic uptake may be reduced; therefore, general anesthesia is recommended to ensure pain control, patient comfort, and surgical safety.

PEARLS

Scleral Buckle

- Precise tumor localization is essential. While this can be challenging with a detached retina, intraoperative ultrasound is helpful.

- Avoid placement of the suture directly over the tumor.
- Avoid external drainage to prevent potential extraocular extension.
- Ultrasound visualization and monitoring of the tumor may be difficult during follow-up, depending on the location of the scleral buckle.

PPV

- Consider performing a local peritomy with cryotherapy at the time of trocar removal and suturing sclerotomies.
- Use valved trocars.
- Determine accurate localization of the tumor to avoid trocar insertion into the tumor, especially in cases of ciliary body melanoma.
- Keep the cutter away from the tumor; accidentally cutting into the melanoma can cause cell dispersion.

PREPARE THE PATIENT

Visual outcomes in UM-associated RD cases are typically poor due to factors such as radiation retinopathy/neuropathy, redetachment, PVR, and the need for reoperation. Counsel patients to set realistic expectations, emphasizing that while anatomic reattachment is possible, functional outcomes may be poor.[9] Understanding the type and timing of RD, tumor characteristics, and treatment history are critical for selecting the appropriate surgical technique. ■

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(Continued from page 34)

The phase 1/2 STELLAR study (NCT06467344) is investigating ACDN-01 (Ascidian Therapeutics), an RNA-based exon editing therapy administered via subretinal injection.

The phase 1/2 GARDian study (NCT05956626) involves OCU410ST (Ocugen), a gene-agnostic modifier gene therapy delivered via subretinal injection. It specifically involves human retinoic acid-related orphan receptor alpha.

The now complete phase 2 STARLIGHT study (NCT05417126) involved multi-characteristic opsin (MCO-010, Nanoscope), an optogenetics therapy that targets surviving retinal cells with the goal of improving vision.

The phase 2 TEASE study (NCT02402660) is investigating oral ALK-001 (Alkeus) as a strategy to replace vitamin A and prevent the formation of toxic vitamin A dimers.[11]

A phase 2b study (NCT03364153) of avacincaptad pegol (Astellas), a complement C5 inhibitor, is active for Stargardt.

The phase 2/3 DRAGON II study (NCT0638808) is investigating tinlarebant (LBS-008, Belite Bio), an oral small molecule that reduces the accumulation of toxic vitamin A-derived byproducts.

A phase 1/2 study (NCT04545736) is evaluating metformin in the treatment of *ABCA4*-related retinopathy. ■

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CREATIVE POSITIONING IN VITREORETINAL SURGERY

A patient's limted mobility may require accommodative solutions to provide the best possible surgical care.

BY ALICIA ALCUAZ ALCALAYA, MD; EDUARDO PÉREZ-SALVADOR GARCÍA, MD, PHD; AND MARÍA JESÚS LÓPEZ PEÑA, MD, PHD

When performing vitreoretinal surgery on patients with significant mobility issues, there are certain accommodations that must be provided in the preoperative, intraoperative, and postoperative periods. In the following sections, we present a case of a patient with ankylosing spondylitis who required a modification to our typical surgical protocols; we also itemize the relevant challenges and offer suggestions for approaching similar cases.

PREOPERATIVE CONSIDERATIONS

A 68-year-old man with a 20-year history of ankylosing spondylitis, chronic ischemic cardiopathy, and moderate bronchial asthma was referred to our ophthalmology practice for poor vision in his right eye.

Due to the patient's nuchal rigidity, we could not assess him at the slit lamp or obtain OCT images. The diagnosis and preoperative exploration were established through indirect ophthalmoscopy, owing to the observation of a sizable macular hole with white-colored deposits in its center. However, we could not ascertain its size or stage preoperatively. Keeping in mind the patient's age and comorbidities, we decided to perform a phacovitrectomy with the insertion of an IOL and internal limiting membrane (ILM) peeling.

For the preanesthesia study, we ordered a chest x-ray (Figure 1), functional respiratory tests, and reports from pneumology, cardiology, and anesthesia specialists. Based on the results of these tests, the surgery was determined to be high risk due to many factors, including a Mallampati score of IV, poor cervical extension, poor buccal opening, thyromental distance > 6 cm, and dental prostheses.

We initially considered operating in a forced Trendelenburg position, which we attempted with the patient during the preanesthesia consultation. However, the patient did not tolerate the position well due to an increase in the venous delay of the craniofacial area; thus, the option of intervening with sedation was disregarded.

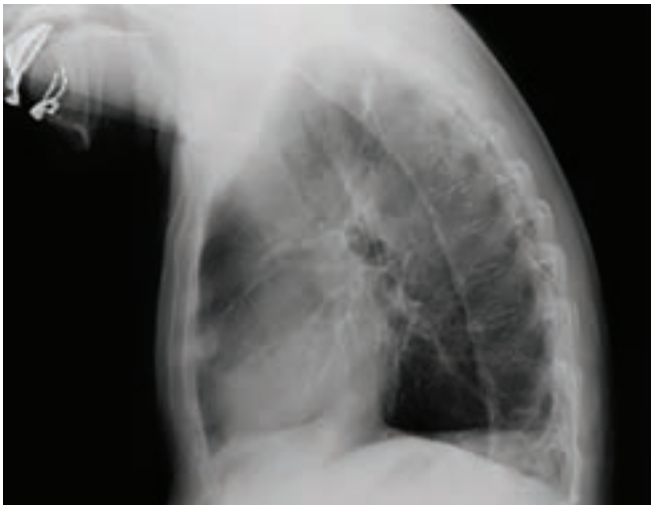

Figure 1. A preoperative x-ray documents the patient's nuchal hyperflexion.

With the estimated duration of the intervention in mind, we opted for fiberoptic intubation while the patient was awake followed by use of general anesthesia.

INTRAOPERATIVE CHALLENGES

Positioning the Patient

Intubation with a fiberscope was met with considerable technical difficulty due to the need to perform it while facing the patient. With the patient's status monitored while fully under anesthesia, he was placed into a forced Trendelenburg position (Figure 2).

The headrest was removed from the stretcher, and an extra module was added to the end toward the patient's feet

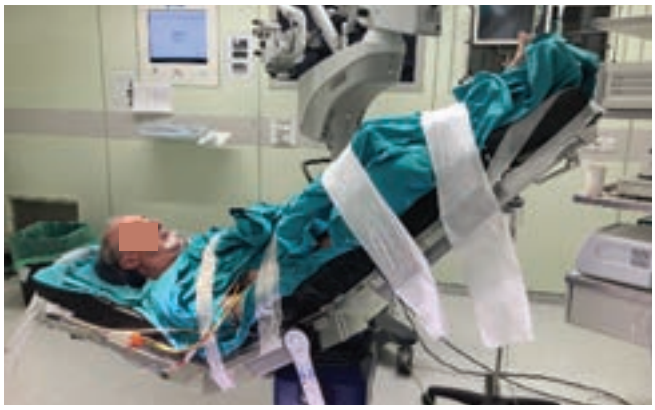

Figure 2. These photos show the patient's final positioning for surgery after making all necessary modifications. Note his superciliary arch.

to accommodate his neck. The idea behind this placement was to ensure the eye remained in a coaxial position with respect to the microscope and to ensure the headrest would not be too low for the surgeon. The patient was secured through several straps to prevent him from sliding down, and shoulder pads were also used to maintain the position.

The process of anesthesia and securing the patient's position required approximately 1 hour and 15 minutes.

Positioning the Surgeon

At this point, the main surgeon placed himself laterally to have suitable access to the eye, as the patient's head and superciliary arch did not allow for any other approach. Because of the stretcher modifications, the surgeon moved the pedals in an uncomfortable position. Moreover, because of the patient's position, the surgical microscope kept making contact with the superior area of the superciliary arch, so it was impossible to see the entire superior hemiretina.

After performing 23-gauge posterior vitrectomy and ILM staining, a contact lens was used to achieve a clearer image of the posterior pole. Because the lens kept moving downward, the trocars were switched to the 7 clock hour position (right hand), inferior nasal (infusion), and superior temporal (endocular light).

During the surgery, a posterior vitreous detachment was found, and it was possible to diagnose the patient with a stage 4 macular hole based on the Gass classification and epiretinal proliferation. Due to the inability to perform intraoperative OCT, no images were taken during the surgery.

When peeling the ILM, the superior zone of the contact lens made contact with the superciliary arch, so the surgeon's assistant had to cut one of lens haptics to make it more horizontal.

After completing the vitrectomy with 25% SF_6, the nylon 10/0 stitch was removed because, due to the patient's short chin-sternum distance, it would be impossible to remove it at the slit lamp.

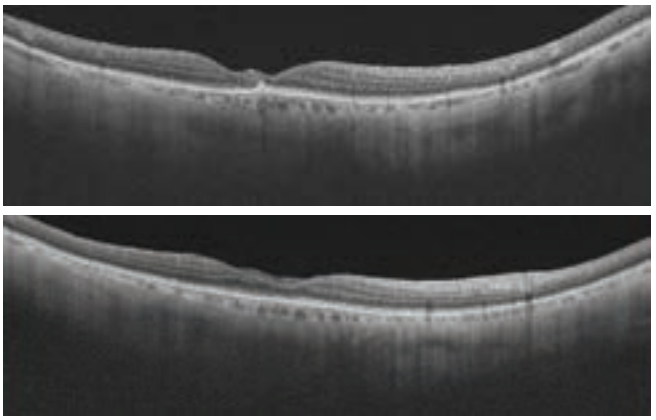

Figure 3. Postoperative OCT obtained on a follow-up visit shows complete hole closure.

POSTOPERATIVE CARE

It is essential to schedule regular postoperative examinations to support visual and anatomic rehabilitation and monitor for complications. In this case, postoperative assessment was also conditioned to the patient's nuchal rigidity. In the follow-up visits, we were able to assess his visual acuity and IOP using a Perkins Mk3 tonometer (Haag-Streit) and obtain fundus imaging with an indirect ophthalmoscope. Only during one visit could we obtain a postoperative OCT image, which confirmed the macular hole closure (Figure 3).

To instill eye drops at home, the patient had to lay face up each time for the caregiver to properly administer them.

MEET THE PATIENT WHERE THEY ARE

When planning for a vitreoretinal surgery, we must assess each patient's characteristics, surgical requirements, and postoperative care regimen. Only by considering all these factors can we choose a more customized—and less aggressive—option with the patient's wellbeing in mind. ■

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CODING ADVISOR
A Collaboration Between *Retina Today* and AMERICAN ACADEMY OF OPHTHALMOLOGY

HOW TO CREATE CLEAN CLAIMS

Here are a few key factors to consider during the drug treatment payment process.

BY JOY WOODKE, COE, OCS, OCSR

The reasons for drug claim denials are endless. Starting with a clean claim will increase the probability of streamlined reimbursement. Here are a few factors that can contribute to accurate coding and billing and prompt payment.

CHOOSE THE APPROPRIATE CPT OR CATEGORY III CODE

When providing treatment, there are multiple procedural codes to consider. A frequently used injection code is CPT code 67028, intravitreal injection of a pharmacologic agent (separate procedure), when treating with anti-VEGF or dual inhibitors for AMD, diabetic retinopathy, and macular edema following retinal vein occlusion, and complement inhibitors to treat geographic atrophy. Additional codes to consider are provided in Table 1.

VERIFY THE HCPCS CODE AND UNITS

Identify the appropriate HCPCS code for the medication used. New treatments are initially billed with not otherwise classified (NOC) HCPCS codes until a permanent code is assigned. When billing with an NOC code, report the medication name, dosage, and invoice amount in item 19 of the claim form. Without this information, the claim may be denied. Once a permanent HCPCS code is assigned, the descriptor will provide the name of the drug and the dosage amount that equates to 1 unit. For example:

- HCPCS code J2781, injection, pegcetacoplan (Syfovre, Apellis), intravitreal, 1 mg: 15 mg are administered, 15 units are billed.
- HCPCS code J2777, injection, faricimab-svoa (Vabysmo, Genentech/Roche), 0.1 mg: 6 mg are administered, 60 units are billed.
- HCPCS code Q5147, injection, aflibercept-ayyh (Pavblu, Amgen), biosimilar, 1 mg: 2 mg are administered, 2 units are billed.

TABLE 1. SELECT RETINA CODES AND DESCRIPTORS

Code	Descriptor
CPT code 67027	Implantation of intravitreal drug delivery system, including removal of vitreous
CPT code 67516	Suprachoroidal space injection of pharmacologic agent (separate procedure)
Category III code 0810T	Subretinal injection of a pharmacologic agent, including vitrectomy and one or more retinotomies

TABLE 2. NATIONAL DRUG CODE CONVERSION TO 11 DIGITS

Drug	10-Digit NDC	11-Digit NDC
0.5 mg ranibizumab (Lucentis, Genentech/Roche)	50242-080-02	50242-0080-02
0.7 mg dexamethasone intravitreal implant (Ozurdex, Abbvie)	0023-3348-07	00023-3348-07
8 mg aflibercept (Eylea HD, Regeneron)	61755-050-01	61755-0050-01

REPORT THE CORRECT NDC

The national drug code (NDC) is essential for accurate claims. However, to be recognized by payers, it must be

TABLE 3. NATIONAL DRUG CODE PACKAGE VARIANCE		
Drug	Packaging	NDC in 5-4-2 Format
Faricimab-svoa (Vabysmo, Genentech/Roche)	Single-dose vial with needle	50242-0096-01
	Single-dose vial	50242-0096-03
	Single-dose prefilled syringe	50242-0096-06
2 mg aflibercept (Eylea, Regeneron)	Single-dose prefilled syringe (buy and bill)	61755-0005-01
	Single-dose prefilled syringe (sample)	61755-0005-54
	Single-dose vial kit (buy and bill)	61755-0005-02
	Single-dose vial kit (sample)	61755-0005-55

converted from a 10-digit to an 11-digit, 5-4-2 sequence. This means a zero must be placed where appropriate to achieve the correct claim submission format (Table 2).

Drug packaging may have different NDC numbers. Single-use versus multidose vials and liquid versus powder vials also have different NDC numbers on the packaging. It is crucial to report the correct NDC for the type of drug used (Table 3).

The NDC is reported on the CMS-1500 and EDI equivalent in item 24a proceed by the N4 qualifier.

USE THE ACCURATE UNIT OF MEASURE

Following the appropriate NDC on the claim in item 24a should be the unit of measure, which reports the volume of the drug injected. Most retina drugs are provided in liquid form and are reported with the volume in milliliters. For example, 2 mg/0.05 mL aflibercept (Eylea, Regeneron) would be reported as ML0.05.

For powder-filled vials of medications that are reconstituted (eg, verteporfin [Visudyne, Bausch + Lomb]), report the number of vials used in units. For example, if one vial was used, report as UN1.

FOLLOW THE FDA LABEL

Each drug has indications and frequency limitations, and following these guidelines will ensure the claims are paid. Off-label use is consistently denied by payers unless they have a published policy with expanded diagnosis coverage or unique frequency limitations.

APPEND THE -JZ OR -JW MODIFIER

Append the -JZ or -JW modifier to the HCPCS code as appropriate. Modifier -JZ should be reported when the wastage is less than 1 unit, as defined by the HCPCS code descriptor, and/or if considered overfill. Retina drugs are frequently reported with modifier -JZ. Modifier -JW, on the other hand, should be appended to the HCPCS code when the wastage is 1 unit or greater (eg, triamcinolone acetonide [Triesence, Alcon]).

LEARN MORE

To confirm the FDA indications, billing units, and whether to report the -JZ or -JW modifier, access the AAO's Table of Common Retina Drugs at aao.org/retinapm. Additional billing guidance can be reviewed at aao.org/injection. ■

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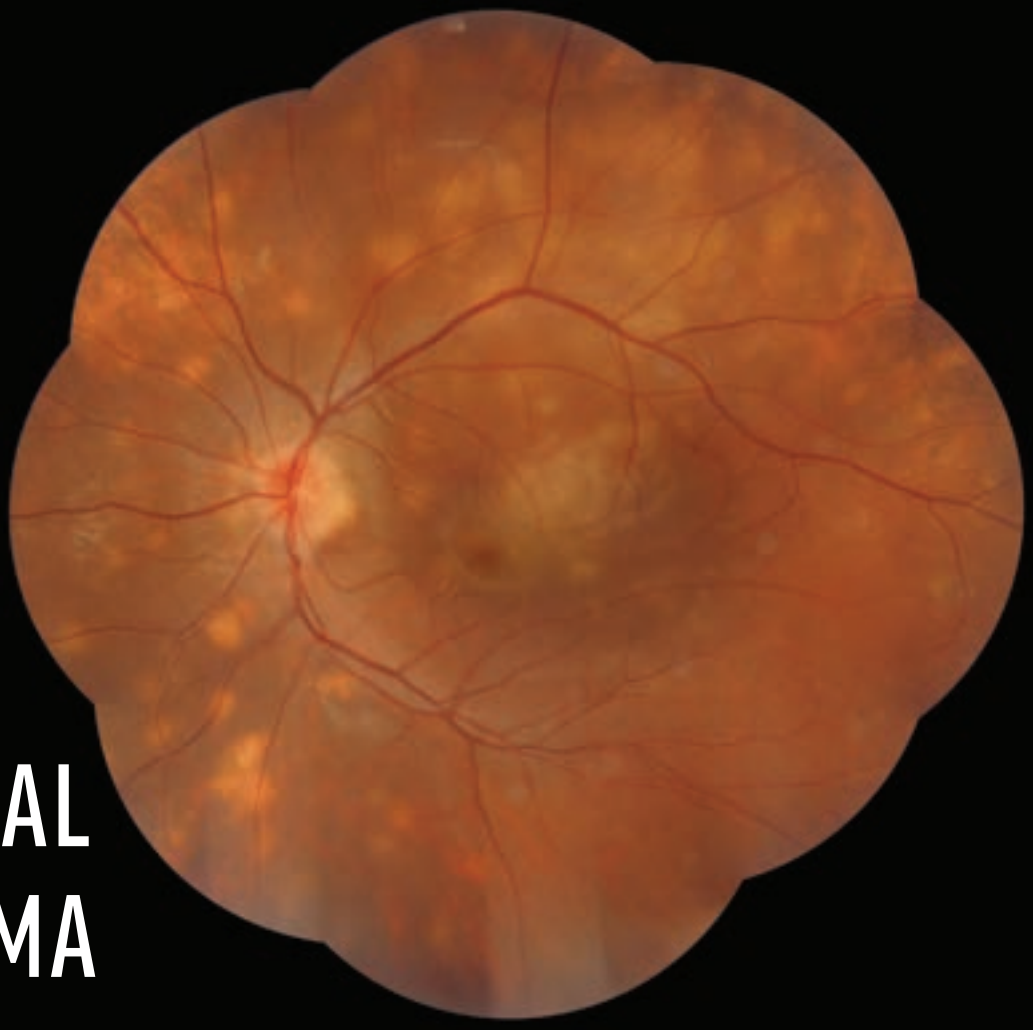
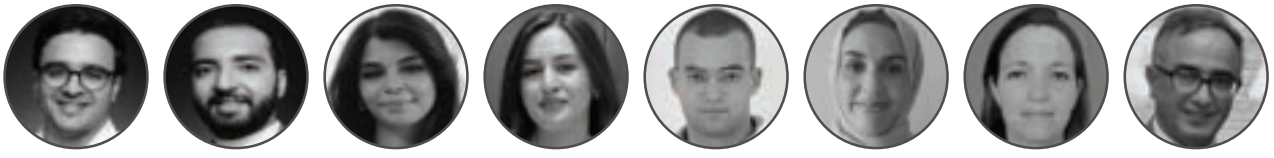


FIGURE 1



Findings on OCT uncovered a rare ocular condition.

BY SOULAYMANE RACHDA, MD; YASSINE ELKHALIFA, MD; SELMA OUAZZANI TOUHAMI, MD; NIIMA ELFAHLI, MD; YOUNES TLEMÇANI, MD, PHD; SARAH BELGHMAIDI, MD, PHD; IBTISSAM HAJJI, MD, PHD; AND ABDELJALIL MOUTAOUAKIL, MD, PHD

A 32-year-old man presented to our clinic with decreased vision in his left eye. He had a history of pulmonary tuberculosis, which had been treated 9 years prior and declared cured.

Fundus examination revealed Bouchut tubercles and a choroidal granuloma at the posterior pole (Figure 1). OCT imaging showed a hyporeflective, dome-shaped lesion (Figure 2, blue arrow), with an overlying attachment between the retinal pigment epithelium-choriocapillaris layer and the neurosensory retina, consistent with the contact sign (Figure 2, white arrow), a finding described by Salman et al in 2006.[1]

The presence of the contact sign is suggestive of a choroidal tuberculoma and contrasts with the OCT features observed in noninflammatory conditions, such as choroidal tumors found in cases of melanoma, metastasis, or circumscribed hemangioma. Management for this case included initiating systemic antitubercular therapy in coordination with infectious disease specialists, along with close ophthalmologic monitoring. ■

1. Salman A, Parmar P, Rajamohan M, Vanila CG, Thomas PA, Jesudasan CA. Optical coherence tomography in choroidal tuberculosis. *Am J Ophthalmol*. 2006;142(1):170-172.

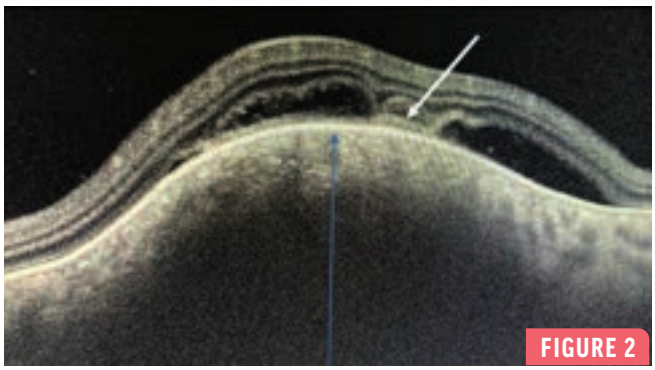


FIGURE 2

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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.

Manufactured for:
Apellis Pharmaceuticals, Inc.
100 Fifth Avenue
Waltham, MA 02451

SYF-PI-20Dec2024-3.0

12/24 US-PEGGA-2400436 v1.0

SYFOVRE®
(pegcetacoplan injection)
15 mg / 0.1 mL

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]

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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

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  - 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.
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- **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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