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Retina Today

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RARE AND INHERITED RETINAL DISEASES

Unraveling the mysteries of diagnosis and management.

MANAGING IRD IN THE CLINIC AND OR

NAVIGATING INCONCLUSIVE TESTING IN IRD

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References: 1. Irannejad A, Tambat S, Abulon DJK. Retropulsion and mass flow of 27-gauge vitrectomy probes: comparison of dual-blade/flat-tipped probes and single-blade/beveled probes. Poster presented at: 18th Congress of the European Society of Retina Specialists; September 20–23, 2018; Vienna, Austria. **2.** Alcon data on file, 2018. **3.** Alcon data on file, 2017.

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WHEN RARE IS RELATIVE


When you specialize in inherited retinal diseases (IRDs), it can be easy to lose perspective of how rare these conditions are. Those of us who manage IRDs see these patients frequently and routinely spot clinical signs of retinitis pigmentosa (RP), classic Stargardt disease, and Leber congenital amaurosis (LCA). However, even these more common conditions do not present to all retina practices often. After all, RP has a prevalence of approximately one in 4,000; that's only 110,000 patients in the United States.[1] Compare that to the nearly 20 million patients diagnosed with AMD.[2]

When we step away from our IRD clinics and engage with the retina community, we are reminded how uncommon these diagnoses are. However, the latest news and conferences bring IRD research and innovation into the spotlight. During one session at this year's Atlantic Coast Retina Club, half of the case presentations were IRDs. In the first half of 2024, 16% of the news stories that ran on Eyewire+ were focused on IRDs; since January, at least 11 companies have announced updates to their IRD clinical trial programs.[1,3-15]

With the advent of gene and cell therapies, IRDs have become an important focus for researchers. Although voretigene neparvovec-rzyl (Luxturna, Spark Therapeutics) for *RPE65*-associated LCA is the only approved genetic therapy for an IRD, many companies are working their way through clinical trials for various inherited conditions.

This issue of *Retina Today* is an ode to the innovation happening in the IRD space. Cristy A. Ku, MD, PhD, and her team at Baylor provide a roundup of gene therapy trials (nearly 30!), while Ishrat Ahmed, MD, PhD, and Mandeep S. Singh, MD, PhD, summarize novel approaches, such as stem cell therapy, optogenetics, and retinal prosthesis. Elizabeth Kellom, MS, CGC, and Kimberly Stepien, MD, explore various genetic testing approaches and what to do if the results are inconclusive. Jonathan F. Russell, MD, PhD, and his colleagues at the University of Iowa discuss managing IRD patients who present with complications, and Kevin C. Allan, MD, PhD, and Alex Yuan, MD, PhD, look at various imaging techniques. Shima Dehghani, MD, and Stephanie M. Llop, MD, highlight clinical trials in uveitis, another rare retinal condition with a robust therapy pipeline—they touch on 16 ongoing phase 3 and 4 trials. Finally, a can't-miss article in this issue is a mystery case compilation to test your diagnostic acumen.

Although the IRD patient population is small compared with other retinal conditions, the research on novel therapeutic approaches is not. Patients with an IRD may feel isolated because of their diagnosis, yet hundreds of researchers and clinicians are working hard to bring new therapies to market. *Rare*, in this case, is a relative term. For those of us working in the IRD space, it doesn't feel as if their condition is all that rare with so much buzz about genetic testing, imaging, monitoring, and (one day) treatment. We should share this enthusiasm and research momentum with our patients; if nothing else, it helps them find hope—and perhaps a clinical trial and potential cure. ■

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3. Ocugen doses first patient in phase 3 clinical trial for OCU400 gene therapy for RP [press release]. Eyewire+. June 20, 2024. Accessed July 1, 2024. tinyurl.com/3626jumz
4. Beacon Therapeutics treats first patient in VISTA trial of AGTC-501 for XLRP [press release]. Eyewire+. June 12, 2024. Accessed July 1, 2024. tinyurl.com/3ah5jrsd
5. Atsena Therapeutics announces positive clinical data from the first cohort of phase 1/2 trial evaluating gene therapy for XLRS [press release]. Eyewire+. May 1, 2024. Accessed July 1, 2024. tinyurl.com/4fu2atje
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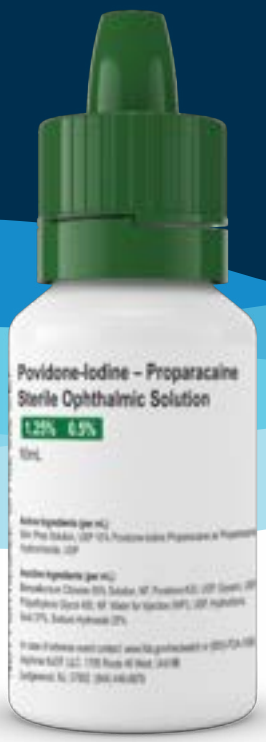

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By Eric S. Li, BS; Elliott K. Vanderford, BS; and Paul C. Kang, MD

Using AI to Identify Exudative Macular Disease
By Claudia P. Acosta, MD; Maria A. Piedrahita, MD; Juan Gonzalo Sanchez, MD; Juliana Muñoz-Ortiz, MD; Julián Martinez; José Zea; Laura Velasquez; Juliana Mesa; Sebastian Menges; and Carolina Sardi, MD, MS

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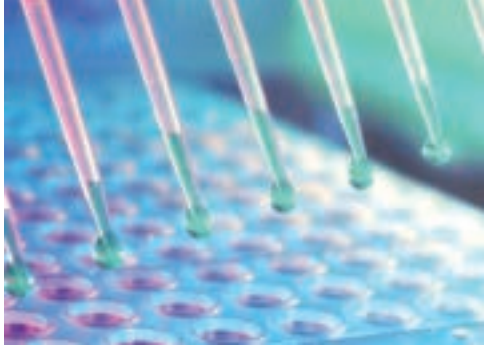

NEW VITRECTOMY DEVICE RECEIVES FDA CLEARANCE

Alcon announced in June that its Unity vitreoretinal-cataract system and Unity cataract system received FDA 510(k) clearance.[1]

This next generation of equipment and consumables in cataract and vitreoretinal surgery seeks to improve workflow efficiency compared with the current systems (Constellation Vision system for vitreoretinal procedures and Centurion Vision system with active sentry for cataract surgery), according to the company.[1]

Alcon will work to update the more than 28,000 Centurion and Constellation devices in the market to its Unity platform over the next decade.[1]

Alcon has tested its new systems during investigational advisory wet lab sessions with more than 200 surgeons from 30+ countries and is launching a program to secure real-world feedback before commercial launch in 2025.[1] The company expects CE Mark in early 2025, and it is continuing regulatory submissions throughout 2024 in markets across the globe.[1]

1. FDA clears Alcon's Unity vitreoretinal-cataract system and Unity standalone cataract system [press release]. Eyewire+. June 24, 2024. Accessed July 3, 2024. eyewire.news/news/fda-clears-alcons-unity-vitreoretinal-cataract-system-and-unity-standalone-cataract-system

MACTEL TREATMENT RECEIVES FDA PRIORITY REVIEW

Neurotech Pharmaceuticals announced in June that the FDA has granted priority review of the company's biologic license application for NT-501 (revakinagene taroretcel), an investigational encapsulated cell therapy for the treatment of macular telangiectasia type 2 (MacTel). With this designation, the FDA has determined the application is sufficiently complete to permit a review and aims to take action within 6 months, compared with 10 months for standard review. The company expects a response in mid-December.[1]

MacTel is a progressive, neurodegenerative retinal disease that results in the deterioration of central vision. NT-501 is an ocular implant designed to deliver sustained doses of ciliary neurotrophic factor—a neuroprotective protein that promotes the survival and maintenance of photoreceptors—directly to the retina to slow the progression of disease and improve long-term visual outcomes for patients.[1]

1. Neurotech receives priority review of BLA for NT-501 as a treatment for macular telangiectasia type 2 (MacTel) [press release]. Eyewire+. June 20, 2024. Accessed July 3, 2024. eyewire.news/news/neurotech-receives-priority-review-of-biologics-license-application-bla-for-nt-501-as-a-treatment-for-macular-telangiectasia-type-2-mactel

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EyewireTV | 06.26.2024

In this episode:

- Alcon Receives FDA Clearance for Next-Generation Unity Surgical Platforms
- FDA Grants Priority Review to Neurotech for Investigational MacTel Cell Therapy
- Nidek Receives CE Mark Approval for Preloaded IOL Injection System

IMMUNOTHERAPY MAY SLOW DIABETIC RETINOPATHY PROGRESSION

Researchers from the University of Oklahoma Health Sciences and Memorial Sloan Kettering Cancer Center are studying a new treatment—anti-ceramide immunotherapy—that aims to address the root cause of diabetic retinopathy and stop progression toward blindness at an earlier stage than previous treatments.[1]

The team, led by Julia Busik, PhD, professor and chair of the department of biochemistry and physiology, used a

mouse model to take a closer look at lipid pathways in the retina and how they are affected by diabetes. They found that ceramide—a type of lipid—is present in the eyes of patients with diabetic retinopathy. Specifically, patients with proliferative diabetic retinopathy experience an imbalance of ceramide in the vitreous, with pathologic long-chain C16-ceramides increasing and protective very long-chain C26-ceramides decreasing. The pathologic ceramides generate proinflammatory and proapoptotic ceramide-rich platforms on endothelial surfaces, leading to cell death.[1,2]

After discovering retinal endothelial ceramide as a treatment target, they characterized diabetic retinopathy as a *ceramidopathy* and concluded that early-stage therapy with anti-ceramide immunotherapy may prevent progression of nonproliferative diabetic retinopathy.[2]

1. Researchers examine potential immunotherapy option for diabetic retinopathy [press release]. Eyewire+. June 21, 2024. Accessed July 3, 2024. eyewire.news/news/researchers-examine-potential-immunotherapy-option-for-diabetic-retinopathy
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Eyewire+ Pharma Update

- **PharmAbcine**, a South Korea-based company, received Safety Review Committee approval to evaluate a higher single dose of its wet AMD treatment candidate, PMC-403 (4 mg vs 3 mg in a previous cohort), in a phase 1 trial.
- **Beacon Therapeutics** raised $170 million in Series B funding, which will be used to support the clinical development of its lead asset, laruparetigene zovaparvovec (AGTC-501), for the treatment of X-linked retinitis pigmentosa and to generate more data from its phase 1/2 dry AMD program.
- **The European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP)** delivered a positive opinion for the extension marketing authorization for 6 mg faricimab (Vabysmo, Genentech/Roche) to include treatment of edema secondary to retinal vein occlusion.
- **The EMA's CHMP** adopted a negative opinion on the marketing authorization application of intravitreal pegcetacoplan (Apellis) for the treatment of geographic atrophy.
- **4D Molecular Therapeutics** recently received FDA clearance of its investigational new drug application for 4D-175, an R100 vector-based intravitreal gene therapy for the treatment of patients with geographic atrophy.
- **Ocugen** dosed the first patient in its phase 3 liMeliGhT clinical trial for OCU400, a modifier gene therapy candidate under investigation for the treatment of retinitis pigmentosa. Ocugen also completed dosing in the second cohort of its phase 1/2 GARDian clinical trial for OCU410ST (AAV-hRORA)—a modifier gene therapy candidate for Stargardt disease.

Want more retina news from *Eyewire+*?

THE PORT DELIVERY SYSTEM RE-ENTERS THE MARKET

Genentech/Roche recently announced the reintroduction of its port delivery system (PDS) with ranibizumab (Susvimo) into the US market, following the FDA's approval of the company's post-approval supplement to the biologics license application. The supplement outlines component-level updates to both the implant itself and the refill needle. Additional manufacturing process improvements were also implemented, according to the company.[1]

The PDS, approved by the FDA in 2021, was voluntarily recalled in October 2022 after ongoing reliability testing revealed that the seal of the septum could fail after repeated refills.[2]

With these updates to the implant and refill needle, testing has confirmed that they now meet performance standards, according to the company.[1]

Genentech/Roche also announced the FDA approval of its prefilled syringe for faricimab (Vabysmo) for the treatment of AMD, diabetic macular edema, and retinal vein occlusion.[3] ■

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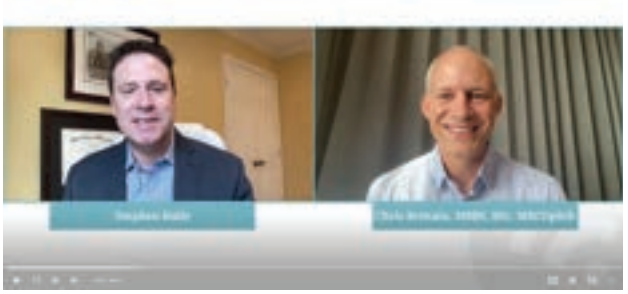


EyewireTV | 07.10.2024

In this episode:
- Genentech Executive Discusses Vabysmo Prefilled Syringe and Susvimo
- J-Code for Glaukos' iDose TR Intracameral Implant Now Active
- Outlook Therapeutics Receives UK Approval for Wet AMD Drug Lytenava

NARINE VIRUNI, MD

WHERE IT ALL BEGAN

I was born and raised in Ukraine and moved to the United States in 2005 during high school. In my early years, I was interested in music and was trained in classical piano. I lived in Los Angeles and attended the University of California, Los Angeles, where I became interested in medicine and majored in physiology. I attended medical school at the University of California, Davis School of Medicine, followed by residency and fellowship at the Johns Hopkins Wilmer Eye Institute.

MY PATH TO RETINA

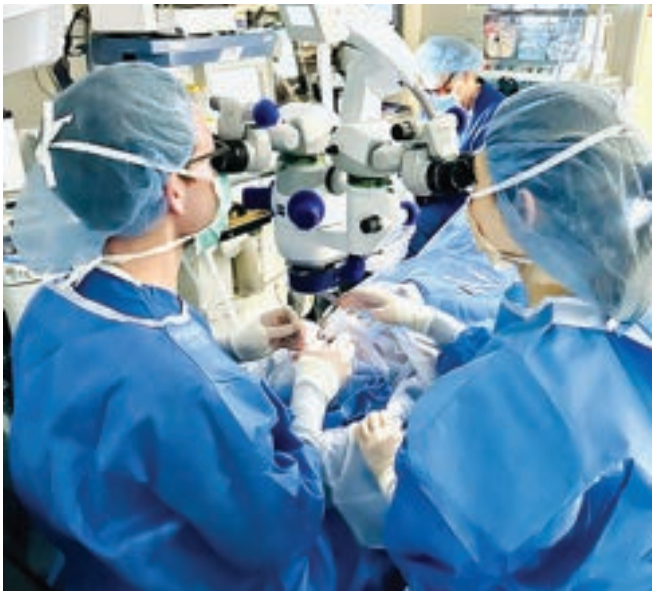
I knew I was going to become a retina specialist a few months into my residency. I found patients with retinal conditions to be the most intellectually stimulating. I enjoyed discussing these cases during retina imaging conferences, where I met Morton F. Goldberg, MD, whose vast knowledge and immeasurable curiousity further inspired me to choose retina as my specialty. I was fascinated by the pathophysiology of retinal diseases and by emerging therapies in our field. I felt that retina was going to boom with exciting new medical and surgical treatments for blinding diseases, and I was excited to be part of that over the course of my career.

SUPPORT ALONG THE WAY

One of my mentors in fellowship was Neil M. Bressler, MD, a dedicated educator and trainee advocate, who always found time, despite his incredibly busy schedule, to discuss patient cases and research projects and provide career and life advice. James T. Handa, MD, was my surgical mentor whom I continue to turn to for advice on tough surgical cases. He also advocated on my behalf and supported me in my personal life. I could not be more grateful for their mentorship and friendship.

AN EXPERIENCE TO REMEMBER

The most memorable experience of my career was spending a year at the Wilmer Eye Institute following my residency and fellowship training to teach and mentor residents as an assistant chief of service. I shared this role with my co-resident and dear friend, Kapil Mishra, MD. We had an invaluable time teaching residents in the clinic and OR, learning from each other, and taking care of many retinal emergencies and trauma patients. This was a year of incredible professional and personal growth for me, and I hope my residents learned as much from me as I learned from them. ■



Dr. Viruni's advice: Always have your moral compass aligned, and do what is best for the patient. Be open to learning new or different ways of doing things. Stay in touch with your mentors, and have a group of trusted colleagues you can turn to for advice. Finally, know what you want in your career, but also be flexible enough to embrace new opportunities.

Narine Viruni, MD, is a retina specialist at the Retina Consultants of Southern Colorado in Colorado Springs, Colorado. She sees a variety of medical and surgical pathology primarily in adult patients, and she participates in numerous clinical trials.

Dr. Viruni is a consultant for Abbvie and Regenxbio. She can be reached at **narine.viruni@gmail.com.**

DEBATES AND CASES AT VBS 2024


Experts shared their clinical experiences and discussed hot topics in retina.

BY KAREN WAI, MD, AND JARED EBERT, MD

The 2024 Vit-Buckle Society (VBS) meeting, held in Miami Beach, Florida, April 4-6, exceeded expectations with its innovative surgical videos, lively debates, and vast educational opportunities. Here, we highlight the surgical cases and medical retina debates.

SURGICAL CASE SESSION IN BRIEF

The Friday morning surgical case session, moderated by Philip J. Ferrone, MD, and Adrienne W. Scott, MD, included an array of exceptional and complex surgical cases.

Ahmed Mansour, MD, MSc, began by noting that funnel retinal detachments (RDs) can be challenging, especially if they present after trauma, and that these cases often have poor outcomes. The optimal time to intervene is 7 to 10 days following the initial injury or closure, he said, but the decision to intervene remains a matter of debate.

He presented two cases of funnel RDs, through which he demonstrated several techniques, including a hand-over-hand technique to remove subretinal proliferative vitreoretinopathy (PVR) and napkin ring fibrosis; the use of chandeliers provides adequate visualization, and radial cuts help to relax and flatten the retina.

Next, Durga S. Borkar, MD, MMCi, highlighted a case of a 72-year-old man who had multiple large posterior retinal breaks and PVR after an initial RD repair with vitrectomy. After peeling the PVR membranes and performing a retinectomy, a large macular break remained. Dr. Borkar placed an amniotic membrane over the large break using a bimanual technique, and the patient did well. However, 2 years later, the amniotic membrane had contracted, which prompted a vibrant discussion regarding how to orient the amniotic membrane, whether methotrexate would be useful, and the best next steps.

Juan Carlos Gutierrez Hernandez, MD, presented the case of a 38-year-old man he treated after a motor vehicle accident. Initially, the team thought the patient had vitreous hemorrhage after a scleral wound repair. However, at the time of vitrectomy, they found a large glass intraocular foreign body. Dr. Gutierrez Hernandez used 0.12 forceps to remove the object through a scleral wound, and the patient did well with a postoperative BCVA of 20/40.

Image courtesy of Kevin Caldwell Photography

Figure 1. Dr. Budoff explains the laser-lock technique with Drs. Ferrone and Scott.

Christopher G. Fuller, MD, stunned the audience (as he usually does) with a one-of-a-kind video that focused on the changes he experienced after the private equity acquisition of his ambulatory surgery center. Some examples included more difficulties with adding on late cases, limitations in the use and selection of instrumentation, and the required use of off-brand preoperative dilating drops.

Greg Budoff, MD, showed off his use of the laser-locking technique to address postoperative IOL tilt (Figure 1). He used the laser on a continuous setting through an anterior paracentesis to laser the optic-haptic junction. He said a grayish discoloration at the edge of the haptic indicates that the junction is locked into a new planar configuration, resolving the IOL tilt.

Hasenin Al-khersan, MD, presented the case of a patient with a large metallic intraocular foreign body, which he removed using an anterior approach. Anterior vitrectomy, lensectomy, and a core vitrectomy revealed a focal rhegmatogenous RD. He used dispersive viscoelastic on the corneal surface to assist with deturgescence and removal of the corneal epithelium, as well as cohesive viscoelastic in the anterior chamber to further assist with deturgescence. Despite these challenges, the RD was successfully repaired.

Ninel Z. Gregori, MD, described a chorioretinal biopsy technique using a 19-gauge blunt-ended needle. During vitrectomy, she uses a laser to demarcate the area of retinal biopsy and separates the retina from the underlying retinal

pigment epithelium with a subretinal cannula. She uses vertical scissors to cut along the laser line, leaving a small hinge of tissue. She then creates a sclerotomy and uses the blunt, unfiltered 19-gauge needle on a 3-cc syringe to gently aspirate the retinal sample.

Next, she uses intravitreal diathermy to cauterize the choroidal vessels at the edges of the biopsy site, excises the intended portion of the choroid with vertical scissors, and uses the 19-gauge blunt-ended needle to remove the choroidal sample with gentle aspiration.

Vinay A. Shah, MD, presented a four-port vitrectomy technique that gives the attending physician access to the intraocular space through a fourth cannula. With this technique, the operating fellow maintains control of two instruments through the superior cannulas, and the attending can provide direct and physical instruction intraoperatively. Dr. Shah also mentioned that as the fellow becomes more comfortable with the four-port technique, the attending can hold the light pipe through one of the cannulas, and the fellow can then hold two non-illuminated instruments.

Patrick C. Staropoli, MD, wrapped up the surgical case session with a case of a patient with a recurrent PVR-associated RD. Intraoperatively, there was a large subretinal plaque beneath the inferior arcade, requiring him to venture into the subretinal space to gain access to the plaque. Using the light pipe and forceps, he lysed the adhesions between the subretinal plaque and underside of the retina, leading to adequate retinal laxity and mobility. Two weeks later, the retina was attached.

MEDICAL RETINA DEBATES

In the first debate, Marianeli Rodriguez, MD, PhD, argued that faricimab (Vabysmo, Genentech/Roche) was the best long-acting agent and listed the advantages of inhibiting both the Ang-2 and VEGF pathways with the drug, which has been associated with reduced vascular leakage and inflammation compared with traditional anti-VEGF agents.

In patients with diabetic macular edema, Dr. Rodriguez noted faricimab's superiority in drying the retina, as well as a significant decrease in central subfield thickness, which was maintained through 2 years. She also pointed out the lack of a single report of retinal vasculitis over the 2-year period. Dr. Rodriguez's arguments were supported by her personal experience extending the interval between injections when switching patients from aflibercept (Eylea, Regeneron) to faricimab.

Merina Thomas, MD, argued for 8 mg aflibercept (Eylea HD, Regeneron), highlighting the extensive experience retina specialists have with the drug and its long-standing safety profile. She presented the results of the PULSAR and PHOTON trials and noted that there is no clinically meaningful difference in IOP when injecting 0.07 cc (8 mg aflibercept) versus 0.05 cc (2 mg aflibercept).

Image courtesy of Kevin Caldwell Photography

Figure 2. Dr. Thomas celebrates her victory during the medical retina debate about which long-acting anti-VEGF agent is best. She is joined on stage by session moderators Dimitra Skondra, MD, PhD, and Ajay E. Kuriyan, MD, as well as her opponent, Dr. Rodriguez.

Both speakers discussed the excellent safety profile of these agents and recommended thoughtful patient selection based on individual needs. The audience voted narrowly in favor of Dr. Thomas and 8 mg aflibercept (Figure 2).

The next medical retinal debate was on the emerging treatment choices for geographic atrophy (GA). Ella Leung, MD, discussed pegcetacoplan (Syfovre, Apellis) and the OAKS/DERBY trial data and dosing flexibility. Dr. Leung highlighted the longer follow-up and larger number of clinical trial participants compared with avacincaptad pegol (Izervay, Iveric Bio/Astellas), as well as the ability to decrease GA progression by as much as 42% compared with 14% with avacincaptad pegol. She also touched on the microperimetry data, photoreceptor loss, and retinal pigment epithelium cell loss in the clinical trials and the low risk of optic neuropathy, occlusive vasculitis, and endophthalmitis.

Sruthi Arepalli, MD, discussed avacincaptad pegol and the results of the GATHER clinical trials. She highlighted the known risk of retinal vasculitis with pegcetacoplan, stating that avacincaptad pegol may be safer than pegcetacoplan and more effective than observation. She referenced the ASRS Research and Safety in Therapeutics Committee report, detailing 13 cases of retinal vasculitis in patients after their first injection of pegcetacoplan.

Finally, Nicolas A. Yannuzzi, MD, argued for the observation of GA. Dr. Yannuzzi pointed out the risk of conversion to wet AMD with both medications and the increased treatment burden for patients who develop wet AMD. He highlighted the treatment burden of these medications in general and discussed the risk of intraocular inflammation and the lack of proven functional benefit. Dr. Yannuzzi noted the high dropout rates of 20% to 30% in the OAKS/DERBY studies and 20% in GATHER2, further underscoring his concerns about treatment efficacy and patient adherence.

The audience agreed with Dr. Yannuzzi, making him the debate winner.

During the third debate, Safa Rahmani, MD, MS, argued for the need to treat choroidal neovascular membranes and diabetic macular edema in pregnant patients according to standard protocol. Dr. Rahmani noted the lack of proven

adverse effects of anti-VEGF agents in pregnancy and the retrospective reports that demonstrate no increased detrimental effects compared with the general population in these patients. She also emphasized the systemic safety of anti-VEGF agents in infants with retinopathy of prematurity.

Irena Tsui, MD, shared reasons to avoid using anti-VEGF agents in patients who are pregnant. She outlined the adverse effects seen in animal studies and noted that the package inserts suggest potential harm of these agents in pregnancy. She highlighted the importance of VEGF in pregnancy/placental physiology and the reports of adverse pregnancy outcomes in patients undergoing anti-VEGF injections in the first trimester.

The audience chose Dr. Rahmani as the winner of the debate by a small margin, voting 55% in favor of the use of anti-VEGF agents in pregnancy.

The last medical retina debate ventured in a very different direction, and Nitish Mehta, MD, shared the experience of a whole-eye transplant at New York University. He emphasized the retinal perfusion seen through postoperative fluorescein angiography. Further, he suggested that whole-eye transplant could serve as a feasible method of addressing many causes of blindness for which there is no treatment.

Frank L. Brodie, MD, MBA, argued against whole-eye transplant, citing the lack of innovation in neuroprotection and the current lack of functional outcomes data. He spoke about the necessary research into optic nerve regeneration and other innovative research that is lacking. Dr. Brodie cited the more than $100 million that the National Institutes of Health has spent on neuroregeneration research, the more than $550 million spent on neuroprotection research in general, and the lack of clinically actionable progress that has been made through this work.

The debate winner, by a large margin, was Dr. Brodie. ■

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SAVE THE DATE: MARCH 20-23, 2025
Austin, Texas
13th Annual Vit-Buckle Society Meeting

DUKE fAVS 2024: 10 YEARS OF EDUCATION

Experts gathered to educate fellows on the latest innovations and techniques.

BY MUSTAFA IFTIKHAR, MD; VENKATKRISH KASETTY, MD; YUXI ZHENG, MD; AND S. TAMMY HSU, MD

The 10th anniversary of the Duke fellows Advanced Vitreous Surgery (fAVS) Course, held March 22-23, 2024, in Durham, North Carolina, started off with a warm welcome from the course director, Lejla Vajzovic, MD, who commemorated Duke University's rich heritage of vitreoretinal surgery and the institution's dedication to education and innovation (Figure 1). This year, the Duke fAVS Course included 112 residents and retina fellows, 11 of whom traveled from outside the United States to participate.

Image courtesy of Kevin Caldwell Photography

Figure 1. Dr. Vajzovic opened with a brief history of Duke's long-standing commitment to the field of retina and a glimpse at how the fAVS Course has grown over the years.

DAY 1 EDUCATION

The conference commenced with a session on the recent advances in pharmacotherapies. Prithu S. Mettu, MD, and Michael J. Allingham, MD, PhD, discussed the treatment landscape for wet AMD and diabetic eye disease, including newer agents in the pipeline. Eleanora G. Lad, MD, PhD, then educated attendees on the emerging use of complement inhibitors for geographic atrophy, such as pegcetacoplan (Syfovre, Apellis) and avacincaptad pegol (Izervay, Iveric Bio/Astellas). She also gave attendees a peek at promising therapeutics under investigation.

Judy E. Kim, MD, FARVO, FASRS, led an informative talk on the role of biosimilars and the challenges retina specialists face with their use, such as navigating step-therapy requirements. Dr. Vajzovic provided a comprehensive update on gene therapies for retinal diseases, touching on everything from various delivery methods to target diseases, promising viral vectors, and more.

This was followed by two enlightening lectures on AI presented by Glenn J. Jaffe, MD, and Daniel S.W. Ting, MD, PhD. They talked about the current and expanding role of AI in ophthalmology—for both clinical practice and research applications.

Yannek I. Leiderman, MD, PhD, shared invaluable insights on how to prepare for the OR, optimize surgical performance, and handle complications and challenging situations as they arise. This was complemented by a talk by Caroline R. Baumal, MD, on best practices for office-based procedures, such as intravitreal injections.

The second half of the morning focused on advances in retinal subspecialties, including uveitis, ocular oncology, and inherited retinal diseases, with lectures by Ramiro S. Maldonado, MD; Prithvi Mruthyunjaya, MD, MHS; Miguel A. Materin, MD; and Sumit Sharma, MD.

The morning concluded with an expert panel that offered wisdom and pearls regarding medical retina cases and best clinical practices. Moderated by Dr. Allingham, the panel—including Drs. Mruthyunjaya, Maldonado, Lad, Sharma, and Ting; Stefanie G. Schuman, MD; John B. Miller, MD; Frank Brodie, MD, MBA; and Sharon Fekrat, MD, FASRS—explored several cases and offered insights into the various treatment options (Figure 2).

Before breaking for lunch, the audience heard from

Image courtesy of Kevin Caldwell Photography

Figure 2. The medical retina case panel was a collegial discussion between (left to right) Drs. Mruthyunjaya, Maldonado, Miller, Lad, Sharma, Brodie, Fekrat, Schuman, and Ting.

the 2023 Robert Machemer, MD, and International Retinal Research Foundation Fellowship winner, Charles DeBoer, MD, PhD. He discussed the process of inventing an extended drug delivery device that uses the lens capsule.

The afternoon sessions began with Kourtney H. Houser, MD, describing secondary IOL fixation techniques. She prefers the AR40 lens (Johnson & Johnson) when using scleral fixation, and she highlighted the importance of fixating the haptics 180° apart to reduce the risk of lens tilt.

Xi Chen, MD, PhD, then described approaches to tackle the pediatric hyaloid. Often, there is another layer in younger patients, even if you think the hyaloid has already been lifted. In pediatric retinal detachments (RDs), more than one surgery may be necessary, and it is important to discuss this with the patient and their family preoperatively. In pediatric tractional RDs (ie, secondary to retinopathy or familial exudative vitreoretinopathy), the goal of the surgery is to relieve the traction, although the hyaloid may not be able to be lifted.

Durga S. Borkar, MD, MMCi, then discussed the role of early vitrectomy for diabetic retinopathy-related vitreous hemorrhage, followed by Dr. Miller providing tips for optimizing 3D heads-up display during vitreoretinal surgery. Dr. Sharma then discussed pearls for addressing uveitic RDs, emphasizing the importance of pre- and postoperative inflammation control and supplementation with a scleral buckle if the break cannot be visualized. In patients with outer retinal and choroidal inflammation, subretinal membranes should be identified and carefully removed.

Leo Kim, MD, PhD, and Carl D. Regillo, MD, discussed the mechanisms of proliferative vitreoretinopathy formation and its management. Dr. Regillo's current approach involves vitrectomy, membrane peeling, endolaser, and silicone oil with oil removal within 3 to 4 months. Dr. Regillo and Cynthia A. Toth, MD, then moderated a surgical rounds panel that walked attendees through the various surgical approaches to many interesting cases.

The day ended with real-world discussions of transitioning from trainee to teacher (by Dr. Baumal) and how to navigate the path after fellowship (by Dr. Mruthyunjaya). High-yield tips were shared to secure your dream job, such as preparing a plan to share with future employers that ties back to your prior clinical and research experiences.

SATURDAY WET LAB EXPERIENCE

One of the staples of the Duke fAVS Course is the wet lab, which provides the opportunity to learn from faculty and try out new techniques. This year, the lab was divided into five rooms and included 16 different stations, allowing fellows and trainees to experience various vitrectomy systems on both model eyes and pig eyes (Figure 3).

Dr. Borkar and Ellie Zhou, MD, led a secondary IOL implant station where trainees could practice their Yamane and scleral-suturing techniques. The next room housed Drs. Chen and Leo Kim teaching PFO-silicone oil exchange. Drs. Baumal, Judy Kim, and Miller provided trainees tips for epiretinal membrane peeling using model eyes. Fellows were encouraged to try various forceps when performing the peeling. In another room, Dr. Jaffe assisted trainees in performing subretinal biopsies, while close by, Dr. Toth showcased Duke's intraoperative OCT and hand-held OCT systems. Drs. Mruthyunjaya and Ting demonstrated the Zeiss intraoperative OCT and 3D visualization system, and Drs. Regillo and Sharma manned the solo-surgery station, using the lighted scleral depressor to perform surgery without an assistant. Drs. Leiderman and Brodie taught at the subretinal injection station. A different room housed a virtual reality surgical simulation for the implantation of the port delivery system (Susvimo, Genentech/Roche) led by Dr. Fekrat, and the last room included the Navilas computer-guided laser and an in-home OCT system.

In addition to these stations, others included models for performing suprachoroidal injections, the Beyonics One virtual reality exoscope (BVI), and various intravitreal implants. This year's lineup of amazing guest faculty, many industry partners, and the latest and greatest technology made the wet lab a huge success.

SATURDAY SESSIONS

Saturday was also brimming with medical retina education. While half of the attendees checked out the wet lab, the other half dove into distinct aspects of the field.

Oleg Alekseev, MD, PhD, delivered a primer on the utility of genetic testing in diagnosing inherited retinal diseases. He discussed various testing methods, illustrating their relevance with compelling differential diagnoses spanning conditions such as pseudoxanthoma elasticum versus Stargardt disease, Bardet-Biedl syndrome versus retinitis pigmentosa, and Batten disease versus Leber congenital amaurosis.

Dr. Allingham then discussed the intricacies of managing retinal vein occlusion, offering guidance on treatment modalities and strategies for cases resistant to standard anti-VEGF therapies. The engaging lectures continued, covering

DUKE fAVS COURSE

Images courtesy of Kevin Caldwell Photography

Figure 3. The wet lab was packed with advanced technology, one-on-one instruction, hands-on learning, and a lot of fun.

topics ranging from the contentious domain of biosimilars and foundational insights into retinoblastoma, to updates on clinical trials for uveitis, advances in autoimmune retinopathy research, and dry AMD. Esteemed moderators and speakers, including Arpita S. Maniar, MD; Amol A. Sura, MD; and Drs. Maldonado and Schuman graced the stage to lend their expertise.

In the afternoon, participants reconvened for two pivotal segments: a panel discussion on career development and practice insights post-fellowship, followed by a showcase of fellow surgical videos. The career panel, featuring Drs. Fekrat, Judy Kim, Leo Kim, Brodie, and Toth, offered invaluable wisdom gleaned from their professional journeys. The group discussed the realities of clinician-scientist roles, the intricacies of innovation, and career advancement strategies.

The day culminated in fellow video presentions, sparking vibrant discussions among panelists, including Drs. Borkar, Vajzovic, Jaffe, Baumal, Brodie, Judy Kim, Leiderman, Miller, and Ting, reminiscent of the collaborative spirit embodied by the Duke Machemer rounds. The conference concluded with a convivial dinner designed to foster camaraderie among attendees and speakers alike. ■

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11th Annual Duke fAVS Course and
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PEDIATRIC RETINAL DETACHMENT ASSOCIATED WITH FEVR


Pearls for managing this condition in the OR.

BY VISHAL AGRAWAL, MD, FRCS, AND AYUSHI GUPTA, MS

Familial exudative vitreoretinopathy (FEVR) is a heritable vitreoretinal disorder characterized by abnormal retinal angiogenesis.[1] FEVR is generally bilateral and asymmetric with a mean age of presentation of 6 to 8 years of age.[1-3] Incomplete peripheral retinal vascularization and subsequent retinal ischemia are the hallmark features of FEVR.[3,4] The resultant hypoxia promotes abnormal neovascularization, which, over time, results in secondary complications such as neovascularization, vitreoretinal traction, peripheral fibrovascular proliferation, macular ectopia, subretinal and intraretinal exudation, retinal folds, vitreous hemorrhage, and retinal detachment (RD; Figures 1 and 2).[2-6] Surgical management of FEVR with scleral buckling (SB), vitrectomy, or both has a reattachment rate of 85.5% with promising visual outcomes.[7]

UNDERSTANDING THE PATHWAYS

The Wnt signaling pathway regulates retinal development, maintenance, and repair in the eye.[8,9] This norrin-driven pathway promotes the development of normal capillary beds with non-fenestrated vessels, and when the pathway breaks down in FEVR, the capillary beds are impaired. This leaves an underdeveloped eye and creates a large area of avascular peripheral retina with an impaired Wnt pathway. All forms of FEVR exhibit some degree of blood-retina barrier breakdown; some will have very poor tight junctions, ischemic drive, and continued exudation, while others may also have frank bleeding and neovascularization.[8,9]

ROLE OF IMAGING AND ANGIOGRAPHY

Widefield imaging allows more detailed views of the retinal periphery, which is particularly beneficial in pediatric retinal pathologies, such as retinopathy of prematurity, Coats disease, and FEVR (Figures 3 and 4). Fluorescein angiography (FA) is essential for accurate diagnosis and successful treatment of patients with FEVR, as many signs appear in the peripheral retina. Peripheral retinal nonperfusion, vessel pruning, avascularity, neovascularization, straightening of vessels, and peripheral vascular anastomoses are typical retinal vascular findings that can be demonstrated on widefield FA. Importantly, FA is useful to guide treatment. It helps to identify the border between the vascular and avascular retina better than fundus visualization alone. It also aids in better defining complete retinal ablation.

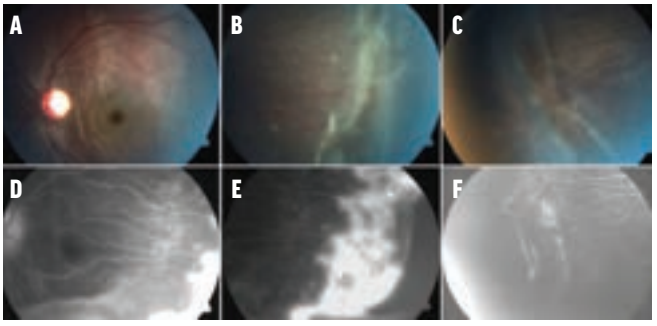


Figure 1. FEVR macula-off RRD with peripheral retinal avascularity and neovascularization can be seen on fundus photography (A-C) and FA (D-F).

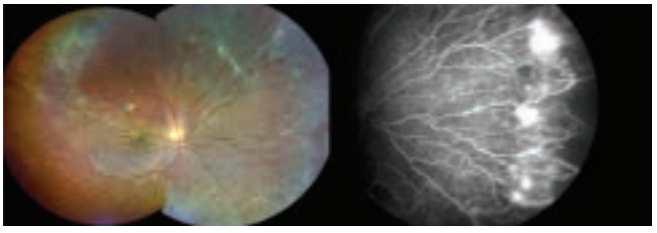


Figure 2. Ultra-widefield color fundus photography and FA demonstrate tractional RD with exudation and peripheral leakage due to neovascularization in a patient with FEVR.

OUR EXPERIENCE

We conducted a prospective interventional study of 14 eyes of 13 children from 5 to 16 years of age with rhegmatogenous RD (RRD) secondary to FEVR and a mean

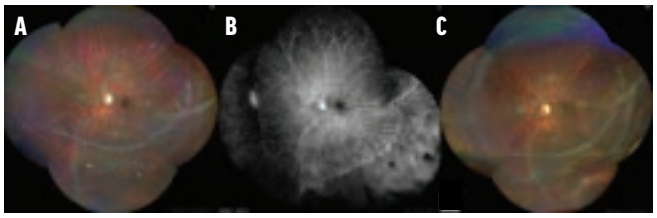


Figure 3. Color montage imaging shows straightening of vessels with peripheral retinal avascularity and localized RD in the inferotemporal quadrant. Pre-SB (A), widefield fundus angiography demonstrates areas of neovascularization nasal to the disc and peripheral avascular areas (B). Status 7 days post-SB (C).

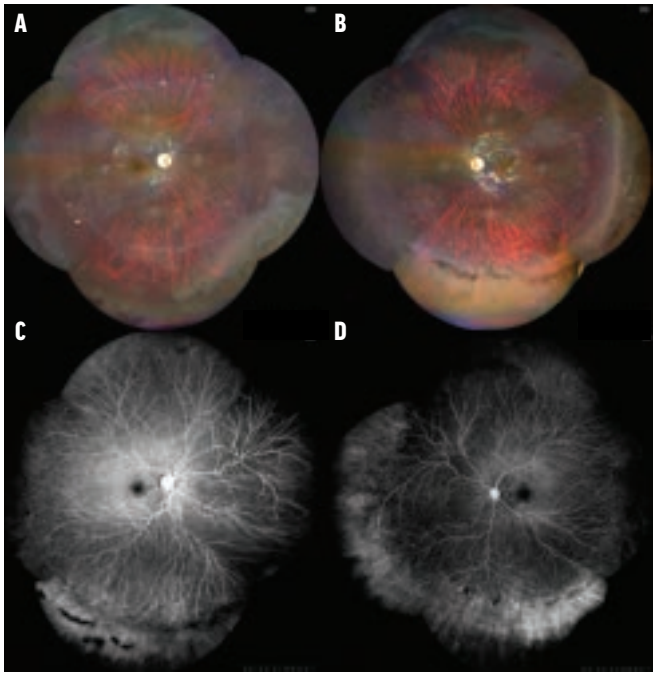


Figure 4. Sibling screening revealed similar findings across both eyes with attached retinas. Color fundus photography (A, B) and widefield angiography (C, D) show straightening of vessels and avascular areas with multiple lattices in the retinal periphery. As the patient had a sibling with RD, both eyes were lasered.

preoperative VA in the surgical eye of 2/60.[10] Diagnosis of FEVR was based on clinical history/examination, FA, and family screening—specifically sibling screening (Figure 4). The diagnostic criteria used to confirm FEVR were: 1) lack of peripheral retinal vascular development in at least one eye, 2) birth at full term or preterm with a disease course incompatible with ROP, and 3) variable degrees of nonperfusion, vitreoretinal traction, subretinal exudation, or retinal neovascularization occurring at any age. The inclusion criteria for the study were: 1) a diagnosis of FEVR, 2) the presence of macula-off RRD, for which the patient underwent surgical intervention, and 3) age ≤ 18 years old. Both eyes of each patient were classified based on the FEVR staging system proposed by Kashani et al.[2]

On fundus evaluation, stage 4A FEVR was noted in six eyes (42.86%), stage 4B FEVR in two eyes (14.28%), and

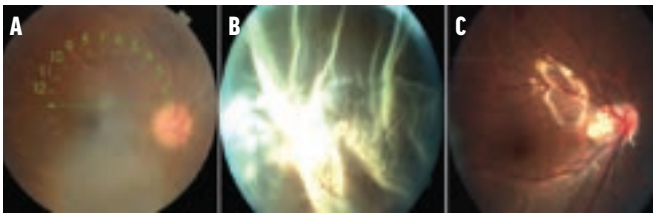


Figure 5. Fundus photos of patients with FEVR and RRD demonstrate the absence of macular drag in one case (A) and proliferative vitreoretinopathy with foveal drag in another (B). After vitrectomy with silicone oil injection in case B, there was complete retinal reattachment (C).

stage 5A in six eyes (42.86%). The fellow eye was phthisical in one patient and normal in another, while stage 1A FEVR was seen in four eyes, stage 1B in one eye, and stage 2A in five eyes.

Surgical Management

The primary objective of surgical management in FEVR is to relieve the anteroposterior and tangential tractions and address the avascular retinal tissue. The intraocular VEGF load can be reduced by a thorough vitrectomy and peripheral retinal tissue ablation using laser photocoagulation. Inducing a posterior vitreous detachment and completing the vitrectomy is critical to relieve the traction on the retina. SB is vital to mitigate the additional peripheral traction.[11] The surgical approach taken depends on the type and location of the RD, as well as the extent of fibrovascular proliferation.

In our study, silicone tires of suitable dimensions along with a 360° encircling buckle were used for patients with less than two quadrants of peripheral retinal proliferation. For patients with at least two quadrant involvement of fibrovascular proliferation or fibrovascular proliferation presence at the posterior pole, a standard three-port, 23-gauge vitrectomy was performed (Figure 5). Triamcinolone acetonide was used for the induction of the posterior vitreous detachment. Extensive vitrectomy was done, especially at the vitreous base and around the fibrovascular proliferative tissues. Careful resection and delamination of the fibrovascular tissue was performed to the maximum extent possible. Retinal reattachment was achieved followed by endophotocoagulation and/or transscleral cryotherapy and silicone oil tamponade. The decision to perform lensectomy was made for patients with fibrovascular proliferation around the ora and/or at the posterior lens surface.

After surgery, the patients were evaluated on day 1, week 1, months 1 and 3, and thereafter every 3 to 6 months, depending on the course of the disease. Silicone oil was removed 6 to 9 months following the primary surgery.

Of the 14 eyes with RRD secondary to FEVR, four (28.57%) underwent SB with silicone oil injection, and the

(Continued on page 36)

TEST YOUR DIAGNOSTIC ACUMEN:
IRD MYSTERY CASES

Can you uncover the cause of each patient's vision loss?

By Sarah J. Garnai, MD; Abigail T. Fahim, MD, PhD; Ronaldo Nuesi, MD; Jesse D. Sengillo, MD; Zachary Kroeger, MD, MS; and Paul Yang, MD, PhD

Retina specialists are experts at spotting the classic signs of AMD and diabetic eye disease. But occasionally, a patient walks in the door with signs and symptoms that have you broadening your differentials and thinking outside the box. The mystery cases presented here are designed to help you hone your diagnostic skills and remember that it isn't rare if it's in your chair.

- Rebecca Hepp, MA, Editor-in-Chief

MYSTERY CASE #1


By Sarah J. Garnai, MD, and Abigail T. Fahim, MD, PhD

A 29-year-old man presented for a routine examination for glasses, where he was found to have uncorrectable vision and cystoid macular edema (CME). He was referred to a retina specialist for further evaluation. His past medical history was significant for sensorineural hearing loss diagnosed at age 6, autism, bipolar disorder, developmental delay, thrombocytopenia, hypothyroidism, Raynaud disease, balance difficulties, and possible nephrolithiasis.

His VA was 20/50 OD and 20/40 OS. Visual field testing demonstrated moderate constriction bilaterally with a cecocentral scotoma in the right eye. Fundus autofluorescence (FAF) showed changes to the fovea and posterior pole in each eye (Figure 1A and B). OCT revealed further retinal changes (Figure 1C and D). Electroretinography demonstrated rod-cone dysfunction, with rods at 25% function bilaterally and asymmetric cone function (60% in the left eye and borderline in the right).

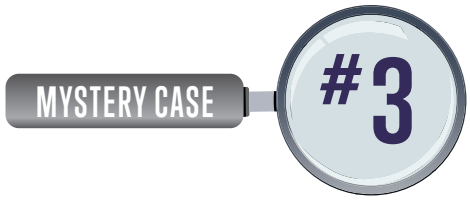
MYSTERY CASE #2


By Ronaldo Nuesi, MD, and Jesse D. Sengillo, MD

A 51-year-old woman with a history of HIV, well controlled on highly active antiretroviral therapy, presented with right-eye redness and pain for 1 day. Her VA was light perception OD and 20/60 OS, which she stated was her baseline. On examination of the right eye, she exhibited 1+ pigmented cell in the anterior chamber, a pale nerve, and retinal changes noted in Figure 2A. In the left eye, she had superior prior laser scars and retinal changes noted in Figure 2B. OCT imaging revealed several findings, including outer retinal loss in the peripheral macula of the left eye (Figure 3). FAF was of poor quality in the right eye but demonstrated a hyperautofluorescent macular ring in the left eye (Figure 4). She had last been seen 10 years prior, at which time she underwent fundus imaging and a full infectious/inflammatory workup that was negative aside from known HIV.

The patient's repeat inflammatory and infectious lab

workup was negative; however, given the presence of bone spicules in the periphery, a hyperautofluorescent ring on FAF, and significant outer retinal loss, an inherited retinal disease was suspected, and genetic testing was performed.



By Zachary Kroeger, MD, MS, and Paul Yang, MD, PhD

A 61-year-old man was referred to our clinic for concern of posterior uveitis. His workup included a complete blood count, comprehensive metabolic panel, erythrocyte sedimentation rate, syphilis testing, tuberculosis serology, and sarcoid markers, all of which were negative. He had an ocular history of wet AMD in each eye and was receiving regular bilateral anti-VEGF injections. Despite regular treatment, he noted a sharp decline in vision in the right eye after his last intravitreal injection 3 months prior. His VA at presentation was 20/50 OD and 20/20 OS with normal IOP.

Fundus examination of the right and left eye was notable for macular drusen and pigmentary changes (Figure 5A and B). FAF of each eye demonstrated areas of hypoautofluorescence with surrounding areas of hyperautofluroescence (Figure 5C and D). Fluorescein angiography (FA) in each eye showed staining of the drusen without leakage (Figure 5E and F). OCT imaging of each eye captured the drusen, pigmentary changes, and ellipsoid attenuation (Figure 6).

He recently underwent an annual physical examination with his primary care physician. Review of systems revealed ongoing hematuria for several years but no other underlying etiology.

RETINAL IMAGING

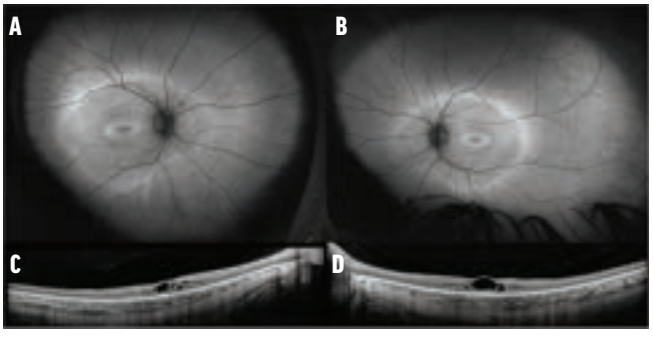


Figure 1. FAF of the right (A) and left (B) eye showed a double hyperfluorescent ring around the fovea and posterior pole bilaterally. OCT of the right (C) and left (D) eye showed a thin retina, severe outer retinal atrophy, bare ellipsoid and outer nuclear layer at the fovea, and schisis-like CME bilaterally.

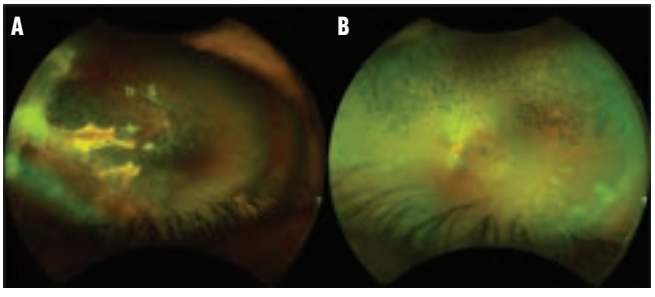


Figure 2. Fundus imaging of the patient's right eye revealed a pale nerve, severe exudation, a tractional retinal detachment, and pigment migration in the periphery (A). The left eye showed superior laser scars, attenuated sclerotic vessels, and an area of inferior pigment migration (B).

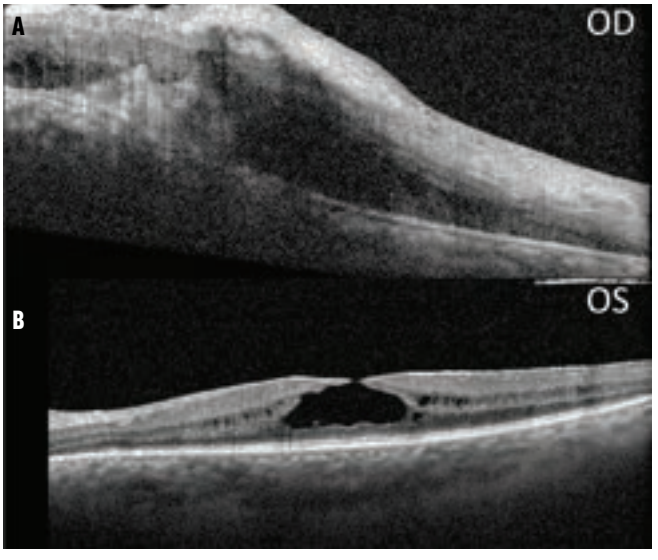


Figure 3. OCT imaging showed foveal dragging with subretinal fibrosis, subretinal fluid, and diffuse outer retinal loss in the right eye (A). The left eye showed peripheral outer retinal loss with a preserved photoreceptor layer centrally, CME, and an early lamellar hole/large cyst in the fovea (B).

FIND THE ANSWERS AND DISCUSSION ON PAGE 22

Find more mystery cases to test your diagnostic skills at *retinatoday.com:*

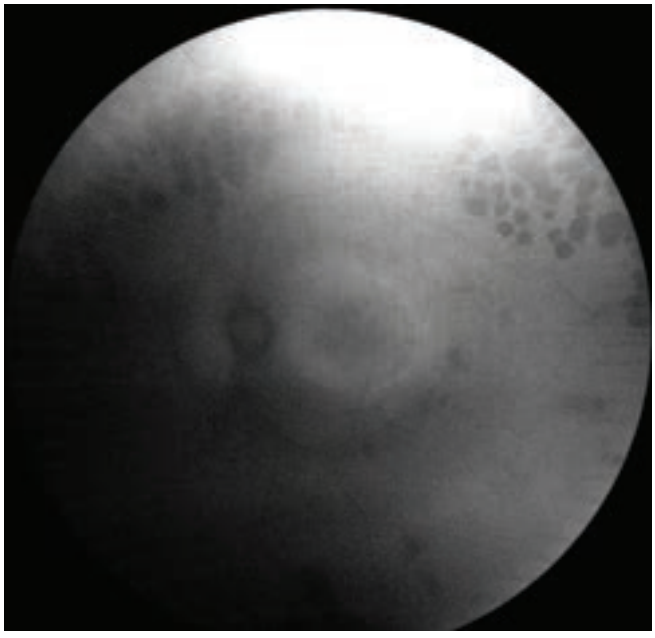


Figure 4. FAF demonstrated a hyperautofluorescent ring in the macula of the left eye.

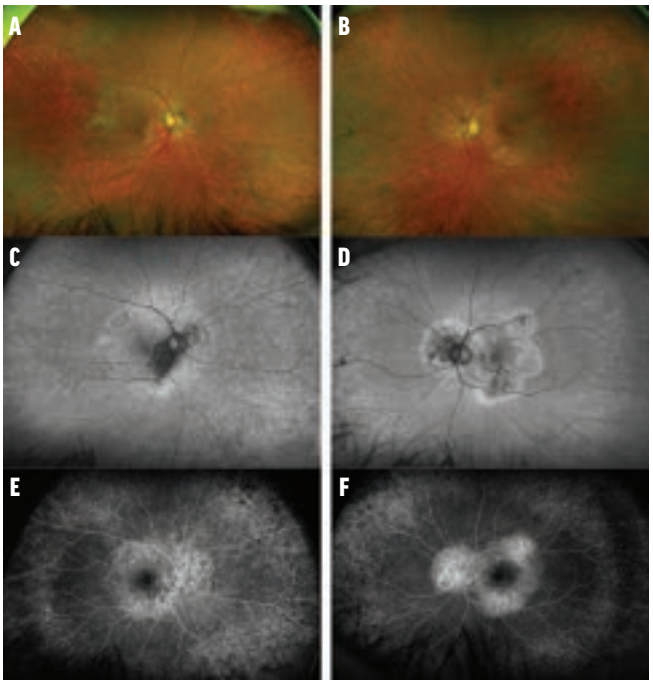


Figure 5. Fundus imaging of the right (A) and left (B) eye showed macular pigment clumping and extensive hard drusen that extended from the macula to the periphery. FAF of the right (C) and left (D) eye showed hypoautofluorescence emanating from the nerves with surrounding areas of hyperautofluroescence. Late frames on FA of the right (E) and left (F) eye showed staining of the macular and peripheral drusen.

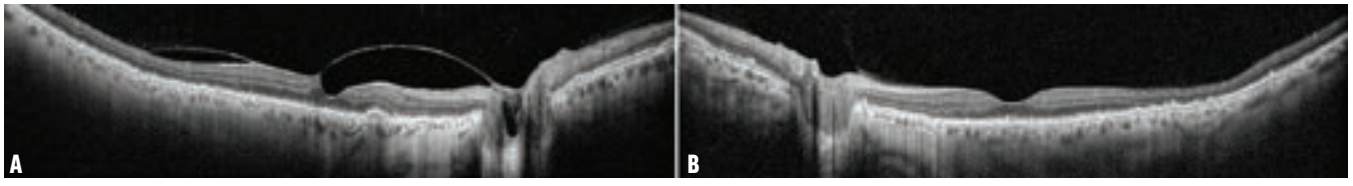


Figure 6. OCT of the right (A) and left (B) eye revealed numerous cuticular drusen, low-lying pigment epithelial detachments, and focal areas of ellipsoid attenuation.

DISCUSSION

Case No. 1: Mucopolysaccharidosis IIIA

Genetic testing was significant for two variants of unknown significance, c.1130G>A(p.Arg377His) and c1186T>C(p.Phe396Leu), in N-sulfoglucosamine sulfohydrolase (*SGSH*), which encodes heparan-N-sulfatase. Homozygous or compound heterozygous mutations in *SGSH* are responsible for mucopolysaccharidosis (MPS) IIIA, also known as Sanfilippo syndrome, an autosomal-recessive lysosomal storage disease that results from impaired degradation of heparan sulfate.[1] Urine mucopolysaccharide testing revealed elevated heparan sulfate, and heparan-N-sulfatase activity in the blood was undetectable, confirming this patient's diagnosis of MPSIIIA despite the technically inconclusive genetic results. These variants were later classified as likely pathogenic in ClinVar.[2]

Patients with MPSIIIA have severe central nervous system involvement, which can include behavioral disturbances, intellectual deterioration, and dementia. Somatic symptoms are relatively mild and include skeletal and joint pathology and hepatosplenomegaly.[3] Ocular manifestations of MPSIIIA include retinopathy with pigmentary retinal degeneration and electroretinography changes and, less commonly, corneal opacification, glaucoma, and optic nerve anomalies.[4]

There is wide phenotypic variability, from severe to attenuated, which has been reported to be correlated with genotype.[5] MPSIIIA frequently leads to early mortality in adolescence or early adulthood; thus, this patient's presentation was relatively mild.

Case No. 2: Retinitis Pigmentosa With Coats-Like Response

Genetic testing identified four variants in the *EYS* gene, of which one was already known to be pathogenic: a heterozygous variant at c.3443+1G>T. With this genetic testing and the constellation of findings, the patient was diagnosed with likely autosomal-recessive retinitis pigmentosa (RP) and a Coats-like response in the right eye. This exudation is thought to be present in up to 5% of RP cases and can present at the initial diagnosis, although it more commonly presents later as the disease progresses.[6] The diagnosis of RP is often made with the combination of clinical examination, patient and family history, and multiple imaging modalities, including FAF, OCT, and electroretinogram.

RP is often diagnosed late and may masquerade as a uveitis-like picture, especially when presenting with CME or a coats-like response. FAF is a useful tool because hyperfluorescent rings are highly suggestive of retinal dystrophies and become smaller as the disease progresses.

There is currently no treatment for *EYS*-associated RP, although the Coats-like exudation has been reported to respond favorably to intravitreal anti-VEGF treatment in some cases.[7,8] The use of oral carbonic anhydrase inhibitors can also be used for RP-associated CME.[9] Genetic and sometimes premarital counseling is recommended for stratifying risk in other family members.

Case No. 3: *CFH*-Associated Early-Onset Macular Drusen

The differential diagnosis included AMD, Sorsby macular dystrophy, dominant drusen (Doyne honeycomb retinal dystrophy), and *CFH*-associated early-onset macular drusen.

Genetic testing revealed a pathogenic nonsense mutation in the *complement factor H* (*CFH*) gene (c.2575C>T; p.Gln859*). Pathogenic variants in the *CFH* gene have been associated with C3 glomerulopathy, atypical hemolytic uremic syndrome, and early-onset macular drusen.[10,11]

The *CFH* gene is responsible for production of the protein complement factor H, which regulates activation of the complement system. Specifically, it protects host cells by downregulating the alternative pathway and limiting the convergence of all pathways through inactivation of deposited C3b on host cell surfaces.[10,11] The early-onset drusen are likely a consequence of complement dysregulation. The drusen are typically basal laminar (or cuticular), have a hard appearance on examination, and may be present as early as the first decade of life. This patient's FA demonstrated a classic drusen appearance, coined *stars-in-sky*. There is one *CFH* variant (Tyr402His) that does not have the phenotype of early-onset macular drusen but instead is thought to increase the retinal pigment epithelium's susceptibility to damage and is a major genetic predictor of AMD.[10,11]

Given his history of hematuria, this patient was referred to a nephrologist for further evaluation. Nephropathy due to *CFH* comes with a poor prognosis, but early detection allows for proper evaluation and access to potential therapies. ■

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NAVIGATING INCONCLUSIVE TESTING IN IRD

The field of genetic testing is constantly changing; here's what you need to know.

By Elizabeth Kellom, MS, CGC, and Kimberly Stepien, MD


The AAO's Task Force of Genetic Testing and the European Reference Network for Rare Eye Disease recommend that all individuals with a presumed or suspected inherited retinal disease (IRD) undergo genetic testing.[1,2] To date, more than 300 causative genes have been identified in IRDs. Emerging genetic testing technologies, such as next-generation sequencing and whole exome sequencing, have led to more accurate IRD diagnoses and reduced testing costs.[3-5]

Although single-gene testing may be sufficient for some diagnoses (eg, *CHM* is the only disease-causing gene for choroideremia), the heterogeneity of IRDs—both the ocular phenotype and underlying genetic causes—makes multigene panels a more logical choice. For example, more than 100 causative genes exist for retinitis pigmentosa, and, in most cases, it cannot be differentiated by phenotype.[1,6] With the advent of next-generation sequencing, multiple genes can be assessed with a single assay.[7]

GENETIC TESTING PEARLS

Before proceeding with genetic testing, clinicians must obtain a comprehensive family history, medical history, ocular examination, and directed ocular imaging. A detailed family history (eg, hearing loss, developmental or cognitive delays, polydactyly, etc) can help establish heritability and determine whether the retinal findings are part of a syndromic disease. These findings should be included in the lab request for genetic testing to aid in the interpretation of results (Figure).

However, an absence of family history is not indicative

AT A GLANCE

- Relevant family ocular and medical history should be included in the request for genetic testing to aid in the interpretation of results.
- A genetic test report may be nondiagnostic because the condition is not genetic, the panel did not include the causative gene, the variant has yet to be classified as disease-causing, or the genetic variant has yet to be discovered.
- Clinicians should consider retesting every 2 to 5 years in patients with a suspected inherited retinal disease with nondiagnostic genetic testing.

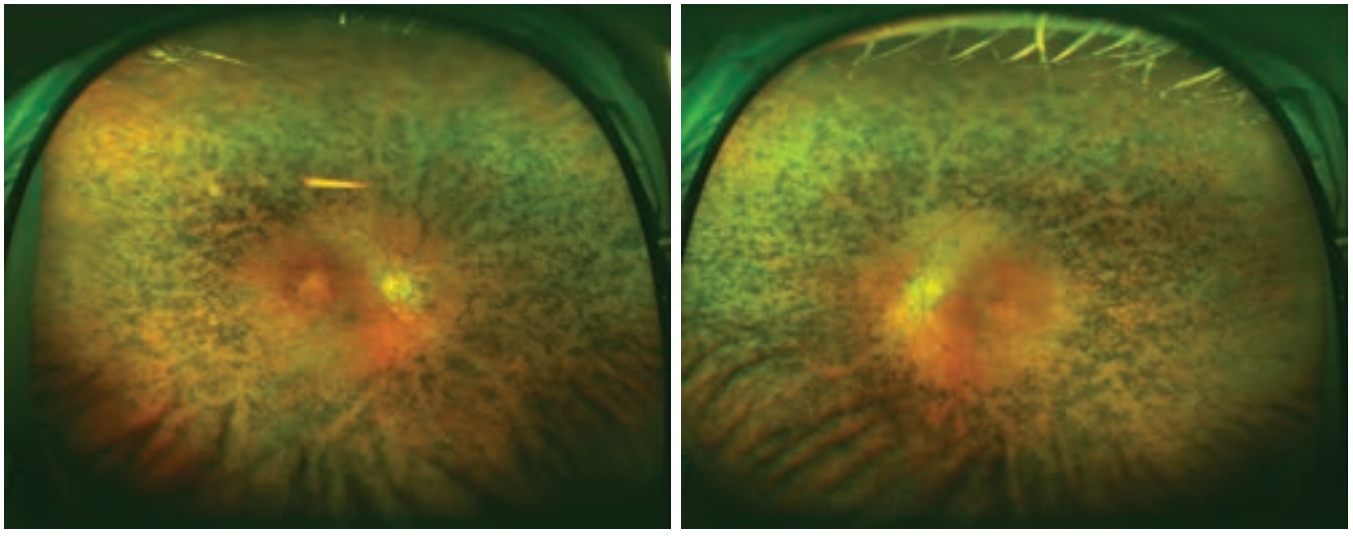

Figure. This patient with congenital hearing loss and progressive vision loss had pathogenic variants in the *MYO7A* gene, consistent with Usher type 1B.

of the likelihood of heritability. The possibility of de novo or recessive variants, limited communication of symptoms within a family, or reduced penetrance can all mask a potential genetic cause.

Patients should undergo genetic counseling to fully understand the benefits, limitations, and possible implications of ocular genetic testing for themselves and their family members. Genetic counseling can ensure accurate interpretation of results, their implications for prognosis, and identification of at-risk family members.

In the United States, telemedicine-based genetic counseling is becoming more prominent, improving access to this important step for community-based retina specialists.

CHOOSING THE RIGHT TEST

The choice of an appropriate IRD gene panel requires careful consideration and can be directed by history and clinical findings in the patient and their family. Testing in the United States should be done in a lab that is CLIA-certified. Certain panels may be more inclusive than others; for example, the panels may include a larger number of genes or genes for associated syndromic diseases such as Joubert syndrome, Bardet Biedl syndrome, or mitochondrial DNA. Some labs have more experience interpreting IRD variances than others, and this, potentially, is reflected in the results. Clinicians must be aware of the potential limitations of the testing to ensure a proper understanding of the potential yield of a diagnostic result, which averages around 60% to 70% (personal data).[3]

Variant interpretation is performed using a five-tier system defined by the American College of Medical Genetics (Table).[8] Variants may be classified as *benign* due to several criteria, including variant frequency in the general population, functional data showing no deleterious effects of the variant on protein function or splicing, or lack of segregation in affected members of a family. *Likely benign* variants are those with an estimated > 90% certainty of being benign; these are typically unreported on standard genetic tests when detected. Pathogenic variants are those with solid evidence of being disease-causing. Variants classified as *likely pathogenic* are those with > 90% certainty of being disease-causing.[8]

A determination of *variant of uncertain significance* (VUS) is used when there is insufficient evidence to fulfill the classification of benign or pathogenic or if the evidence for benign or pathogenic is contradictory.[8] VUSs should be reported with caution and should not be used in clinical decision making.[8] As evidence regarding a variant evolves, VUSs may be reclassified. Thus, clinicians should periodically inquire if a VUS has been reclassified if it is related to the primary phenotype and if the lab has not proactively provided an update.

HANDLING A NEGATIVE TEST IN THE CLINIC

It is discouraging when a genetic test result comes back negative or nondiagnostic, and there are several possible explanations for such results. The retina pathology may not be related to an inherited cause, but rather some other etiology such as trauma, toxicity, inflammation, or infection. Further ocular imaging, patient history, or lab testing may aid in proper diagnosis. A great example of this is a patient with a pigmentary maculopathy associated with long-term pentosan polysulfate sodium use that may mimic an IRD.[9]

However, negative testing does not mean that a patient's condition is not genetic. Every ocular genetic testing panel has limitations, and it is possible the panel did not include the causative gene. Directed further testing after a negative panel can sometimes lead to a diagnosis. For example, in a patient with early-onset hearing loss, diabetes, and macular

TABLE. AMERICAN COLLEGE OF MEDICAL GENETICS GENETIC VARIANT CLASSIFICATION AND INTERPRETATION[8]	
Interpretation Result	**Variant Interpretation**
Benign	Not disease-causing
Likely benign	Unlikely to be disease-causing
Uncertain significance	Insufficient evidence to support or reject variant pathogenicity; further data needed
Likely pathogenic	Likely to be disease-causing
Pathogenic	Disease-causing

degeneration, mitochondrial DNA testing could be pursued to rule out maternally inherited diabetes and deafness. Additionally, complete sequencing of some genes is limited by inclusion or exclusion of intronic regions or complicated by the presence of pseudogenes. A patient with skin laxity, peau d'orange appearance of the retina, and angioid streaks may clinically fit a diagnosis of pseudoxanthoma elasticum, but causal variants in *ABCC6* are detected in just under 90% of cases, likely due to the presence of a pseudogene.[10]

Another factor is that variant classification is a dynamic process. For example, the detection of causal variants is reduced in some genes such as *ABCA4* and *USH2A*.[11] The detection rate improved for *ABCA4* when the variant c.5603A>T (p. Asn1868Ilez), a common polymorphism, was shown to be a risk factor for late-onset Stargardt disease when paired with a disease-causing variant.[12] Previously, this was considered a benign variant and not reported on genetic tests.

A variant or two may be reported that matches the patient's phenotype and suspected mode of inheritance but is still classified as a VUS. In these cases, further clinical testing (eg, an electrooculogram for a *BEST1* variant) or familial testing may provide evidence that could lead to reclassification of the variant. A variant may also be classified as a VUS due to not matching the patient phenotype. However, the understanding of the spectrum of disease related to certain genes changes over time. Neuronal ceroid lipofuscinoses genes, such as *CLN3* and *MFSD8*, have only recently been known to cause non-syndromic retinal disease.[13,14]

It is possible that the causative gene or variant in a known gene has yet to be discovered. As more ocular genetic testing is performed, the number of variants identified continues to grow. Research has also led to the identification of new disease-causing genes.[15]

Clinicians should consider retesting every 2 to 5 years in patients with a suspected IRD with nondiagnostic genetic testing. New testing will be substantially different than previous analyses, and the potential diagnostic utility of this may vary. In all situations, clinicians must coordinate between the patient and a genetic counselor to facilitate appropriate genetic testing.

NEVER GIVE UP

Genetic testing for individuals with an IRD is highly recommended but can come with possible challenges in interpretation. For patients with a presumed IRD, solving the case can potentially be life-changing, as it can direct medical decision making, give peace of mind in understanding of the disease, identify family members at risk, and help guide patients toward any current or emerging clinical trials. ■

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MANAGING IRDS IN THE CLINIC AND THE OR

Here's what we have learned from performing procedures on patients with various inherited retinal diseases.

By Farzad Jamshidi, MD, PhD; Ian C. Han, MD; and Jonathan F. Russell, MD, PhD

Currently, there is only one FDA-approved gene therapy to treat an inherited retinal disease (IRD), voretigene neparvovec-rzyl (Luxturna, Spark Therapeutics) for patients with biallelic *RPE65* disease.[1] Despite many gene and stem cell-based therapies under investigation, all other IRDs remain untreatable for the underlying cause of disease. However, it is important for retina specialists to remember that some patients may still require intervention. We recently reviewed our institutional experience of performing retinal procedures on more than 100 patients with IRDs and found that procedural and/or surgical interventions can be critical.[2]

SECONDARY CHOROIDAL NEOVASCULARIZATION

In our large cohort, the most commonly performed procedure in patients with an IRD was intravitreal injection of anti-VEGF medication for secondary choroidal neovascularization (CNV) in macular dystrophies such as pattern dystrophy, Best disease, and Stargardt disease.

Discerning the presence and activity of secondary CNV in patients with an IRD can be difficult. For instance, the presence of vitelliform deposits in Best disease make fluorescein angiography and OCT difficult to interpret. In an early characterization of Best disease by J. Donald M. Gass, CNV was considered a late-stage finding (ie, after the regression of the vitelliform lesion and the development of atrophy). However, using OCT angiography (OCTA), we have found that earlier stages of Best disease can also have CNV, including 50% of those with a typical vitelliform lesion (Gass stage 2).[3]

OCT characteristics such as focal choroidal excavations and nodular hyperreflective sub-retinal pigment epithelium pillars can hint at the presence of CNV.[4]

One of the most counter-intuitive yet characteristic signs of CNV activity in Best disease is an acute drop in visual acuity accompanied by diminution or resolution of subretinal material/fluid. This differs from most other macular diseases, in which the accumulation of subretinal material/fluid worsens vision. To explain this phenomenon, we proposed that when exudative fluid related to CNV enters the subretinal space, it changes the ionic composition of the subretinal fluid to a level that markedly differs from baseline. While vitelliform deposits tend to be well

AT A GLANCE

- The authors found that the most commonly performed procedure in patients with an inherited retinal disease (IRD) is intravitreal injection of anti-VEGF medication for secondary choroidal neovascularization.
- The second most common procedure for patients with an IRD is intravitreal steroids for the suppression of cystoid macular edema and intraocular inflammation.
- Vitreoretinal surgery in patients with an IRD is typically indicated for the removal of vitreous hemorrhage or retinal detachment repair.

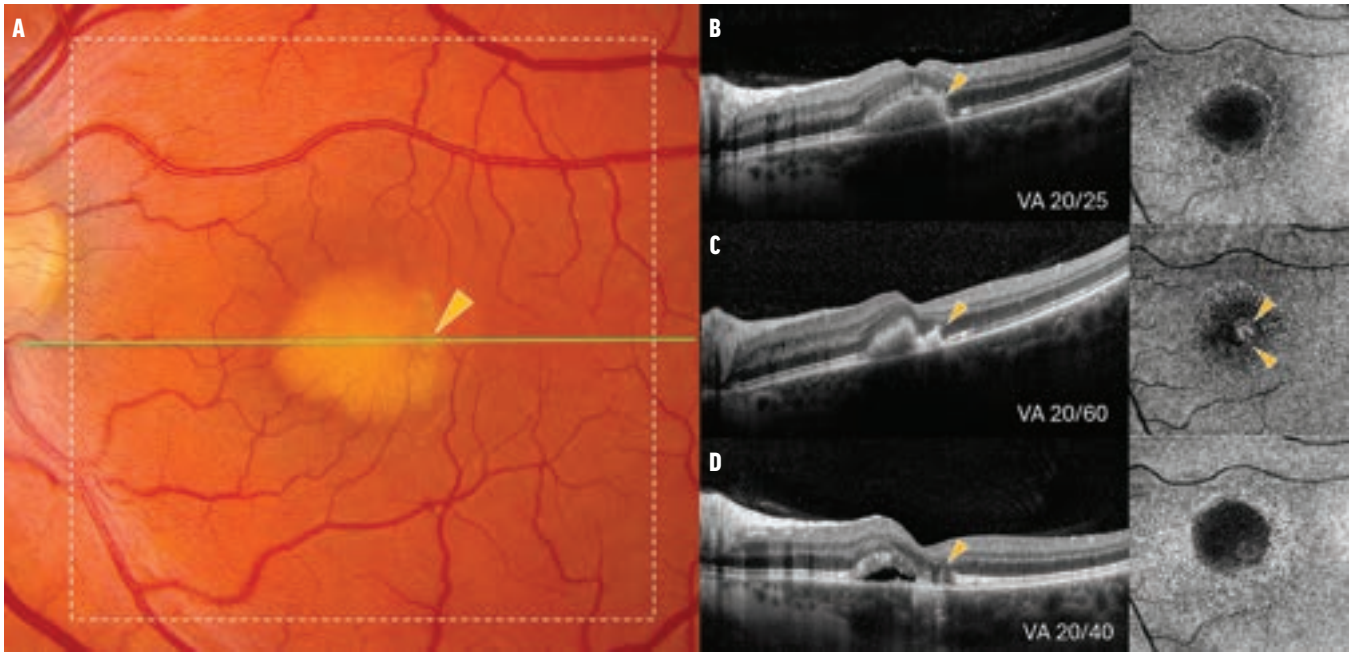


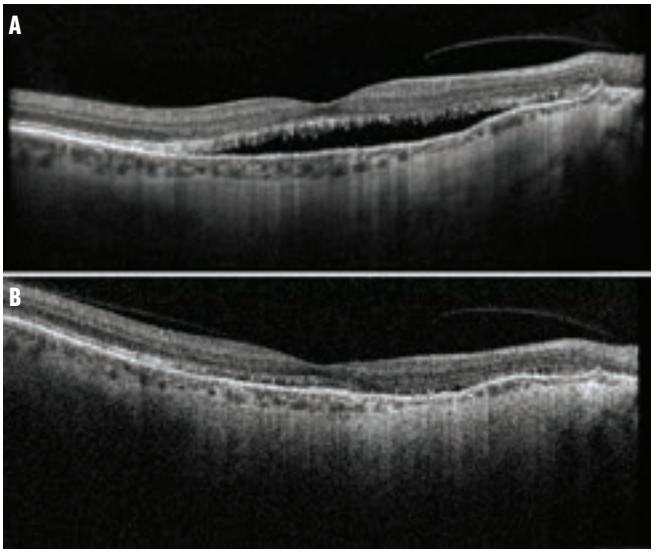
Figure 1. This patient with Best disease was treated with anti-VEGF injections for secondary CNV. Fundus photography showed a subfoveal vitelliform lesion (A, arrow). Baseline OCT confirmed the vitelliform lesion (B, arrow), and swept-source OCTA showed no apparent CNV. An acute decline in visual acuity coincided with partial collapse of the vitelliform material and a new hyperreflective sub-retinal pigment epithelium pillar (C, arrow), while OCTA showed new CNV. After anti-VEGF injection, the lesion regressed (D, arrow) with improved visual acuity and reconstitution of the vitelliform material as a paradoxically positive prognostic sign.

tolerated by photoreceptors, subretinal fluid from CNV is not, resulting in acute visual acuity decline. CNV activity reduces the amount of subretinal hyperreflective deposits, which return (along with visual acuity) after anti-VEGF injections cause CNV quiescence. Multiple injections may be required to see a complete rebound of subretinal material/fluid and vision, and the process can repeat itself later. Through careful monitoring and timely anti-VEGF injections, vitelliform lesions can sometimes be nurtured for years, avoiding the atrophic stage of Best disease and preserving vision (Figure 1).[3]

Similarly, in pseudoxanthoma elasticum (PXE), subretinal fluid may be present as a part of the disease process and is often not indicative of the presence of, or leakage from, CNV.[5] Fluctuation and resolution of subretinal fluid can be observed in PXE without intervention (Figure 2). Like Best disease, a reduction in visual acuity, rather than the appearance of or changes in subretinal fluid, can hint at CNV activity and a change in the composition of the subretinal milieu in PXE. Similar phenomena can occur in patients with cuticular drusen.[6] Thus, clinicians should not reflexively begin intravitreal anti-VEGF injections for any new subretinal fluid in patients with macular dystrophies, especially if there is no decline in visual acuity.

INTRAOCULAR INFLAMMATION

In our cohort study, the second most common procedure for patients with an IRD was intravitreal steroids



Images courtesy of stonerounds.org

Figure 2. In this patient with PXE, the presence of subretinal fluid was not associated with active CNV on examination, OCT (A), or OCTA. Four years later, without any interventions, the fluid reduced spontaneously (B).

for the suppression of cystoid macular edema (CME) and intraocular inflammation.[2] We used this modality primarily in autosomal-dominant neovascular inflammatory vitreoretinopathy, a very rare condition featuring retinal degeneration with progressive and relentless intraocular inflammation, CME, neovascularization of the retina and iris, vitreous hemorrhage, fibrosis, and tractional retinal

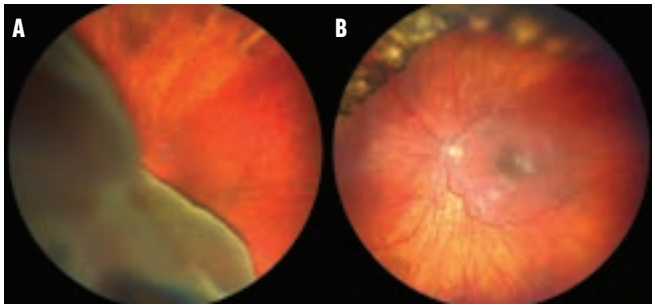


Figure 3. Widefield fundus photography of the left eye of a young girl who presented with a VA of hand motion revealed a retinal detachment and a 7-clock-hour giant retinal tear, resulting in a folded retina nasally (A). After surgical repair with vitrectomy, scleral buckle, and silicone oil followed by secondary cataract surgery with oil removal, she regained a VA of 20/50 (B). Molecular investigation revealed a pathologic variant in *COL2A1* consistent with Stickler syndrome.

detachments.[7] Injectable steroid implants can provide longer-term control of uveitis, neovascularization, and CME. However, retinal fibrosis tends to continue and eventually requires vitreoretinal surgery.[8] We do not advocate intravitreal steroids for CME or low-grade intraocular inflammation in more typical forms of IRD.

HEMORRHAGE AND DETACHMENTS

Vitreoretinal surgery in patients with an IRD is typically indicated for the removal of vitreous hemorrhage or retinal detachment repair (9.5% of patients with an IRD requiring a procedure in our cohort).[2] Inherited vitreoretinopathies—including Stickler syndrome, Knobloch syndrome, and familial exudative vitreoretinopathy—often feature rhegmatogenous and/or tractional retinal detachments because of collagen composition defects or anomalous vascular proliferation (Figure 3). In X-linked retinoschisis, non-clearing vitreous hemorrhage or schisis detachments can occur. Cataract surgery complications such as dropped nuclei or dislocated IOLs are common in retinitis pigmentosa (RP) because of zonular instability. Epiretinal membranes in patients with an IRD are common but are rarely visually significant and can usually be observed.

CATARACTS

As retina specialists, we primarily focus on posterior segment procedures; however, deciding whether cataract surgery is indicated is a common clinical challenge, especially for patients with RP. In general, the preoperative integrity of the ellipsoid zone is indicative of better long-term visual outcomes from cataract surgery.[9] Nguyen et al retrospectively looked at 296 patients with RP who underwent cataract extraction and found that 39% of patients had a visual improvement of at least 15 ETDRS letters.[10] Interestingly, 73% of patients reported subjective improvement, which did not correspond to improved BCVA. This could be due, in part, to a placebo effect of surgery or unmeasured aspects of visual function (eg, color vision and contrast), which may not have been reported. The authors found a higher rate of zonular instability, posterior capsular opacification, and CME in these patients postoperatively.[10] Careful postoperative monitoring and, if necessary, treatment of these complications is important.

TREAT WHAT YOU CAN

Although definitive treatments for the underlying genetic causes for most IRDs remain under investigation, secondary pathologies commonly require procedural and surgical interventions. Most commonly, injections of anti-VEGF agents for active CNV can improve vision in macular dystrophies, but clinicians must be aware of the counter-intuitive imaging findings often seen with Best disease and PXE. Close follow-up and timely treatment may enable clinicians to preserve vision in many of these patients until more definitive gene and stem cell-based therapies are widely available, at which point many more patients with IRDs will likely merit surgical intervention. ■

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THE IRD GENE THERAPY PIPELINE

New research is giving hope to patients with inherited retinal diseases.

By Daniel A. Rodriguez, MD; Likhita Nandigam, BS; and Cristy A. Ku, MD, PhD



Inherited retinal diseases (IRDs) are a heterogenous group of diseases characterized by dysfunction and degeneration of photoreceptors and/or the retinal pigment epithelium (RPE) stemming from defects in at least 349 genes.[1] Since the 2017 FDA approval of voretigene neparvovec-rzyl (Luxturna, Spark Therapeutics) for the treatment of *RPE65*-associated Leber congenital amaurosis (LCA), more than 30 gene therapies have entered the pipeline to address LCA, retinitis pigmentosa (RP), Stargardt disease, Usher syndrome, choroideremia, and achromatopsia (Table). Here, we highlight recent updates for many of these clinical trials.

LEBER CONGENITAL AMAUROSIS

More than 25 genes are associated with LCA,[2] and gene replacement of *GUCY2D* and *LCA5* is under investigation. The 12-month interim results from a phase 1/2 study (NCT03920007) of subretinal gene augmentation of *GUCY2D* (ATSN-101, Atsena Therapeutics) report safety and improvements in dark-adapted full-field stimulus testing (FST), multi-luminance mobility testing, and BCVA in patients receiving the highest dose.[3-5]

Preliminary reports on the first three adults treated with gene replacement of *LCA5* with OPGx-LCA5 (Opus Genetics) showed safety and early signs of biological activity (NCT05616793), with expected treatment of the next escalation dose in mid-2024.[6]

Mutations in *CEP290* are associated with an estimated 10% to 30% of LCA cases,[7,8] making it an important target. Rather than attempting replacement of this extremely large gene (~7.5 kB), RNA and gene editing have been employed to target the common intronic mutation, c.2991+1655A>G, that is present in at least one allele in 77% of patients.[9]

Sepofarsan (ProQR Therapeutics) is an antisense oligonucleotide that binds *CEP290* mRNA transcript to block aberrant splicing. In the phase 1b/2 dose-escalation study (NCT03140969), five of 11 patients showed a clinically meaningful improvement in BCVA and FST.[10,11] Longer-term analysis of a young patient treated in the contralateral eye in the extension study (NCT03913130) demonstrated a peak biologic response at 3 months, which lasted 3 years, across multiple measures in anatomy and visual function. Further development of sepofarsen, however, is on pause.[12]

CRISPR-Cas9 gene editing has also been used to remove the *CEP290* c.2991+1655A>G intronic mutation.[13] While the

AT A GLANCE

- There are more than 30 gene therapies in the pipeline to treat inherited retinal diseases (IRDs).
- Therapeutic strategies for IRDs include gene augmentation and replacement, RNA and gene editing, CRISPR-Cas9 gene editing, and optogenetics.
- Challenges remain in adequate timing of intervention and expectations in meeting outcome measures, which may differ in each disease.

phase 1/2 study (NCT03872479) is currently paused, interim results showed promising improvements in FST and an average of 0.21 logMAR BCVA improvement with clinically significant improvement over 0.3 logMAR in four patients.[14]

RETINITIS PIGMENTOSA

RP is the most common IRD with a prevalence of one in 4,000 and is associated with more than 100 genes.[15] X-linked RP generally shows a more severe phenotype compared with other inheritance patterns. More than 70% of X-linked RP is caused by the *RP3* gene encoding for the RP GTPase regulator (RPGR) protein, in which males show severe vision loss by the third to fourth decade of life.[16]

Subretinal AAV5-hRKp-*RPGR* (MGT009, MeiraGTx/Janssen) demonstrated overall safety and improvement in perimetry in phase 1/2 trials, although three patients on the highest dose showed inflammatory responses and/or a decrease in retinal sensitivity (NCT03252847).[17] The phase 3 study (NCT04671433) is administering the low and intermediate doses with an extension study for a subgroup randomly assigned to delayed treatment (NCT04794101).

rAAV2tYF-GRK1-*RPGR* (AGTC-501, Beacon Therapeutics) uses adeno-associated virus (AAV) 2 with three tyrosine-to-phenylalanine capsid mutations designed to improve transduction efficiency.[18] The 12-month interim results from the phase 2 study (NCT04850118) show promising improvements in microperimetry, FST, and mobility testing.[19]

4D Molecular Therapeutics developed a proprietary R100 AAV capsid variant to widely transduce all retinal layers, including photoreceptors to intravitreally deliver gene replacement of *RPGR*. The active phase 1/2 clinical trial is testing two doses of 4D-125 (NCT04517149).

Gene replacement for *PDE6A*-associated RP (STZ Eyetrial) is currently active in a phase 1/2 trial (NCT04611503). However, initial findings showed that two of nine treated patients had moderate to severe vision loss with foveal thinning, and another five had temporary decreases in vision.[20]

Gene replacement of *PDE6B* (EyeDNA/Coave Therapeutics) is recruiting in a phase 1/2 trial (NCT03328130) with positive results at 5 years—eyes treated with the low dose showed a 12-letter difference compared with untreated eyes. The 2-year results of six patients with less advanced disease receiving the higher dose showed stability of vision loss and improvements in FST and foveal anatomy.[21]

Gene replacement of *RLBP1*, currently in a phase 1/2 trial in Sweden, used a self-complementary AAV8 capsid (scAAV8-*RLBP1*) that has been shown in preclinical models to have greater transduction efficacy than other vectors.[22]

To target autosomal-dominant RP caused by mutations in *RHO*, a dose-escalation phase 1/2 trial administered intravitreal antisense oligonucleotides (QR-1123, ProQR Therapeutics) to block transcription of the common *P23H-RHO* mutation (NCT04123626). Preliminary results reported safety and improvements in perimetry, with repeated dosing planned in the phase 2 trial.[23]

Gene-agnostic strategies expressing neurotrophic factors and modifier genes are being evaluated. One trial is exploring subretinal SPVN06 (SparingVision) to express *rod-derived cone viability factor*, which promotes cone photoreceptor survival (NCT05748873). Expression of *NR2E3* (Ocugen), a nuclear hormone receptor that modulates retinal homeostasis, has been found to rescue retinal degeneration in RP mouse models. A phase 1/2 trial (NCT05203939) is recruiting for RP associated with *RHO* and *NR2E3* mutations and LCA associated with *CEP290* mutations[24]; a phase 3 trial is recruiting for RP associated with *RHO* and any other gene (NCT06388200).

X-LINKED RETINOSCHISIS

Two phase 1/2 trials are investigating gene therapy for X-linked retinoschisis. VegaVect is exploring intravitreal gene replacement with AAV8-scRS-IRBP-*hRS* (NCT02317887), and Atsena Therapeutics is looking at subretinal gene replacement with AAV.SPR-hGRK1-*hRS1syn* (ATSN-201; NCT05878860).

STARGARDT DISEASE

Stargardt disease, associated with autosomal-recessive mutations in *ABCA4*, has an incidence of one in up to 10,000.[25]

A gene-agnostic strategy (Ocugen) is currently underway with AAV5 expressing *human retinoic acid receptor-related orphan receptor alpha*, thought to regulate lipid metabolism, oxidative stress, and inhibition of the complement system. A phase 1/2 trial is enrolling with safety reported in the phase 1 dose-escalation cohort (NCT05956626).[26]

An optogenetics approach is ongoing (NCT05417126) with intravitreal injection of AAV2 expressing multi-characteristic opsin (MCO-010, Nanoscope) under the mGluR6 promoter for patients with Stargardt disease associated with *ABCA4*, *PROM1*, and *ELOVL4* mutations. Preliminary phase 2a results showed clinically significant improvements in BCVA and a 3 dB gain in mean sensitivity in perimetry.[25,27]

Gildeuretinol acetate (ALK-001, Alkeus Pharmaceuticals), designed to reduce the dimerization of vitamin A, is showing promise as an oral therapy for patients with Stargardt disease caused by a mutation in *ABCA4*. Preliminary data from TEASE-3 (NCT02402660) demonstrated that treated patients showed no progression and remained asymptomatic during therapy (between 2 and 6 years).[28]

USHER SYNDROME

Usher syndrome, an autosomal-recessive condition, leads to deafness and retinal degeneration. *USH2A* is the most common cause of syndromic and non-syndromic RP, and two mutations in exon 13, c.2299delG and c.2276G>T,

TABLE. ACTIVE GENE THERAPY TRIALS FOR INHERITED RETINAL DISEASE

Gene	Treatment Agent (Sponsor)	Treatment Strategy	Trial ID	Phase	End Date
Leber Congenital Amaurosis					
GUCY2D	AAV8-GRK1-*GUCY2D* (ATSN-101, Atsena Therapeutics)	Gene replacement	NCT03920007	1/2	05/2023
LCA5	AAV8-*hLCA5* (OPGx-LCA5, Opus Genetics)	Gene replacement	NCT05616793	1/2	08/2024
CEP290	EDIT-101 (Editas Medicine)	Alter splicing error	NCT03872479	1/2	05/2025
CEP290	Sepofarsen (QR-110, ProQR Therapeutics)	Alter splicing error	NCT03913143	2/3	01/2022
Retinitis Pigmentosa/Rod-Cone Dystrophy					
RPGR	AAV.R100-*hcoRPGR* (4D-125, 4D Molecular Therapeutics)	Gene replacement	NCT04517149	1/2	06/2026
RPGR	AAV5-hRKp.*RPGR* (MeiraGTx/Janssen)	Gene replacement	NCT04671433	3	09/2024
			NCT04794101	3	09/2029
RPGR	rAAV2tYF-GRK1-*RPGR* (AGTC-501, Beacon Therapeutics)	Gene replacement	NCT06333249	1/2	04/2023
			NCT03316560	1/2	11/2023
			NCT04850118	2/3	08/2025
RPGR	AAV8-*RPGR* (BIIB112, Biogen/NightstaRx)	Gene replacement	NCT03584165	3	06/2024
PDE6A	rAAV.*hPDE6A* (STZ Eyetrial)	Gene replacement	NCT04611503	1/2a	07/2027
PDE6B	AAV2/5-*hPDE6B* (EyeDNA/Coave Therapeutics)	Gene replacement	NCT03328130	1/2	12/2029
RLBP1	scAAV8-*RLBP1* (CPK850, Novartis)	Gene replacement	NCT03374657	1/2	05/2026
RHO	Antisense oligonucleotide (QR-1123, ProQR Therapeutics)	Reduce mutant P23H protein	NCT04123626	1/2	06/2022
Gene agnostic: *RHO, PDE*	AAV-RdCVF-*RdCVFL* (SPVN06, SparingVision)	Overexpression of *rod-derived cone viability factor*, a cone neurotrophic factor	NCT05748873	1/2	03/2025
Gene agnostic	OCU400-301 (Ocugen)	Overexpression of *NR2E3*	NCT06388200	3	06/2025
Gene agnostic	AAV2-*ChR2* (RST-001, AbbVie)	Optogenetics	NCT02556736	1/2	06/2020
Gene agnostic	rAAV2.7m8-CAG-ChrimsonR-tdTomato (GS030-DP/-MD, GenSight Biologics)	Optogenetics and visual interface stimulating glasses	NCT03326336	1/2a	12/2022
Gene agnostic	AAV2-CAG-ChronosFP (BS01, Bionic Sight)	Optogenetics	NCT04278131	1/2	12/2024
Stargardt Disease					
ABCA4	EIAV-*ABCA4* (SAR422459, Sanofi)	Gene replacement	NCT01736592	1/2	08/2023
ABCA4	AAV5-*hRORA* (OCU410-ST, Ocugen)	Regulate pathways in oxidative stress/lipofuscin formation	NCT05956626	1/2	10/2025
ABCA4	Gildeuretinol acetate (ALK-001, Alkeus Pharmaceuticals)	Reduce the dimerization of vitamin A	NCT02402660	2	03/2025
Usher Syndrome					
USH2A	Antisense oligonucleotide (QR-421a, ProQR Therapeutics)	Induce skipping of exon 13	NCT05158296	2/3	12/2024
Choroideremia					
CHM	AAV R100 (4D-110, 4D Molecular Therapeutics)	Gene replacement	NCT04483440	1	06/2024
Achromatopsia					
CNGA3	AAV8.*hCNGA3* (STZ Eyetrial)	Gene replacement	NCT02610582	1/2	06/2027
CNGA3	rAAV2tYF-PR1/7-*hCNGA3* (AGTC-402, AGTC)	Gene replacement	NCT02935517	1/2	08/2022
CNGB3	rAAV2tYF-PR1.7-*hCNGB3* (AGTC-401, AGTC)	Gene replacement	NCT02599922	1/2	06/2022

constitute approximately 35% of pathogenic allele-causing disease.[29] One clinical trial is investigating the efficacy of an intravitreal antisense oligonucleotide (QR-421a, ProQR Therapeutics) to induce in-frame skipping of exon 13.[30] A phase 1b/2 study of 14 treated patients showed improvements in BCVA, perimetry, and ellipsoid zone architecture.[31] The phase 2/3 study is evaluating two different loading doses, followed by maintenance dosing at 3 months and every 6 months thereafter. Although further development is on pause,[12] Théa recently acquired this program.[32]

CHOROIDEREMIA

Choroideremia is an X-linked recessive chorioretinal degenerative disease caused by mutations in *CHM*, which

encodes the REP1 protein. It has a prevalence of one in 50,000 to 100,000 and presents with nyctalopia in childhood or early adolescence.[33] Despite early-onset severe chorioretinal degeneration, small irregular islands of relatively preserved retina remain throughout the disease process.

The phase 1/2 trial of subretinal rAAV2.REP1 (University of Oxford) revealed surgical complications of foveal damage, which led to the use of an automated injection system, intraoperative OCT, and the subretinal saline pre-bleb technique to limit retinal stretch and reflux into the vitreous space.[34-36] To decrease the risk of retinal damage from surgical intervention, 4D Molecular Therapeutics is exploring an intravitreal delivery of REP1 (4D-110) in a phase 1 dose-escalation study (NCT04483440) using the same AAV R100 capsid variant technology employed in targeting *RPGR*.[37]

ACHROMATOPSIA

Achromatopsia is an autosomal recessive disease with an estimated 70% to 80% of cases associated with *CNGA3* or *CNGB3*, encoding for the subunits of cone cyclic nucleotide-gated channels.[38] The 3-year outcomes of gene replacement of *CNGA3* in the STZ Eyetrial (NCT02610582) reported no serious adverse events, although no statistical significance was reached between treated and untreated eyes, given improvements also observed in the untreated eye.[39]

Treatment of *CNGA3* with AGTC-402 (AGTC) in the phase 1/2 clinical trial (NCT02935517) was halted due to lack of consistent biological improvement and three cases of severe inflammation.[40] The phase 1/2 trial targeting *CNGB3* (NCT02599922) showed promising results, although the program has since stopped due to a sponsorship change.

CHALLENGES AHEAD

While the IRD clinical trial landscape expands, challenges remain in adequate timing of intervention and expectations in meeting outcome measures, which may differ in each disease. With developments in intravitreal antisense oligonucleotides, further research is needed to evaluate treatment durability and balance potential adverse effects. Lastly, novel gene-agnostic strategies are emerging, which may better encompass treatment for these rare diseases. ■

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NOVEL APPROACHES TO TREAT INHERITED RETINAL DISEASE

Gene-agnostic strategies may one day provide treatment options for patients with retinal degeneration.

By Ishrat Ahmed, MD, PhD, and Mandeep S. Singh, MD, PhD


In recent years, there has been significant progress in our understanding of the pathogenesis of inherited retinal diseases (IRDs). Variants in more than 300 genes have been identified; however, the molecular diagnosis remains unknown in approximately 30% to 50% of patients with an IRD.[1-3] As such, the development of therapeutic approaches that are gene-agnostic is essential to provide treatment options for all patients with an IRD, not just those with specific variants. Here, we provide an overview of select gene variant-agnostic approaches, including pharmacologic therapies, optogenetics, stem cell therapy, and retinal prosthesis.

PHARMACOLOGIC THERAPIES

Treatments that slow disease progression and promote cell survival are particularly attractive because they are gene variant-agnostic. Although promising for other retinal diseases, encapsulated cell technology releasing ciliary neurotrophic factor did not yield long-term improvements in functional outcomes in patients with IRDs.[4] There are several other neurotrophic factors being investigated, including pigment epithelium-derived factor and rod-derived cone viability factor.[5] There has also been interest in targeting pathways that promote cellular dysfunction. This includes N-acetylcysteine, which reduces oxidative stress and may improve cone photoreceptor function; one therapeutic agent is currently in a phase 3 clinical trial (NCT05537220).[6]

THE PROMISE OF STEM CELLS

Stem cell therapy aims to restore vision through the release of neurotrophic factors and/or cell repair, regeneration, or replacement. Cell replacement requires proper

AT A GLANCE

- Stem cell therapy aims to restore vision in patients with inherited retinal diseases through the release of neurotrophic factors and/or cell repair, regeneration, or replacement.
- Optogenetics uses light-sensitive channels to enable remaining retinal circuitry to respond to light stimuli.
- Retinal prosthesis involves an implantable device that converts light into electrical signals that are transmitted to the remaining retinal circuitry.

alignment and integration of donor photoreceptors with the remaining neuronal circuitry of the recipient retina. Induced pluripotent stem cells (iPSCs) have significantly advanced the field of stem cell therapy by providing a renewable therapeutic cell source. iPSCs are derived from the trans-differentiation of somatic cells using a set of pluripotency transcription factors.[7,8] Using stepwise protocols, these cells can be differentiated into retinal progenitor cells followed by rod and cone photoreceptors.[9-11]

Photoreceptor transplantation in preclinical models has demonstrated successful integration of donor photoreceptors within the recipient retina, and, crucially, cone transplantation has gained traction as a possible treatment for foveal atrophy in AMD (Figure).[12] Studies in preclinical models also demonstrated the transfer of cytoplasmic material from donor to recipient photoreceptors,[13] and the therapeutic implications of this mechanism across multiple genetic variants is being studied. Several challenges remain, including graft rejection and inflammatory manifestations. Gene editing of autologous iPSCs or gene editing of HLA haplotype resulting in an immunocompatible iPSC line would potentially bypass concerns for graft rejection.[14]

REDIRECTING LIGHT

Optogenetics uses light-sensitive channels to enable the remaining retinal circuitry to respond to light stimuli.[15] This requires transfecting existing neurons (ie, bipolar or retinal ganglion cells) with genes encoding light-sensitive channels. Since viable photoreceptors are not absolutely necessary for optogenetics-based therapies, this approach can be used for advanced disease stages. Delivery approaches being studied include adeno-associated virus and nanoparticles.

GENE-DEPENDENT APPROACHES: AN UPDATE

Voretigene neparvovec-ryzl (Luxturna, Spark Therapeutics), which targets biallelic *RPE65*-associated retinal dystrophy with viable retinal cells, was the first FDA-approved gene therapy for IRD.[1] Initial functional improvement was noted following the subretinal delivery of voretigene neparvovec-ryzl, but questions arose regarding the degree of long-term therapeutic effect.[2-5] A subset of patients also developed progressive post-treatment chorioretinal atrophy, although these lesions have not generally been associated with vision loss.[5] Adeno-associated virus-mediated inflammation and direct toxicity are hypothesized to contribute to chorioretinal atrophy.

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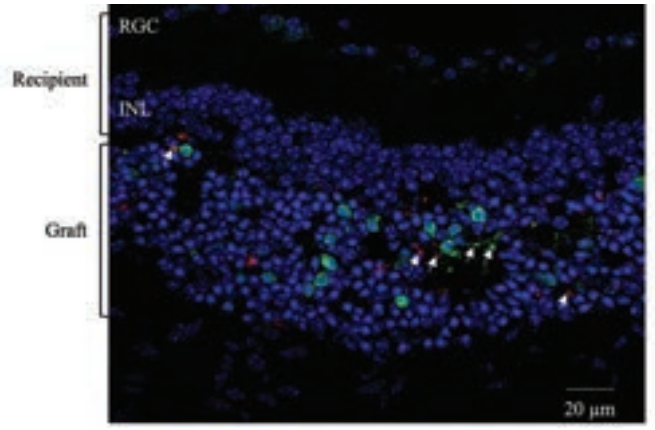

Figure. Cone photoreceptor cells were collected from a cone-rich donor mouse strain and transplanted into the subretinal space of an immunodeficient recipient mouse in an allogeneic approach.[12] Three months post-transplantation, numerous donor cones survived and elaborated key cellular structures, including cone outer segments (arrows). Abbreviations: INL, inner nuclear layer; RGC, retinal ganglion cell. *Data (unpublished) from Kang Li, Ying Liu, and Singh M at Wilmer Eye Institute, Johns Hopkins University.*

In 2021, Sahel et al published a case report of a blind patient treated with ChrimsonR-based optogenetics, demonstrating object recognition and improved performance on psychophysical tests and electroencephalography.[16] ChrimsonR, which is activated with red-shifted wavelengths, requires lower light intensities and is thought to reduce light-mediated retinal damage.[17] This technology requires goggles to detect changes in light intensity and project them as red-shifted (595 nm) light pulses onto the retina in real time. Optogenetics clinical trials include several types of opsins: ChrimsonR (GenSight Biologics), ChR2 (AbbVie), ChronosFP (Bionic Sight), and MCO-010 (Nanoscope Therapeutics).[15]

Retinal prosthesis involves an implant that converts light into electrical signals that are transmitted to the remaining retinal circuitry. Various implant designs include epiretinal, subretinal, suprachoroidal, optic disc, and cortical.[18] The Argus II device (Second Sight Medical) was approved by the FDA in 2013. Briefly, visual signals from a camera are converted into a brightness map that is transmitted wirelessly to the implant, which then transmits these signals to functioning neurons as pulse amplitudes. Five-year follow-up data show persistent improvement on functional vision assessment tasks, such as locating objects or directionality of motion.[19] However, visual gains were modest, and patients required intensive vision rehabilitation. Of note, the best visual acuity attained with the Alpha AMS retinal prosthetic device (Retina Implant AG) was 1.39 LogMAR and 20/500 or 6/150 Snellen.[20] Future directions include the use of AI to improve the implant and visual processing algorithms.[21]

THE WAY FORWARD

There has been a rapid advance in clinical trials encompassing both variant-dependent and variant-independent

therapeutic strategies for IRDs. With exciting variant-independent therapeutics in the pipeline, we can envision a future when every IRD patient, regardless of the causal gene variant, will have at least one treatment option to consider. In addition to enabling molecular diagnosis, providing heredity information to families, monitoring progression, and addressing ocular comorbidities and systemic associations, retina specialists may soon be able to create active therapeutic partnerships with their patients with IRD. ■

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(Continued from page 19)

FEVR IS A LIFELONG DISEASE THAT REQUIRES REGULAR EXAMINATIONS AND CAN GIVE RISE TO RRD AT AN EARLY AGE.

remaining 10 (71.43%) underwent primary vitrectomy with silicone oil injection.

After a mean follow-up of 3.32 years, the mean VA improved from 2/60 to 6/24 ($P < .00001$) at the final visit. Successful reattachment was achieved in 13/14 eyes.

TAKEAWAYS

FEVR is a lifelong disease that requires regular examinations and can give rise to RRD at an early age. A meticulous clinical and angiographic evaluation of each eye can help with the correct diagnosis and appropriate treatment. Timely surgical intervention, either with SB or vitrectomy, and vigilant follow-ups are highly effective in achieving anatomical and functional long-term success. ■

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RT ONE TO Watch

Retina Today

KENNETH C. FAN, MD, MBA

WHERE IT ALL BEGAN

I grew up in a small town in Maine, where I always imagined I would pursue a career in science (there was a short period when I thought I would be a soccer player, but I definitely lacked the physical talent). My father is a chemist, and his passion for scientific exploration exposed me and my brother to the lab very early in our lives. After graduating from Dartmouth College, I worked in translational bench-to-bedside research at Massachusetts General Hospital in cancer genetics; that's where I discovered my desire to pursue medicine.

MY PATH TO RETINA

I still remember when I first got the hang of indirect ophthalmoscopy. James Banta, MD, one of the legendary educators at Bascom Palmer Eye Institute (BPEI), was the first to show me. However, it was my chiefs and senior residents who really helped me visualize my first giant retinal tear, toxocariasis, acute retinal necrosis, and retinal detachment. After scrubbing into my first buckle-vitrectomy as a first year, with chief resident Sarah Read, MD, PhD, I was hooked.

SUPPORT ALONG THE WAY

I have many amazing mentors who have played a critical role in my journey. Stephen P. Christiansen, MD, at Boston University, and Teresa C. Chen, MD, at Massachusetts Eye and Ear Infirmary, were instrumental in guiding me to ophthalmology when I was a fledgling medical student. Nina Berrocal, MD, at BPEI, has been a constant guiding light for me, from the management of tough surgical cases all the way to how to raise my kids wisely. Harry W. Flynn Jr, MD, also at BPEI, taught me the power of observation and the durability of the scleral buckle as a surgical tool. I am lucky enough to continue my relationships with many of my mentors even now.

AN EXPERIENCE TO REMEMBER

My chief resident year was professionally the most amazing year of my life. Among all the crazy experiences, my most memorable patient was a 16-year-old who came to me with bilateral open globes, multiple metallic intraocular foreign bodies, lens violation, and retinal detachments from a motor vehicle accident. With my third-year resident at the time, Anne Kunkler, MD, we took him emergently to surgery in a grueling 5-hour case to repair both globes.

The patient required a few additional surgeries, but I'm delighted that he is now 20/50 OD and 20/30 OS! ■

Dr. Fan's advice: Be open to every opportunity that presents itself, even if it may be out of your comfort zone! You never know what future opportunities or relationships may come from opening that door.

Kenneth C. Fan, MD, MBA, practices at the Retina Consultants of Texas in Houston, where he spends 70% of his time in the clinic, 20% in the OR, and 10% participating in research. A large portion of his practice is dedicated to patients with inherited retinal diseases. Dr. Fan is a consultant for Abbvie, Alimera, Bayer, and Regenxbio. He can be reached at **kcfmd@retinaconsultantstexas.com.**

THE LATEST THERAPIES AND TRIALS IN UVEITIS

New pharmaceuticals and delivery methods are improving our management strategies for chronic inflammation.

By Shima Dehghani, MD, and Stephanie M. Llop, MD


Uveitis remains a significant cause of visual impairment, particularly in its severe forms.[1] Here, we provide an update on completed and ongoing clinical trials in uveitis (Table).

INITIAL TREATMENT CHOICES: NONINFECTIOUS UVEITIS

Traditional treatment for uveitis often involves immunosuppression with systemic corticosteroids, either alone or in conjunction with other antiinflammatory medications. This approach, however, is often fraught with severe side effects, including increased blood pressure, diabetes, and osteoporosis.[2]

To mitigate these side effects, local delivery mechanisms for steroids have been explored. In 2005, the FDA approved the intravitreal 0.59 mg fluocinolone acetonide intravitreal implant (Retisert, Bausch + Lomb). However, follow-up data up to 10 years from the MUST trial has since shown better visual acuity with systemic therapy over the implant and increased rates of visual impairment related to chorioretinal lesions, glaucoma, cataracts, and elevated IOP with the implant.[3-6] Given these findings, it was concluded that systemic therapy is moderately superior to the fluocinolone implant for the treatment of noninfectious uveitis.

Newer-generation steroid implants, such as the 0.7 mg dexamethasone intravitreal implant (Ozurdex, Abbvie) and the 0.18 mg fluocinolone acetonide implant (Yutiq, Alimera Sciences), have introduced lower doses

Find a table of important trials in uveitis at *retinatoday.com:*

AT A GLANCE

- Local delivery mechanisms for steroids have been explored to mitigate the side effects of systemic steroids when treating uveitis.
- Biologics such as adalimumab are often used as additional agents following the failure of or incomplete response to conventional immunosuppressants in treating uveitis.
- Macular edema is a prevalent complication in uveitis, and several trials are exploring various treatment approaches.

and are linked to fewer side effects, notably reduced rate of cataract progression and decreased need for glaucoma intervention.[7] Current clinical trials are rigorously testing these implants in noninfectious intermediate and posterior uveitis, aiming to confirm their efficacy and safety profiles. These trials include monotherapy with the dexamethasone implant and one or two fluocinolone acetonide implants.[8-10]

EXPANDING OPTIONS WITH IMMUNOSUPPRESSANTS

The management of severe uveitis often includes an immunosuppressive agent.[2] Antimetabolites are commonly used as first-line agents due to their affordability, favorable safety profile, and good patient tolerance. The FAST trial compared the efficacy and safety of two common immunosuppressants, methotrexate and mycophenolate mofetil, as first-line corticosteroid-sparing treatments. Results indicated similar efficacy in reducing treatment failure rate and time to steroid-sparing control of inflammation, as well as improving visual acuity and resolution of macular edema.[11] Abnormalities in liver function tests were more common with methotrexate, and mycophenolate mofetil did not confer an additional risk of CD4 lymphopenia in patients with uveitis followed up to 12 months.[11]

A subanalysis of the FAST trial showed that patients with retinal vasculitis are more likely to experience treatment failure with both methotrexate and mycophenolate mofetil compared with patients without retinal vasculitis. Therefore, clinicians should consider other classes of corticosteroid-sparing medications, such as biologics, for these patients.[11,12]

THE GROWING ROLE OF BIOLOGICS

Biologics such as adalimumab are often used as additional agents following the failure of or incomplete response to conventional immunosuppressants in treating uveitis.

VISUAL I evaluated adalimumab as a glucocorticoid-sparing treatment for active noninfectious uveitis. Adalimumab extended the time to treatment failure (24 weeks vs 13 weeks for placebo), improved visual acuity, and reduced inflammation, although it led to more adverse events such as injection site and allergic reactions. Both groups experienced serious infections at similar rates.[13]

VISUAL II focused on preventing flare-ups in patients with inactive uveitis controlled by systemic corticosteroids. Adalimumab significantly reduced the risk of flare-ups and vision loss following corticosteroid withdrawal, showing a lower treatment failure rate (39% vs 55%) and a significantly longer time to treatment failure (> 18 months vs 8.3 months) compared with placebo.[14]

VISUAL III, an ongoing extension study, is evaluating the long-term safety and efficacy of adalimumab in patients from VISUAL I and II. Early results (78 weeks follow-up) are showing sustained quiescence and reduced corticosteroid use in most patients (60% to 90%).[15]

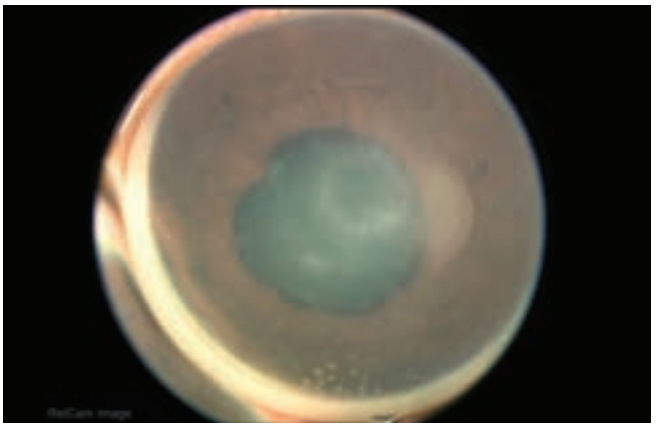

Figure 1. This 7-year-old patient presented with chronic anterior and intermediate uveitis with keratic precipitates, posterior synechiae, and early cataract in the right eye.

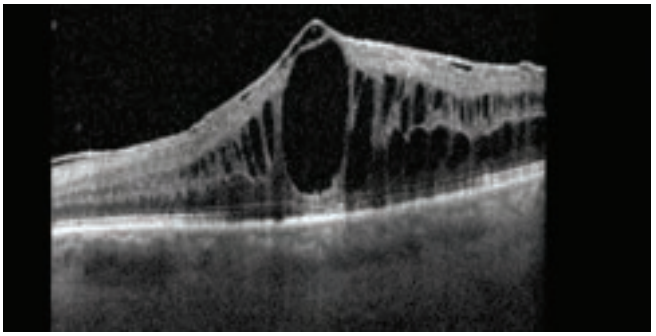

Figure 2. This spectral-domain OCT macula scan shows cystoid macular edema.

The SYCAMORE trial evaluated the efficacy of adalimumab in treating juvenile idiopathic arthritis (JIA)-associated uveitis in patients who were already receiving a stable dose of methotrexate (Figure 1). The trial found that adalimumab significantly lowered the rate of treatment failure compared with placebo (27% vs 60%), although it was associated with a higher incidence of adverse events.[16]

Additional ongoing trials are investigating anti-TNF agents as first-line treatments alone or in combination with other immunosuppressants for various forms of uveitis.[17-24] Notable among these is the ADVISE trial comparing adalimumab with conventional immunosuppression as a first-line corticosteroid-sparing treatment in noninfectious, intermediate, posterior, and panuveitis and the ADJUST trial, which is assessing the feasibility of discontinuing adalimumab after stable disease control in JIA-associated uveitis.[19,20]

ADDRESSING A COMMON COMPLICATION

Macular edema is a prevalent complication in uveitis (Figure 2).[1] The 7-year follow-up results of the MUST trial revealed that macular edema could be resolved in 94% of patients when treated, although approximately 50% experienced a relapse.[25] Similarly, a 12-month follow-up subanalysis of the FAST trial indicated that

TABLE. ONGOING PHASE 3 AND 4 CLINICAL TRIALS IN UVEITIS

Study [Sponsor]	Phase	Outcome Measures
Adalimumab vs Conventional Immunosuppression for Uveitis Trial (ADVISE)[18] [JHSPH Center for Clinical Trials]	3	Corticosteroid-sparing success, prednisone discontinuation, visual acuity, macular edema, uveitis complications
Efficacy, Safety, and Costs of Methotrexate, Adalimumab, or Their Combination in Noninfectious Nonanterior Uveitis (Co-THEIA)[34] [Hospital San Carlos, Madrid]	3	Clinical response, resolution of inflammation by week 16 and maintained until week 52, hospital anxiety and depression scale, time to inflammatory relapse, cost effectiveness, uveitis complications
A Study of Baricitinib (LY3009104) in Participants From 2 Years to Less Than 18 Years Old With Active JIA-Associated Uveitis or Chronic Anterior Antinuclear Antibody-Positive Uveitis[35] [Eli Lilly and Company]	3	Percentage of responders, defined as a 2-step decrease in inflammation
A Study of TRS01 in Subjects With Active Noninfectious Anterior Uveitis[36] [Tarsier Pharma]	3	Anterior chamber cell count changes with use of TRS01 eye drops
The Use of Two YUTIQ Versus Sham for Treatment of Chronic Noninfectious Intraocular Inflammation Affecting the Posterior Segment (TYNI)[9] [Texas Retina Associates]	3	Recurrence of uveitis at 6 and 12 months
Systemic and Topical Antivirals for Control of Cytomegalovirus Anterior Uveitis: Treatment Outcomes (STACCATO)[37] [University of California, San Francisco]	3	Change in viral load, disease quiescence, the effect topical steroids prior to enrollment have on pretreatment viral load
Preventing Extension of Oligoarticular JIA (LIMIT-JIA)[38] [Duke University]	3	Efficacy of subcutaneous abatacept in preventing extension of JIA and changes in number of participants with active anterior uveitis
Assessing the Efficacy and Safety of Intravitreal Injections of 440 ug DE-109 Sirolimus for the Treatment of Active, Noninfectious Uveitis of the Posterior Segment of the Eye (LUMINA)[39] [Santen]	3	Change in vitreous haze as a measure of inflammation control
Fluocinolone Acetonide Intravitreal Implant 0.18 mg in the Treatment of Chronic Noninfectious Posterior Segment Uveitis[10] [Alimera Sciences]	4	Change in BCVA and central subfield thickness, recurrence of inflammation, presence of vascular leakage
Adalimumab in JIA-Associated Uveitis Stopping Trial (ADJUST)[19] [Nisha Acharya]	4	Time to treatment failure
Biologic Therapy in Pediatric JIA Uveitis[24] [Kasr El Aini Hospital]	4	Steroid-sparing effects of the medications and adverse effects
A Clinical Trial of Infliximab for Childhood Uveitis[22] [Xiaomin Zhang]	4	Change in BCVA, anterior chamber cell grade, vitreous haze grade
A Study to Assess Change in Disease Activity and Adverse Events of Adalimumab in Chinese Participants Requiring High Dose Corticosteroids for Active Noninfectious Intermediate, Posterior, or Panuveitis[21] [Abbvie]	4	Percentage of patients who achieve disease quiescence in both eyes and no active lesions, changes in BCVA, anterior chamber grade, vitreous haze grade, adverse events
Ozurdex Monotherapy Trial (OM)[8] [Ottawa Hospital Research Institute]	4	Change in vitreous haze, BCVA, and central retinal thickness; adverse effects
Efficacy and Safety of Adalimumab in Noninfectious Anterior Pediatric Uveitis with Peripheral Vascular Leakage[40] [Peking Union Medical College Hospital]	4	Change in uveitic flare, extent of vascular leakage, keratic precipitates, vitreous haze, BCVA, adverse events
Topical 2% Ganciclovir Eye Drop for Cytomegalovirus Anterior Uveitis/ Endotheliitis[41] [Singapore National Eye Centre]	4	Median concentration of ganciclovir in aqueous, clinical efficacy in clearing cytomegalovirus viral load, resolution of anterior uveitis/ endotheliitis, and an aqueous tap negative for cytomegalovirus

50% of patients in both groups showed some persistent macular edema at 12 months.[26]

The POINT trial compared three regional corticosteroid treatments: periocular triamcinolone acetonide, intravitreal triamcinolone acetonide, and the intravitreal dexamethasone implant. The results showed that intravitreal injections were more effective than periocular injections in reducing macular thickness and improving visual acuity, although they raised concerns due to potential side effects such as glaucoma and cataract formation.[27]

The MERIT trial compared the efficacy and safety of two alternative intravitreal treatments, methotrexate and ranibizumab (Lucentis, Regeneron), with the dexamethasone implant for managing persistent or recurrent uveitic macular edema in patients with minimally active or inactive noninfectious uveitis. At 12 weeks,

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dexamethasone proved superior in reducing macular thickness and improving vision, although it also posed a higher risk of increased IOP. The results also suggested its effect might diminish before 12 weeks, indicating a potential need for earlier retreatment. Results from the 24-week follow-up are pending.[28]

Given the ongoing concerns about the side effects associated with intraocular steroids, alternative approaches have been investigated. The PEACHTREE trial evaluated the efficacy and safety of suprachoroidal triamcinolone acetonide injectable suspension (Xipere, Bausch + Lomb and Clearside Biomedical) in improving vision in patients with noninfectious uveitis complicated by macular edema over 12 weeks, finding that it significantly improved vision with a lower rate of IOP elevation compared with dexamethasone implants in the MERIT trial.[29] Additionally, the MAGNOLIA study, an observational extension of the PEACHTREE trial over 24 weeks, showed that the beneficial effects of suprachoroidal triamcinolone acetonide lasted up to 6 months, with glaucoma and cataract rates similar to those seen in sham treatments.[30] A post-hoc analysis of the PEACHTREE trial further evaluated the safety and efficacy of suprachoroidal triamcinolone acetonide in treating uveitic macular edema, comparing patients with and without systemic corticosteroids or steroid-sparing therapies at baseline. This analysis revealed no significant safety issues between the groups and confirmed that suprachoroidal triamcinolone acetonide significantly enhanced both visual and anatomical outcomes, irrespective of patients' baseline systemic therapy status.[31]

FUTURE DIRECTIONS AND ONGOING TRIALS

As uveitis treatment evolves, integrating new findings is crucial. Treatment choices—systemic, implant-based, or biologic—are tailored based on each patient's specific needs. Ongoing research aims to refine and enhance these strategies for better outcomes. ■

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SUBTHRESHOLD YELLOW LASER FOR RECURRENT CENTRAL SEROUS CHORIORETINOPATHY

A small retrospective study showed stable results and no side effects after 3 years.

By Giacomo Costa, MD, and Marco Balestrieri, MD


Central serous chorioretinopathy (CSC) is a retinal pathology characterized by the detachment of the neurosensory retina from the underlying retinal pigment epithelium (RPE) in the macular area, secondary to the accumulation of subretinal fluid.

A high proportion of CSC cases resolve spontaneously within an average of 3 months, with a complete recovery of visual acuity. There are rare cases of recurrent or persistent edema associated with CSC that cause irreversible visual impairment.[1,2]

Different types of treatments have been proposed over the years for chronic and recurrent forms of CSC, including the instillation of NSAID eye drops, the oral administration of diuretics, the intravitreal injection of anti-VEGF factors, photodynamic laser therapy (PDT), and argon laser treatment. Despite these approaches, there is currently no consensus regarding a standardized therapeutic algorithm for CSC.[3]

SUBTHRESHOLD LASER THERAPY

More recently, subthreshold laser therapy has been shown to be effective in inducing resorption of subretinal fluid in cases of chronic CSC.[4-6]

The yellow subthreshold laser (YSL) is a retinal technology that can activate a biological response without causing thermal damage to the tissue. One such laser produced commercially is the Yellow Scan Laser Photocoagulator (YLC-500 Vixi; NIDEK) with the Low Power Mode (LPM) function. The LPM software, when combined with the Power Ratio (PR) setting, decreases the laser's energy delivery by a specific ratio to subthreshold levels to create minimally invasive photocoagulation.

The therapeutic efficacy of the YSL is linked to its ability to regulate the expression of heat shock proteins (HSP) and cytokines within target tissues.[7] HSP are a large group of ubiquitous molecules activated by various stimuli; they are able to protect cells by blocking apoptotic and inflammatory stimuli that cause cellular damage.[8] A certain amount of laser energy incites the expression of HSP,[9] which help restore the blood-retina barrier.[10] Thanks to these characteristics, it is possible to treat any retinal area with the YSL, including the macula, even using a large number of spots, without producing any thermal damage to the tissue and while maintaining contrast sensitivity.

RETROSPECTIVE STUDY

We, the authors, conducted a retrospective study (unpublished), in accordance with the principles of the Helsinki Declaration, in which we treated 18 eyes of 18 patients with chronic CSC with the YLC-500 Vixi yellow laser. The patients' average age was 50.7 ±12.7 years. Their baseline visual acuity was a mean of 0.66 ±0.17, and their baseline macular thickness was 397 ±45 µm. Of the patients enrolled, 80% had not previously undergone treatment with YSL or any other laser therapy; 18% had undergone 1 PDT treatment; and only 1 patient had undergone more than 1 treatment with PDT.

The study's inclusion criteria were: (1) the presence of subretinal fluid for ≥ 3 months after diagnosis, and (2) ineffectiveness of other medical or parasurgical therapies (eg, the instillation of topical NSAIDs, the use of eplerenone, PDT). The exclusion criteria were: (1) the presence of secondary neovascular membranes, and (2) the presence of other retinal diseases (diabetic retinopathy, maculopathies, retinal occlusive vasculopathies) or of the optic nerve (glaucoma).

Preoperatively, we measured the patients' BCVA, examined the anterior and posterior segments of each eye at the slit lamp, and we performed digital retinal fluorescein angiography (FA) and macular OCT (HRA2; Heidelberg Engineering). We diagnosed CSC via OCT by detecting the presence of subretinal fluid involving the macular area; in 6 of the 18 patients, it was also possible to detect a focal leakage area that identified the "leakage point." All eyes included in the study had a chronic form of CSC, as identified by the presence of subretinal fluid for a duration of more than 3 months and a decrease in visual acuity.

TREATMENT PLAN AND PROTOCOLS

We began the treatment with the LPM function to perform a "titration" by placing a barely visible burn in the peripheral retina, which we generally performed outside the vascular arcades. We defined the power level necessary to produce this visible burn as the "threshold." We then set the PR from the threshold value to achieve the intended "undershoot" best for that particular patient.[11] We repeated this process for each patient in the study, thus allowing us to customize the treatment per individual. It has been shown that no thermal damage to tissues can be detected if the energy delivery remains below 30% of that needed to produce the "threshold" spot.[12]

All patients were treated with the same protocol: a treatment spot size of 100 to 150 µm, an exposure time of 0.01 seconds, and a laser power of 100 to 150 mw (this was LPM on the NIDEK laser of 577 nm). Using a Focal Grid contact lens (Area Centralis; Volk Optical), we performed a titration. Then, we set the laser's PR to 30% and executed a grid of 6 spots on the leakage point that we identified with FA, or a circular pattern that spared the foveal center.

RESULTS

All patients showed a statistically significant reduction in central macular thickness at 12 months after treatment, and an increase in VA at 6 months. These values were confirmed in the follow-up visits at 24 and 36 months (Figures 1 and 2).

No patients involved in the study developed chorioretinopathy scars that were observable on examination of the ocular fundus or on follow-up examinations (FA and OCT). In addition, we found no changes in the outer retinal layers (the external limiting membrane, IS-OS layer, or the RPE). Furthermore, no patients have reported the appearance of scotomas.

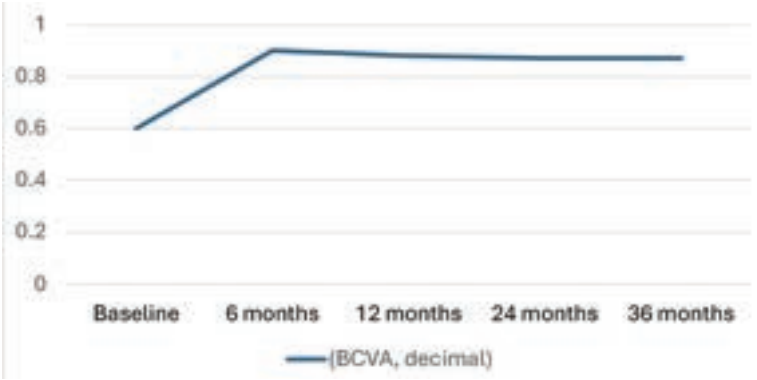

Figure 1. Visual acuity from baseline to 36 months in a retrospective study of 18 eyes of 18 patients with CSC treated with the YLC-500 Vixi.

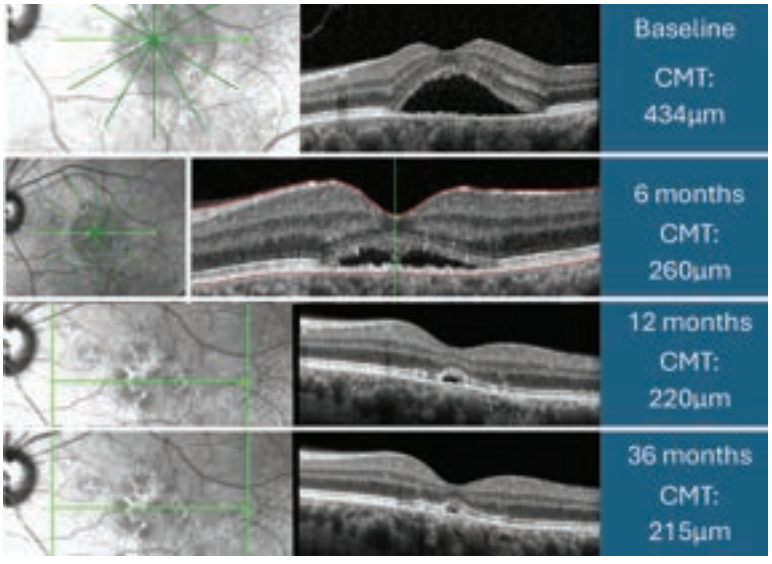

Figure 2. The follow-up examinations of fundus photos and OCT images of a patient.

CONCLUSION

YSL has proven to be an effective and safe treatment for CSC. Treating the leakage point with the argon laser is certainly an effective treatment in relapsing forms of CSC (although it is contraindicated if leakage is found too close to the foveal region). Moreover, it is not always possible to detect a leakage point using FA in patients suffering from recurrent forms of CSC. PDT is also an effective treatment for chronic forms of CSC, even in cases of proximal leakage at the foveal avascular zone.[13] In this study, treatment with YSL showed no visible side effects in any of the patients.

We believe that YSL represents a new and effective therapeutic option in all chronic recurrent forms of CSC. We are encouraged that we found no visible side effects in any of the patients undergoing treatment, including scarring in the RPE. ■

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LESSONS FROM A CASE OF PRIMARY INTRAOCULAR LYMPHOMA

Here's how we were able to narrow in on this diagnosis.

BY FLAVIUS BECA, MD

With myriad ocular presentations in the retina space, both the budding specialist and the seasoned expert rely on a well-formulated systematic approach to arrive at the correct differential diagnosis. When you inevitably find yourself tracking down potential culprits, a few guiding principles can help keep trainees on the path to an accurate diagnosis (see *Clinical Pearls for the Trainee*).

CASE PRESENTATION

A 76-year-old Hispanic man presented to our ophthalmic emergency department with 2 weeks of blurred vision in the right eye, which he described as a black spot with growing spiderwebs. A review of systems and medical history were unrevealing. His ocular history was limited to uncomplicated cataract surgery 5 years prior. An otherwise benign examination was documented during another emergency visit 6 months prior, at which point he had been diagnosed with a subconjunctival hemorrhage.

At the time of presentation, the patient's VA was reduced to 20/60 OD, and a posterior examination revealed mild vitreous cells with unilateral optic nerve edema and small scattered white chorioretinal spots in the periphery of the affected eye. The patient was seen by the on-call retina fellow, who determined he did not have acute retinitis and would not require a tap and inject. However, a broad infectious and inflammatory differential was entertained, for which labs were ordered, and the patient was instructed to return to the clinic for further imaging.

The next day, multimodal imaging of the right eye, including color fundus imaging, fundus autofluorescence (FAF), and fluorescein angiography (FA) revealed pinpoint peripheral hypoautofluorescent spots, leakage at the disk, and early staining of small scattered subretinal lesions throughout the periphery (Figure 1). ICG angiography was normal in each eye. OCT imaging appeared to confirm a unilateral process with significant vitreous cell and vitritis, which degraded the image quality, although subtle hyperreflective outer retinal changes and normal choroidal thickness could be visualized (Figure 2).

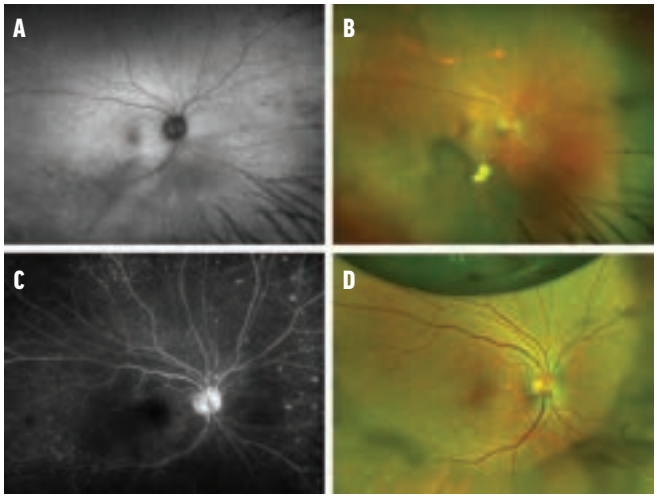

Figure 1. FAF of the right eye on day 2 revealed scattered pinpoint hypoautofluorescent spots, partially blocked by vitreous debris, in the nasal and inferotemporal periphery. Fundus pseudocolor imaging of the right eye on day 2 showed vitreous opacities and haze, blurred optic nerve margins, and pinpoint hypopigmented chorioretinal lesions in the periphery (B). The cream-colored lesion in the macula is an imaging artifact. Early-phase FA on day 2 demonstrated optic nerve staining and pinpoint staining throughout the periphery (C). Pseudocolor fundus imaging of the right eye following vitrectomy displayed mild inferior blurred disc margins and pinpoint peripheral hypopigmented chorioretinal spots (D).

Further discussion with the patient revealed a remote history of a cardiac arrythmia status post-ablation, for which he was still anticoagulated, and a 2-year diagnosis of Waldenström macroglobulinemia, a rare indolent lymphoma characterized by a monoclonal gammopathy,

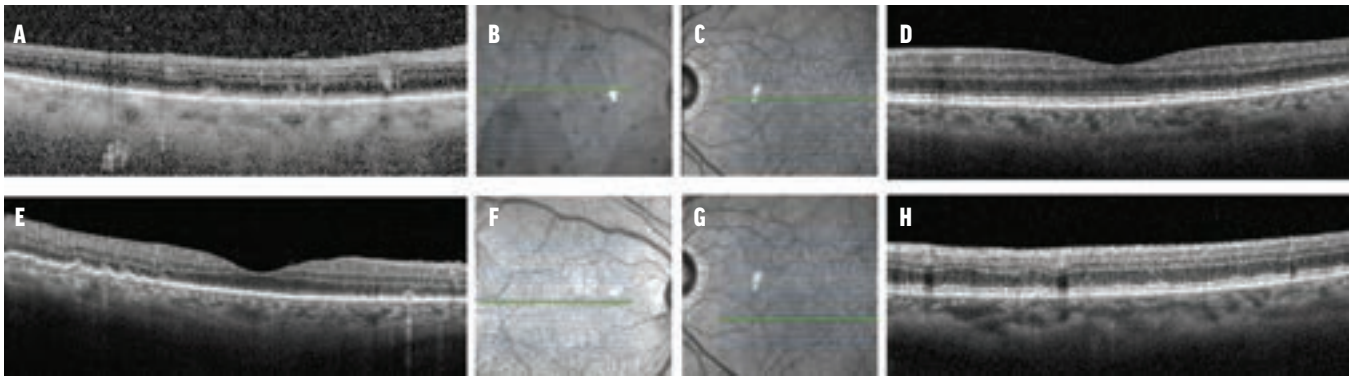

Figure 2. OCT of the right eye on presentation showed image degradation secondary to vitreous debris, subretinal deposits with possible retinal pigment epithelium thickening, and pachychoroid (A). The near-infrared image with the green cut corresponded to the OCT slab seen in panel A (B). The near-infrared image of the left eye with the green cut corresponded to the OCT slab seen in panel D (C). OCT of the left eye on presentation appeared normal (D). OCT and near-infrared imaging 19 days later showed further changes (E-H).

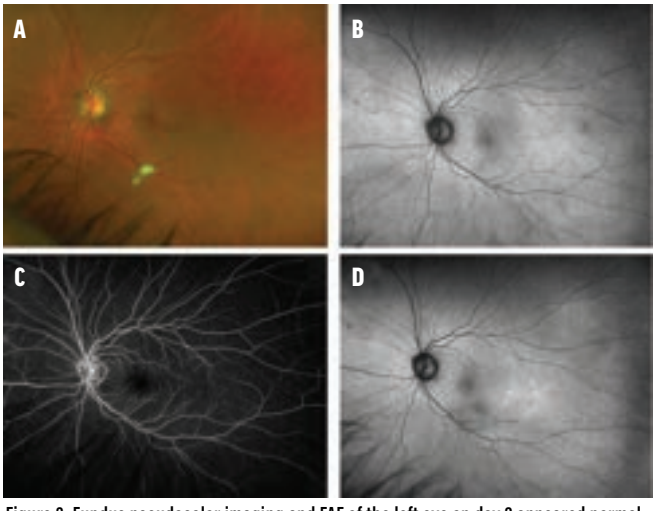

Figure 3. Fundus pseudocolor imaging and FAF of the left eye on day 2 appeared normal (A, B). Early-phase FA of the left eye on day 2 appeared normal (C). FAF of the left eye on day 5 demonstrated scattered pinpoint hyperautofluorescence mostly in the temporal macula (D).

for which he had been told he didn't need treatment.

The patient was evaluated by a second retina fellow and the uveitis fellow on call. Both felt his presentation likely represented an infectious or idiopathic posterior uveitis; however, as labs were pending, oral steroids were deferred.

The patient returned to the clinic 3 days later reporting worsening symptoms in the right eye. On examination, his vision was unchanged, and while the right eye was stable, the left eye now showed evidence of hypopigmented peripheral subretinal lesions with corresponding pinpoint hyperautofluorescent spots on multimodal imaging (Figure 3). A white dot syndrome was deemed highest on the differential, although lymphoma remained in consideration. As bloodwork had been drawn and some of the patient's labs were back (mildly elevated rheumatoid factor, otherwise normal CBC, CMP, ESR, and CRP, and negative RPR and ANA), the patient was started on 40 mg oral prednisone daily.

The patient returned 5 days later as scheduled, now with decreased VA to 20/100 OD. Though he remained 20/20 OS, he was symptomatic of new floaters. At this point, both eyes had developed anterior chamber cells with fine keratic precipitates, and dense vitritis was evident in the right eye.

The patient underwent an uncomplicated vitrectomy 2 days later and noted immediate improvement in vision.

By the patient's follow-up visit 1 week later, pathology

(Continued on page 52)

CLINICAL PEARLS FOR THE TRAINEE

Pearl #1: Rule out the dangers, make a differential, and move on. In the acute setting, for the undifferentiated patient, timing and visual acuity come first. Once the cannot-miss diagnoses are ruled out, lay out the groundwork for your next steps. Basic labs will help rule out differentials and open the door to treatment escalation.

Pearl #2: Keep a mental list of your undifferentiated patients. Review the list on a regular basis and reconsider your evolving repository of cases as you continue to hone your differential diagnosis skills.

Pearl #3: Trust, but verify. In training, we find ourselves in multispecialty, tertiary-level clinics with many providers of various levels of training. We all carry the biases of our perspectives and trainings. This patient, for example, was first seen by a provider whose examination and history were nearly perfect, except for one small detail: the subtle clinical clue of the patient's Waldenström macroglobulinemia. Integrating a complex medical history is precisely the role of the physician.

RISING STARS IN RETINA

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

Suzie A. Gasparian, MD

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

My experiences as a resident at our county hospitals inspired me to become a vitreoretinal surgeon.

In witnessing the range of retinal disease manifestations—local to systemic and acute to chronic—the beautiful complexity of the retina was revealed to me, and treating these patients filled me with excitement.

Seeing the most advanced stages of retinal pathology and having the ability to safeguard and restore vision as a retina specialist was truly eye-opening.

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

I am extremely grateful for the mentorship I received throughout my residency at Loma Linda University and fellowship at Baylor College of Medicine. During my fellowship training, Christina Y. Weng, MD, MBA, has been particularly influential, empowering and inspiring me as a clinician and surgeon. She is continuously exploring the latest scientific advancements, imparting her exceptional surgical expertise, and sharing her innovative ideas with me.

Her mentorship has flourished into a lifelong friendship, and for that I am forever grateful.

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

I vividly recall receiving a phone call from a resident at 2:00 AM regarding an elderly patient who presented with a macula-on rhegmatogenous retinal detachment—a patient whose VA of 20/20 was actively being threatened by this complication. Within an hour, we made it to the OR to repair his retinal detachment. And within the month, he could see perfectly again. This singular experience encapsulates the essence of hope in times when hope seems to be rapidly fading.

As a vitreoretinal surgeon, possessing the unique skills to combat serious retinal conditions and profoundly affect patients' lives by preserving their vision is truly an honor.

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

I am passionate about providing exceptional care to my patients with retinal diseases in both the clinic and the OR. With an unwavering curiosity, I am motivated to participate in clinical trials to fuel the advent of novel sight-saving therapies. Additionally, I look forward to the opportunity to mentor aspiring retina specialists.

FIRST CAREER MILESTONE

Dr. Gasparian is joining Retina Consultants of Southern California.

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

I encourage residents to seize any opportunity they have to witness the breathtaking view of the intricate retina through the OR microscope. If you weren't already convinced about pursuing a career in retina, the sight of it might sway your decision! ■

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IMAGING TIPS AND TRICKS FOR RETINOPATHY OF PREMATURITY

Keep these clinical pearls in mind to better document disease and monitor progression.

BY EMILY COLE, MD, MPH; YANNET DANIEL; EMILY ETON, MD; AND NITA VALIKODATH, MD, MS

Obtaining fundus images is an important part of retinopathy of prematurity (ROP) care to document disease and monitor progression. In many settings, digital fundus imaging is the basis for effective telehealth screening and expanded access to care. In addition, multimodal imaging with fluorescein angiography (FA) and OCT can be helpful in identifying subtle pathology not visualized on the fundus examination. However, imaging the neonatal fundus can present challenges both in the OR and neonatal intensive care unit (NICU).

In this article, we describe patient factors that should be considered to optimize imaging for ROP and discuss tips and tricks for fundus photography, FA, and handheld OCT.

PATIENT FACTORS

Carefully considering patient factors is important, especially in the NICU. In the multicenter eROP study, a team of certified ophthalmic imagers and patient care providers obtained retinal images. Incomplete image sets were most commonly due to poor access to the eye, poor dilation, Bell reflex, technical difficulties with the imaging equipment, and unstable medical status of the baby.[1]

Adequate dilation promotes ease of imaging and improves field of view for an appropriate fundus examination. Various combinations of topical mydriatrics, including phenylephrine and cyclopentolate, are available; with attention to systemic status and vital signs, multiple rounds may be administered to ensure complete dilation.[2]

Infants with ROP often have comorbid respiratory issues resulting in the presence of an endotracheal tube attached to a ventilator. To improve access to the eye, the ventilator apparatus can be moved away from the patient's eye, or the endotracheal tube can be extended with permission from the patient's care team. This allows the imager to better access the eye to ensure high-quality fundus photographs. It is also important that the patient is suctioned adequately prior to imaging to prevent aspiration and minimize discomfort. Furthermore, it is ideal to image infants prior to feedings to minimize aspiration risk.

In the NICU setting, comfort measures such as swaddling, oral sucrose, use of a pacifier, presence of a certified child life specialist, and, if appropriate, bedside sedation may be used to help soothe the baby prior to imaging. In addition, it is imperative to have an assistant positioned opposite the imaging equipment to secure the infant.

IMAGING

Fundus Photography

Current contact-based camera systems for fundus photography in ROP include, but are not limited to, the RetCam Envision (Natus), 3Nethra Neo (Forus Health), and Phoenix Icon (Neolight). Contact-based systems can image anterior segment structures and provide color images of the posterior pole. Imaging requires the use of an eyelid speculum and coupling gel. Limitations of contact-based fundus imaging include challenges associated with ring-based imaging, which can lead to variable exposure across an image and decreased image clarity with darkly pigmented fundi, small pupils, and media opacity.[3,4] The Bell reflex can be managed with the use of a pediatric scleral depressor; however, be mindful that excess scleral depression can distort fundus imaging.

Alternatively, noncontact imaging systems have been used in ROP, including the Optos ultra-widefield imaging system, which can capture up to 200° of the fundus. Use of the Optos requires holding the infant in the "flying baby" position in front of the camera while supporting the head and chest.

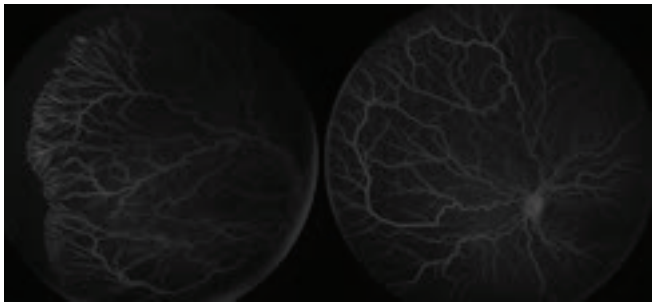

Figure 1. FA imaging shows a peripheral avascular retina and persistent vessel tortuosity following regression of disease in a neonate with severe cardiopulmonary disease.

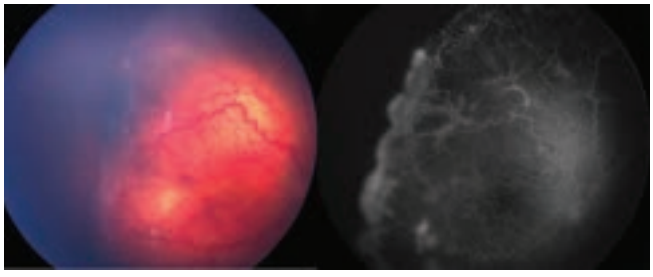

Figure 2. This side-by-side comparison shows the utility of FA alongside fundus photography in the case of type 1 ROP treated previously with bevacizumab that later developed flat neovascularization within a fibrotic ridge.

Fluorescein Angiography

FA is most commonly obtained using contact-based imaging modalities and is performed in the OR as part of an examination under anesthesia (Figures 1 and 2). With the increased use of anti-VEGF injections in ROP, FA can help to provide valuable information on the presence and degree of peripheral avascular retina and can guide laser treatment. It may also improve the sensitivity of diagnosis of stage 2 or worse disease.[4,5]

When performing FA, weight-based dosing of fluorescein dye should be calculated with a range of 5.0 mg/kg to 7.7 mg/kg. Communication with the anesthesiologist is critical regarding timing of dosing and image capture. Note that the dye should be injected as close to the intravenous catheter as possible so that the arm-to-retina timing and subsequent filling of circulation is accurate. The pressure from the imaging handpiece can impede initial flow into the choroidal and retinal vasculature; thus, the handpiece should be briefly lifted and replaced after the dye is flushed.

OCT Imaging

OCT is not currently a standard part of ROP imaging; however, OCT images can visualize the foveal pit and, in the case of preretinal hemorrhage, better assess the foveal anatomy and need for surgical intervention. Thus, OCT has great potential to supplement current ROP screening and monitoring techniques. Radial scans of the fovea can highlight foveal pit development, and peripheral scans of the temporal retina can evaluate 3D features of the ridge. OCT also has the ability to differentiate retinoschisis from retinal detachment, resulting in very different patient management.[4]

Prior to imaging, the reference arm of the device should be adjusted based on the age of the patient. While portable handheld OCT devices have made it possible to image preterm infants, one challenge of these examinations is maintaining immobility with the handheld device. The Heidelberg Spectralis features a Flex Module, which addresses this issue and allows for imaging of supine individuals with the device affixed to a moveable arm.[6] Widefield OCT can also be used to capture far peripheral pathology and for ROP disease detection, progression, and regression.[7]

OCT angiography is primarily used as a research device but may have clinical utility in the near future to characterize angiographic features of the ridge in ROP.[8]

WHY IMAGING MATTERS

With the right tools and careful assessment, pediatric retina specialists can capture the necessary imaging to ensure proper diagnosis, management, and treatment of ROP to prevent visual impairment and blindness. ■

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A MASQUERADE: LEUKEMIA RETINOPATHY OR VIRAL INFECTION?

Ocular symptoms thought to be related to malaria turned out to be signs of systemic malignancy.

BY BRIAN WOLLOCKO, MD; SAMUEL GELNICK, MD; AND ERIC SHRIER, DO, FAAO

A 35-year-old man who had recently immigrated from West Africa presented to the emergency department with fever, nausea, vomiting, diarrhea, headache, and malaise. The ophthalmology service was consulted for blurry vision. The patient reported a medical history of malarial infection, and initial bloodwork showed pancytopenia with an elevated lactate level and creatinine, suggesting acute kidney injury.

INPATIENT TESTING

Given the patients demographic and medical history, he was admitted for a presumed malarial infection and was started on a broad-spectrum antibiotic and an antiviral medication for enteric fever, typhoid, and malaria. The patient underwent a blood smear, which showed schizont-stage and ring-stage parasites; a polymerase chain reaction test of his stool was positive for giardia. He denied any past ocular history, family history, and previous medication use.

On examination, the patient's VA was 20/70 OD and 20/50 OS, and his IOP, extraocular muscles (EOM), and pupil examination findings were within normal limits. He reported no history of flashes, floaters, or sudden loss of vision. The anterior examination was unremarkable, although the dilated examination revealed scattered intraretinal and preretinal hemorrhages involving the posterior pole of each eye with peripheral areas of whitening in his right eye (Figure 1).

In the setting of a known malarial infection with significant systemic symptoms, including pancytopenia, the patient was diagnosed with malarial retinopathy. No acute intervention was recommended, and treatment of the malarial infection was initiated by his primary care team.

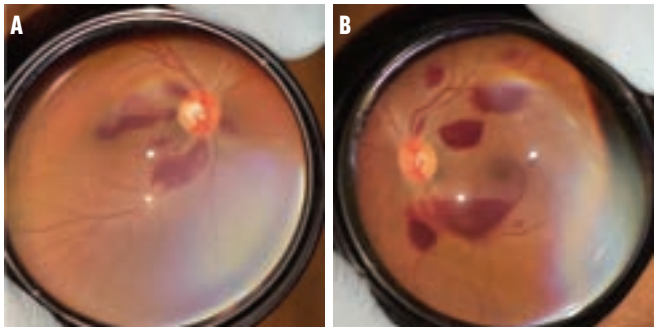

Figure 1. Dilated examination revealed scattered intraretinal and preretinal hemorrhages involving the posterior pole of the right (A) and left (B) eye.

WORSENING VISION

Seventeen days after his initial presentation, ophthalmology was consulted again because the patient reported worsening vision in his left eye for 1 day (but improvement in the right-eye vision). On examination, his BCVA was 20/20 OD and 20/400 OS. His IOP, EOM, pupils, and anterior examination findings remained within normal limits.

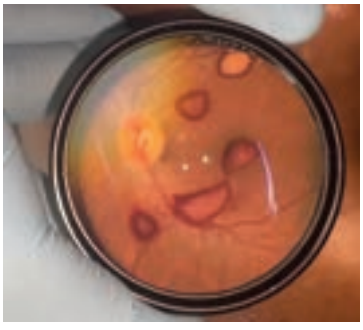

Figure 2. A dilated examination 17 days later revealed worsening of the intraretinal and preretinal hemorrhages involving the posterior pole of the left eye with a large preretinal hemorrhage overlying the macula.

A dilated examination showed significant improvement in the retinal hemorrhages with continued peripheral whitening in the right eye, but there was

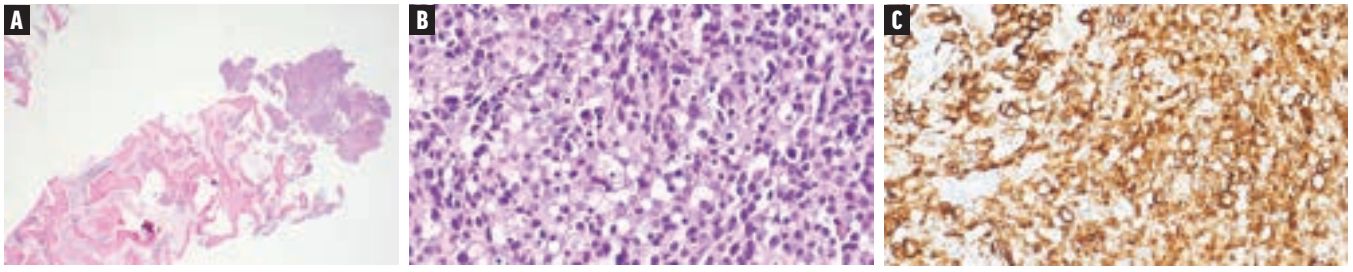

Figure 3. A bone marrow biopsy showed significantly increased cellularity in low-power field (A) and high-power field (B) in the marrow and positive staining for CD34 and CD117 proteins (C).

evolution and worsening of the intraretinal and preretinal hemorrhages involving the posterior pole of the left eye with a large preretinal hemorrhage overlying the macula (Figure 2). While the patient's malaria symptoms generally improved, his lab workup showed persistent pancytopenia resistant to transfusions.

BONE MARROW BIOPSY

The patient underwent a repeat blood smear that showed large blast cells, prompting a consultation with the hematology and oncology services, who recommended performing a bone marrow biopsy. The biopsy showed significantly increased cellularity in the marrow (Figure 3A and B) and positive staining for CD34 and CD117 proteins (Figure 3C), as well as myeloperoxidase. These findings confirmed a diagnosis of acute myeloid leukemia (AML) with superimposed malarial and giardia infections at the time of presentation. The patient's fundoscopic findings were understood to be signs of leukemic retinopathy in the setting of newly diagnosed AML.

TREATMENT APPROACH

The patient was initiated on systemic chemotherapy and monitored with serial examinations, which showed continued improvement in his retinal findings. A repeat bone marrow biopsy confirmed the treatment effect prior to discharging the patient from the hospital. Fluorescein angiography was performed upon his discharge, which showed peripheral ischemia in each eye with small hyperfluorescent foci correlating to an area of retinal whitening in the right eye (Figure 4). The patient was continued on systemic treatment, and his vision returned to baseline.

LEUKEMIC RETINOPATHY

Ocular manifestations of AML can be seen in acute or chronic disease, and all parts of the eye can be affected, although retinal involvement is most common. Critically, ocular involvement is present in a third of cases at the time of presentation and serves as an indicator of poor prognosis.[1] Leukemic ocular involvement can be primary, with direct infiltration of leukemic cells into ocular tissues, including the development of pseudohypopyon, subretinal or choroidal neoplastic collections, and optic nerve

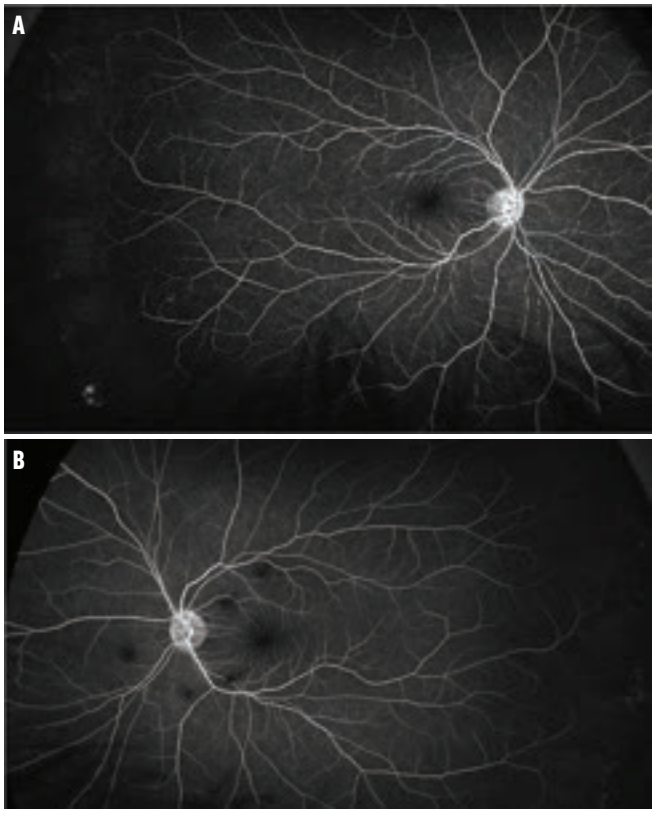

Figure 4. Fluorescein angiography performed upon the patient's discharge from the hospital showed peripheral ischemia in the right (A) and left (B) eye with small hyperfluorescent foci correlating to an area of retinal whitening in the right eye.

or vessel infiltration. More commonly, however, leukemic ophthalmic manifestations are secondary, resulting from systemic abnormalities, such as pancytopenia. Secondary findings may include retinal hemorrhages, cotton-wool spots, vascular occlusion, microaneurysms, peripheral neovascularization, and opportunistic infections.[2,3]

The ocular findings of leukemia are shared by various other ophthalmic pathologies such as anemia, thrombocytopenia, hyperviscosity, and several infectious or inflammatory conditions, including infectious endocarditis.[4,5] As such, it is critical to remain educated on the signs and symptoms and maintain a high index of suspicion for leukemia. In this case, the patient provided a history that fit the diagnosis of malarial retinopathy, and his findings were consistent with a

presentation of malarial retinopathy, specifically in an adult, which tends to be milder than its devastating presentation in children.[6] It is possible that the patient's peripheral ischemic changes were, in fact, related to the malarial infection.

Ultimately, the diagnosis of leukemic ocular involvement is made when consistent examination findings arise in the setting of a positive bone marrow biopsy, as was the case for our patient. This diagnosis is made histologically based on findings of increased marrow cellularity; staining for CD34 and CD117 indicates cellular immaturity, and other staining may help to identify cellular lineage, such as myeloperoxidase for cells of myeloid origin.[7]

Ophthalmic manifestations are often not individually addressed; rather, clinicians treat the underlying illness. Under the management of hematology and oncology, patients should be initiated on systemic chemotherapy and followed closely. From an ophthalmic standpoint, these patients should be managed with serial examinations, and even severe cases of leukemic retinopathy typically resolve with systemic therapy. An exception to this generalization would be neovascularization arising from complications of leukemic retinopathy, which can be treated with intravitreal injection of anti-VEGF agents.

THE GOOD NEWS

With appropriate management, ophthalmic manifestations of systemic leukemia have a favorable prognosis, with many patients maintaining functional visual acuity. ■

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(Continued from page 46)
and flow cytometry had confirmed an atypical B-cell population consistent with large B-cell lymphoma. The implications of these findings, along with the diagnosis of a primary intraocular lymphoma, were discussed with the patient, along with an ocular oncology referral.

At this point, the patient's hematologist/oncologist joined the care team, and an outpatient brain and orbit MRI was performed. Per his oncologist, the patient reported no additional localizing symptoms and had already had a PET-CT scan 3 months prior, and no further workup was obtained.

Over the following 2 weeks, now 30 days from initial presentation, the patient was evaluated by the ocular oncology service and started on bilateral intravitreal methotrexate. He continues to receive treatment.

DISCUSSION

Primary intraocular lymphoma is most often a high-grade, non-Hodgkin, diffuse, large B-cell lymphoma, a severe disease with poor systemic prognosis due to tropism for brain involvement. A total of 15% to 25% of primary central nervous system lymphoma cases develop ocular involvement; 56% to 90% of primary intraocular lymphoma patients eventually progress to involve the central nervous system.[1,2] Medical history of malignancy should raise suspicion for second malignancy.

Diagnosis of primary intraocular lymphoma is often delayed, with one series reporting a median time of 25 months from symptom onset.[3] Uveitis and systemic workups are often negative, prompting a diagnosis of idiopathic uveitis, which is then treated with steroids. As patients often temporarily improve on steroids, this can further delay a definitive diagnosis, which often requires a vitreous biopsy.

There is no consensus on the treatment of primary intraocular lymphoma. When disease is limited to the eye alone, radiotherapy, intravitreal chemotherapy (ie, methotrexate), systemic chemotherapy, or combination therapy have been reported to be effective treatment modalities.[4,5] ■

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THINK OUTSIDE THE BOX: CODING FOR NEW RETINA DRUGS

Stay updated as guidelines change.

BY JOY WOODKE, COE, OCS, OCSR

Several new drug treatments have made their way into retina practices recently, which should remind everyone just how essential it is to carefully consider coding and documentation guidelines. When outlining practice protocols, retina specialists and practice managers must recognize that new drug guidelines may stray from the standard protocols regarding treatment frequency, indications, billing practices, and required modifiers.

TREATMENT FREQUENCY

Frequency limitations for intravitreally injected medications are determined by the FDA label. For more than a decade, payers limited anti-VEGF treatments to no sooner than every 28 days. This limitation was based mostly on the FDA label for ranibizumab (Lucentis, Genentech/Roche) and 2 mg aflibercept (Eylea, Regeneron), and then the off-label use of bevacizumab (Avastin, Genentech/Roche). However, many new retina drugs have different frequency limitations per their unique FDA label.

For example, 8 mg aflibercept (Eylea HD, Regeneron) can be administered every 28 days, give or take a week, for the first three doses. Then the treatment can be extended to 8 to 12 (diabetic retinopathy [DR]) or 16 (wet AMD or diabetic macular edema [DME]) weeks.

Geographic atrophy (GA) therapies—pegcetacoplan (Syfovre, Apellis Pharmaceuticals) and avacincaptad pegol (Izervay, Iveric Bio/Astellas)—also have varied treatment intervals per their individual labels. Pegcetacoplan can be injected every 25 to 60 days, while avacincaptad pegol is a monthly injection, given every 28 days, give or take a week, for up to 12 months.

TREATMENT INDICATION

Medical necessity for intravitreal injections is also determined by the FDA label. This corresponds to specific ICD-10 codes that are payable with the intravitreal injection, CPT code 67028, and the HCPCS code for the drug.

For example, 8 mg aflibercept/0.07 mL and 2 mg aflibercept/0.05 mL have similar indications; however, the former does not include treatment for macular edema following retinal vein occlusion (RVO) or retinopathy of prematurity, while the latter does.

Faricimab (Vabysmo, Genentech/Roche), a dual pathway treatment, has indications for wet AMD, DME, and macular edema following RVO. DR, however, is not currently an FDA-approved indication.

Both pegcetacoplan and avacincaptad pegol are indicated for GA secondary to AMD. The FDA approval of these new GA drugs in 2023 was a significant change in covered diagnosis codes for an intravitreal injection.

Additionally, newer to the retina space are two ranibizumab biosimilars, ranibizumab-nuna (Byooviz, Samsung Bioepis/Biogen) and ranibizumab-eqrn (Cimerli, Coherus BioSciences). These two drugs have similar indications as ranibizumab with one exception: ranibizumab-nuna is not indicated for DR or DME.

TABLE. NEW RETINA DRUGS AT A GLANCE

Drug	HCPCS	Descriptor	Dosage	Billing Units	UOM	-JZ or -JW Modifier	Indications
Byooviz (Samsung Bioepis/Biogen)	Q5124	Injection, ranibizumab-nuna, biosimilar, (Byooviz), 0.1 mg	0.5 mg/0.05 mL	5	ML0.05	-JZ	wet AMD, macular edema following RVO, myopic choroidal neovascularization
Cimerli (Coherus BioSciences)	Q5128	Injection, ranibizumab-eqrn (Cimerli), biosimilar, 0.1 mg	0.3 mg/0.05 mL; 0.5 mg/0.05 mL	3; 5	ML0.05	-JZ	DR, DME; wet AMD, macular edema following RVO, myopic choroidal neovascularization
Eylea HD (Regeneron)	J0177	Injection, aflibercept HD, 1 mg	8 mg/0.07 mL	8	ML0.07	-JZ	DR, DME, wet AMD
Izervay (Iveric Bio/ Astellas)	J2782	Injection, avacincaptad pegol, 0.1 mg	2 mg/0.1 mL	20	ML0.1	-JZ	GA secondary to AMD
Syfovre (Apellis Pharmaceuticals)	J2781	Injection, pegcetacoplan, intravitreal, 1 mg	15 mg/0.1 mL	15	ML0.1	-JZ	GA secondary to AMD
Vabysmo (Genentech/Roche)	J2777	Injection, faricimab-svoa, 0.1 mg	6 mg/0.05 mL	60	ML0.05	-JZ	wet AMD, DME, macular edema following RVO

Abbreviations: DME, diabetic macular edema; DR, diabetic retinopathy; GA, geographic atrophy; RVO, retinal vein occlusion.

TREATMENT BILLING

For injected medications, billing units are reported in item 24g of the CMS-1500 or EDI loop 2400. The HCPCS descriptor indicates the dosage in mg that would equal 1 unit. The total billing units are then calculated accordingly.

For example, 0.1 mg of faricimab, HCPCS J2777, would equate to 1 unit. The dosage for faricimab is 6 mg/0.05 mL, so the billing units would be 60. The Table provides this information for other new drugs.

To reduce denied claims, practice managers and billing experts must appropriately report the unit of measure (UOM) on the claim in item 24a of the CMS-1500 or EDI loop 2410, following the NDC number and indicating the volume of the drug. The UOM is measured in ML, the liquid medication volume. Many retina drugs have a volume of 0.05 mL (eg, 2 mg aflibercept, faricimab, ranibizumab, bevacizumab), but new drugs may vary.

For example, 8 mg aflibercept has a volume of 0.07 mL and would be reported on the claim as ML0.07. GA treatments pegcetacoplan and avacincaptad pegol are reported with ML0.1, as the volume of each is 0.1 mL.

TREATMENT MODIFIER

For each new drug, clinicians must consider if a -JW or -JZ modifier is appropriate. When the discarded drug is less than 1 unit as determined by the HCPCS descriptor, or is considered overfill, append the -JZ modifier to the HCPCS code for the drug. Most new drugs are reported with the -JZ modifier; however, there are many examples of -JW modifier use in retina practices.[1]

NEW TO PRACTICE

CPT code 67028, intravitreal injection of a pharmacologic agent (separate procedure), is reported for most retina treatments. However, there are new CPT codes that represent a new approach. For example, CPT code 67516, suprachoroidal space injection of a pharmacologic agent (separate procedure), effective January 1, 2024, is currently used for suprachoroidal triamcinolone acetonide (Xipere, Bausch + Lomb and Clearside Biomedical). Additionally, Category III code 0810T, subretinal injection of a pharmacologic agent, including vitrectomy and one more retinotomy, is used to bill for a novel delivery method for gene therapy.

As retina treatments continue to evolve, remember that the status quo may be challenged, whether that is frequency limitations, indications, or coding. To stay current with these changes, visit aao.org/retinapm. ■

1. Practice management for retina. American Academy of Ophthalmology. Accessed May 14, 2024. aao.org/retinapm

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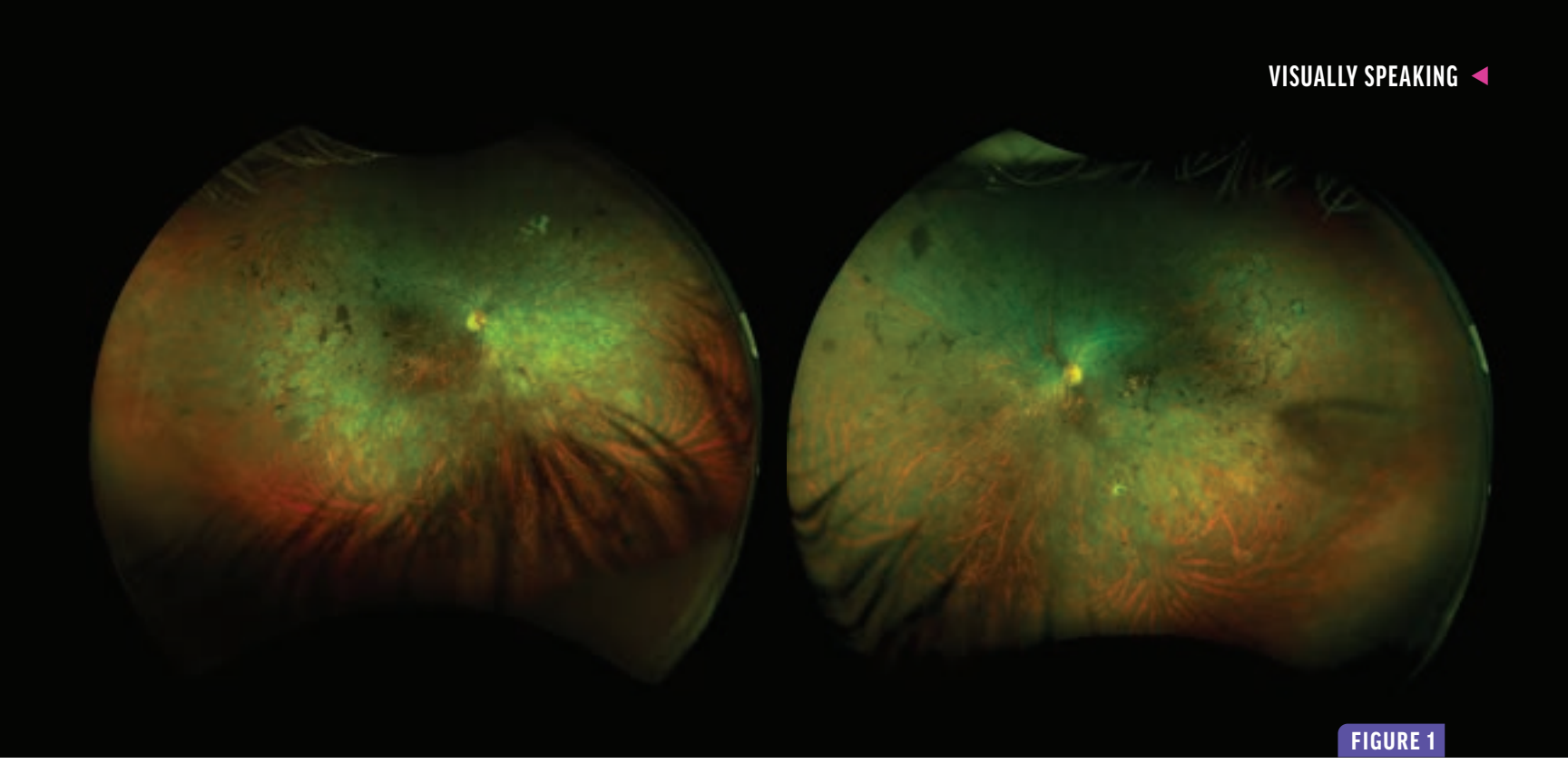

FIGURE 1

UNCOVERING *ABCA4*-ASSOCIATED RETINOPATHY

Genetic testing revealed a pathogenic variant common to several retinal degenerative diseases.

BY MIGUEL AFONSO, MD; JOÃO RAMALHÃO, MD; AND ANA MARTA, MD

A 49-year-old female patient presented with a long-standing history of decreased vision and night blindness since childhood. Past medical history was unremarkable, and the patient's family history revealed consanguinity, with parents who were cousins. Two of the patient's first cousins also experienced similar cases of visual impairment, as well as another distant relative.

Her BCVA was counting fingers OU. Fundoscopy revealed a bilateral pale optic disc, diffuse retinal pigment epithelial degeneration, and pigment clumping in each eye (Figure 1). Fundus autofluorescence showed symmetric demarcated areas of atrophy, mostly nonconfluent, throughout the posterior pole without peripapillary sparing (Figure 2).

GENETIC TESTING

The patient had been diagnosed with Stargardt disease in her early life, before coming to our service. She was referred to our department's ocular genetic specialist, who conducted a genetic workup for the first time. Testing using a next-generation sequencing 190 gene panel identified a specific pathogenic variant in the *ABCA4* gene, likely in homozygosity. The variant has been associated with various retinal conditions, including Stargardt disease, cone-rod dystrophy, retinitis pigmentosa, and retinal dystrophy. The patient was advised to avoid vitamin A supplementation and to limit sun exposure by using sunglasses. She was also referred to a low vision consultation. ■

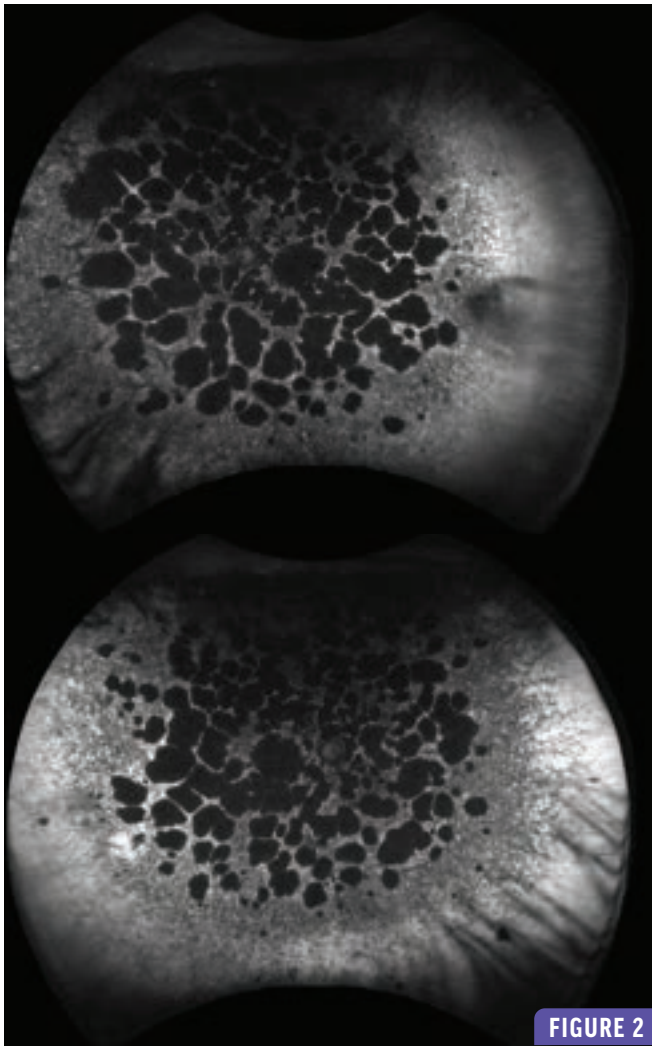

FIGURE 2

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If you have images you would like to share, email Manish Nagpal, MS, FRCS, FASRS, at drmanishnagpal@yahoo.com.

Note: Photos should be 400 dpi or higher and at least 10 inches wide.

INDEX OF ADVERTISERS

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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.

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.

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

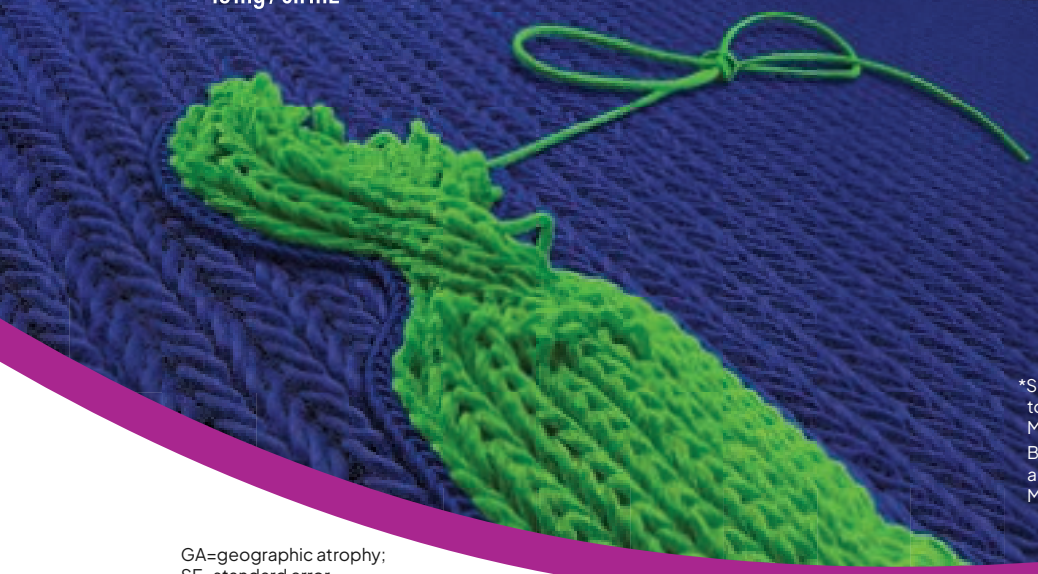
Advise patients that following SYFOVRE administration, patients are at risk of developing endophthalmitis, retinal detachments, retinal vasculitis with or without retinal vascular occlusion and neovascular AMD. If the eye becomes red, sensitive to light, painful, or if a patient develops any change in 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-30NOV2023-2.0

12/23 US-PEGGA-2200163 v4.0

SYFOVRE®
(pegcetacoplan injection)
15 mg / 0.1 mL



GA unravels so much SAVE RETINAL TISSUE BY SLOWING PROGRESSION[1-3]

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

Monthly	Every Other Month (EOM)
OAKS trial (mm^2): (3.11 vs 3.98) **22%**	OAKS trial (mm^2): (3.26 vs 3.98) **18%**
DERBY trial (mm^2): (3.28 vs 4.00) **18%**	DERBY trial (mm^2): (3.31 vs 4.00) **17%**

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

*Slope for baseline to Month 24 is an average of slope of baseline to Month 6, Month 6 to Month 12, Month 12 to Month 18, and Month 18 to Month 24.[1]

Based on a mixed effects model for repeated measures assuming a piecewise linear trend in time with knots at Month 6, Month 12, and Month 18.[1]

GA=geographic atrophy;
SE=standard error.

Explore the long-term data

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

INDICATION

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

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

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

References: 1. SYFOVRE (pegcetacoplan injection) [package insert]. Waltham, MA: Apellis Pharmaceuticals, Inc.; 2023. **2.** Pfau M, von der Emde L, de Sisternes L, et al. Progression of photoreceptor degeneration in geographic atrophy secondary to age-related macular degeneration. *JAMA Ophthalmol*. 2020;138(10):1026-1034. **3.** Bird AC, Phillips RL, Hageman GS. Geographic atrophy: a histopathological assessment. *JAMA Ophthalmol*. 2014;132(3):338-345. **4.** Data on file. Apellis Pharmaceuticals, Inc.

Apellis