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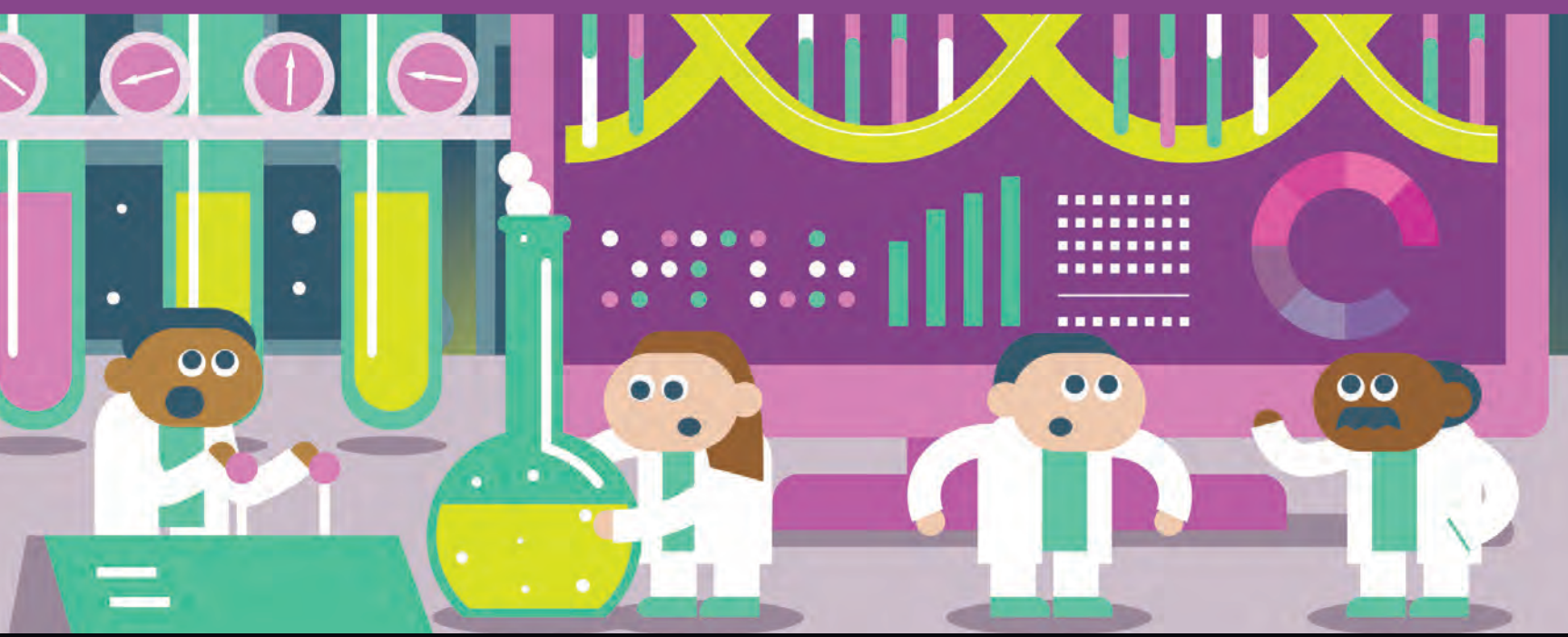
RARE AND INHERITED RETINAL DISEASES

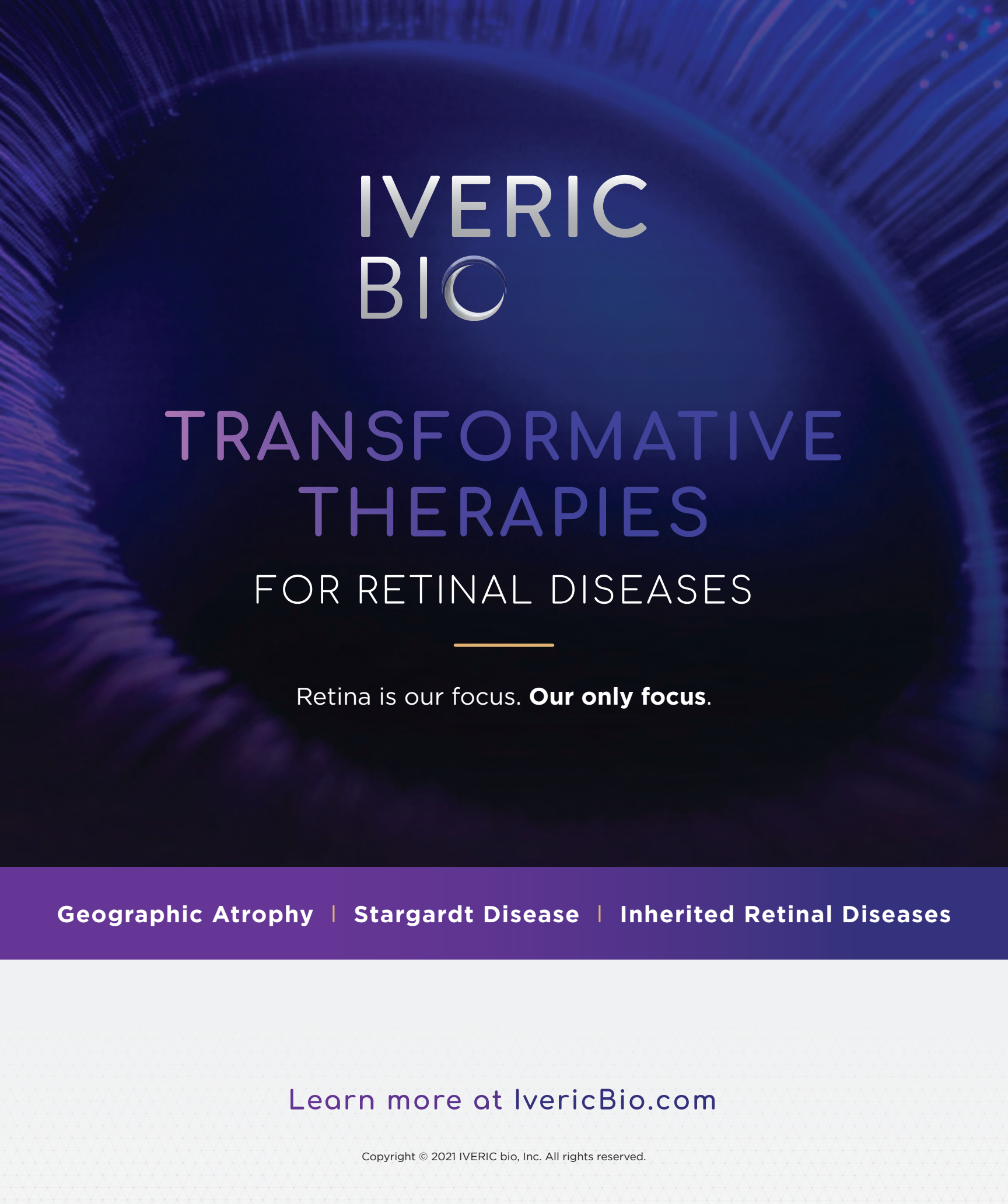
Focus on the Genes



THE UPS AND DOWNS OF GENE THERAPY RESEARCH

THE ROLE OF GENETIC COUNSELORS

A PRIMER ON PEDIATRIC UVEITIS



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ALL ABOARD THE RESEARCH TRAIN

Some of the most intriguing sessions at our retina conferences are the ones that have us scratching our heads and asking, "What is the unifying diagnosis?" That question is often followed by, "My colleague is a rockstar for diagnosing that case." For most of us, these once-a-year cases that come through our practices stand out vividly amid thousands of routine intravitreal injections and postoperative evaluations.

Patients with inherited retina diseases (IRDs) often present as a diagnostic challenge because of variable presentations and because of the difficulties we may encounter when ordering and interpreting genetic testing. Furthermore, patients with syndromic forms have other systemic comorbidities that need to be addressed, and we don't have approved therapies for the vast majority of these conditions.

Researchers at the National Institutes of Health recently published findings in *JAMA Ophthalmology* detailing what seems to be an early-onset variant of Sorsby fundus dystrophy.[1] Unlike those with a typical Sorsby presentation, patients with this rare variant reportedly present with scotomas and macular changes but preserved central vision and no choroidal neovascularization. Genetic testing revealed heterozygous variants located in the TIMP3 signal peptide sequence, leading the team to conclude that they had discovered a novel form of macular dystrophy.[1]

Imagine if a patient with this variant walked through your door with an atypical presentation of diffuse maculopathy that genetic testing showed was caused by TIMP3 signal peptide defects. You would be documenting all your findings and eagerly drafting a case presentation for the next conference. You may also be phoning a friend or two—I know I would be. That patient is going to have a lot of questions about their diagnosis and visual prognosis, and we don't have great answers for them.

The senior author of the aforementioned study, Robert B. Hufnagel, MD, PhD, director of the Ophthalmic Genomics Laboratory at the National Eye Institute, noted in a press release that he hopes the discovery will lead to novel therapies for patients with this new IRD.[2]

Statements like that used to be little more than lip service, but times have changed. Patients with *RPE65*–associated retinal dystrophy have access to a gene therapy, and researchers are working hard to expand the list of approved therapies in the coming years.

The field of gene therapy research—even its clinical use—is exploding. Of the 15 FDA-approved cellular and gene therapies (not including cord blood), nine were approved in the past 2 years.[3] Most of these are in the field of oncology, with the notable exception of voretigene neparvovec-rzyl (Luxturna, Spark Therapeutics) for the treatment of *RPE65*–associated retinal dystrophy.

Myriad trials are moving forward in the retina space, with plenty of ups and downs to keep us on our toes. Some phase 1/2 trials continue to show promise, but the field was dealt a few hard blows when three trials recently failed to meet their primary endpoints.

That doesn't mean researchers are giving up. Far from it. Traditional gene augmentation strategies already seem like well-trodden approaches with the advent of CRISPR/Cas9 systems that can open up new therapeutic avenues such as the regulation of gene expression, base and prime editing, and multiplexed genome targeting. The work being done is impressive and will likely lead to ground-breaking therapies in the near future.

This issue of *Retina Today* examines where these advances stand. We may not have anything concrete to offer patients yet, but any hope we can give them will be well received.

The field of retina is a fast-moving train with a lot to digest regarding clinical trial successes and failures and novel therapies and clinical approaches. We could all use some shorthand of it all, particularly when it comes to IRD clinical research. I hope this issue fits the bill. ■

AARON NAGIEL, MD, PHD

1. Guan B, Huryn LA, Hughes AB, et al. Early-onset TIMP3-related retinopathy associated with impaired signal peptide. [Preprint published online June 9, 2022] *JAMA Ophthalmol*.
2. National Institutes of Health. NIH researchers discover new genetic eye disease. Accessed June 16, 2022. www.nih.gov/news-events/news-releases/nih-researchers-discover-new-genetic-eye-disease
3. US Food and Drug Administration. Approved cellular and gene therapy products. Accessed June 16, 2022. www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products

SPOTLIGHT ON UVEITIS:

This issue also contains a subfocus on uveitis to help you manage this equally challenging condition. Similar to patients with inherited retinal diseases, those with uveitis present with any number of subtle or not-so-subtle examination findings, which can complicate their diagnosis and treatment. The clinical tips and tricks in this issue may come in handy the next time a patient with uveitis needs extra care to get their disease under control. Our expert authors tackle pediatric uveitis, OCT biomarkers, and how to manage patients without a local uveitis referral.

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(fluocinolone acetonide intravitreal implant) 0.18 mg

Discover continuous calm in uveitis[1]

YUTIQ is designed to deliver a sustained release of fluocinolone for up to 36 months for patients with chronic non-infectious uveitis affecting the posterior segment of the eye[1]

- Proven to reduce uveitis recurrence at 6 and 12 months[1]*
  At 6 months–18% for YUTIQ and 79% for sham for Study 1 and 22% for YUTIQ and 54% for sham for Study 2 (*P*<.01). At 12 months–28% for YUTIQ and 86% for sham for Study 1 and 33% for YUTIQ and 60% for sham for Study 2.
- Extended median time to first recurrence of uveitis[1,2]
  At 12 months–NE† for YUTIQ/92 days for sham in Study 1; NE for YUTIQ/187 days for sham in Study 2.
- Mean intraocular pressure (IOP) increase was comparable to sham[1,2]
  Study was not sized to detect statistically significant differences in mean IOP.

For more information, visit **YUTIQ.com**

*Study design: The efficacy of YUTIQ was assessed in 2 randomized, multicenter, sham-controlled, double-masked, Phase 3 studies in adult patients (N=282) with non-infectious uveitis affecting the posterior segment of the eye. The primary endpoint in both studies was the proportion of patients who experienced recurrence of uveitis in the study eye within 6 months of follow-up; recurrence was also assessed at 12 months. Recurrence was defined as either deterioration in visual acuity, vitreous haze attributable to non-infectious uveitis, or the need for rescue medications.

†NE=non-evaluable due to the low number of recurrences in the YUTIQ group.

INDICATIONS AND USAGE

YUTIQ® (fluocinolone acetonide intravitreal implant) 0.18 mg is indicated for the treatment of chronic non-infectious uveitis affecting the posterior segment of the eye.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

Ocular or Periocular Infections: YUTIQ is contraindicated in patients with active or suspected ocular or periocular infections including most viral disease of the cornea and conjunctiva including active epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections and fungal diseases.

Hypersensitivity: YUTIQ is contraindicated in patients with known hypersensitivity to any components of this product.

WARNINGS AND PRECAUTIONS

Intravitreal Injection-related Effects: Intravitreal injections, including those with YUTIQ, have been associated with endophthalmitis, eye inflammation, increased or decreased intraocular pressure, and choroidal or retinal detachments. Hypotony has been observed within 24 hours of injection and has resolved within 2 weeks. Patients should be monitored following the intravitreal injection.

Steroid-related Effects: Use of corticosteroids including YUTIQ may produce posterior subcapsular cataracts, increased intraocular pressure and glaucoma. Use of corticosteroids may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses. Corticosteroids are not recommended to be used in patients with a history of ocular herpes simplex because of the potential for reactivation of the viral infection.

Risk of Implant Migration: Patients in whom the posterior capsule of the lens is absent or has a tear are at risk of implant migration into the anterior chamber.

ADVERSE REACTIONS

In controlled studies, the most common adverse reactions reported were cataract development and increases in intraocular pressure.

Please see brief summary of full Prescribing Information on adjacent page.

References: 1. YUTIQ® (fluocinolone acetonide intravitreal implant) 0.18 mg full US Prescribing Information. EyePoint Pharmaceuticals, Inc. May 2021. **2.** Data on file.

EyePoint® Pharmaceuticals

480 Pleasant Street, Suite B300, Watertown, MA 02472
08/2021
US-YUT-2100061

YUTIQ® (fluocinolone acetonide intravitreal implant) 0.18 mg, for intravitreal injection
Initial U.S. Approval: 1963

BRIEF SUMMARY: Please see package insert for full prescribing information.

1. INDICATIONS AND USAGE. YUTIQ® (fluocinolone acetonide intravitreal implant) 0.18 mg is indicated for the treatment of chronic non-infectious uveitis affecting the posterior segment of the eye.

4. CONTRAINDICATIONS. 4.1. Ocular or Periocular Infections. YUTIQ is contraindicated in patients with active or suspected ocular or periocular infections including most viral disease of the cornea and conjunctiva including active epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections and fungal diseases. **4.2. Hypersensitivity.** YUTIQ is contraindicated in patients with known hypersensitivity to any components of this product.

5. WARNINGS AND PRECAUTIONS. 5.1. Intravitreal Injection-related Effects. Intravitreal injections, including those with YUTIQ, have been associated with endophthalmitis, eye inflammation, increased or decreased intraocular pressure, and choroidal or retinal detachments. Hypotony has been observed within 24 hours of injection and has resolved within 2 weeks. Patients should be monitored following the intravitreal injection *[see Patient Counseling Information (17) in the full prescribing information]*. **5.2. Steroid-related Effects.** Use of corticosteroids including YUTIQ may produce posterior subcapsular cataracts, increased intraocular pressure and glaucoma. Use of corticosteroids may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses. Corticosteroids are not recommended to be used in patients with a history of ocular herpes simplex because of the potential for reactivation of the viral infection. **5.3. Risk of Implant Migration.** Patients in whom the posterior capsule of the lens is absent or has a tear are at risk of implant migration into the anterior chamber.

6. ADVERSE REACTIONS. 6.1. Clinical Studies Experience. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. Adverse reactions associated with ophthalmic steroids including YUTIQ include cataract formation and subsequent cataract surgery, elevated intraocular pressure, which may be associated with optic nerve damage, visual acuity and field defects, secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera. Studies 1 and 2 were multicenter, randomized, sham injection-controlled, masked trials in which patients with non-infectious uveitis affecting the posterior segment of the eye were treated once with either YUTIQ or sham injection, and then received standard care for the duration of the study. Study 3 was a multicenter, randomized, masked trial in which patients with non-infectious uveitis affecting the posterior segment of the eye were all treated once with YUTIQ, administered by one of two different applicators, and then received standard care for the duration of the study. Table 1 summarizes data available from studies 1, 2 and 3 through 12 months for study eyes treated with YUTIQ (n=226) or sham injection (n=94). The most common ocular (study eye) and non-ocular adverse reactions are shown in Table 1 and Table 2.

Table 1: Ocular Adverse Reactions Reported in ≥ 1% of Subject Eyes and Non-Ocular Adverse Reactions Reported in ≥ 2% of Patients

Ocular		
ADVERSE REACTIONS	**YUTIQ (N=226 Eyes) n (%)**	**Sham Injection (N=94 Eyes) n (%)**
Cataract[1]	63/113 (56%)	13/56 (23%)
Visual Acuity Reduced	33 (15%)	11 (12%)
Macular Edema	25 (11%)	33 (35%)
Uveitis	22 (10%)	33 (35%)
Conjunctival Hemorrhage	17 (8%)	5 (5%)
Eye Pain	17 (8%)	12 (13%)
Hypotony Of Eye	16 (7%)	1 (1%)
Anterior Chamber Inflammation	12 (5%)	6 (6%)
Dry Eye	10 (4%)	3 (3%)
Vitreous Opacities	9 (4%)	8 (9%)
Conjunctivitis	9 (4%)	5 (5%)
Posterior Capsule Opacification	8 (4%)	3 (3%)
Ocular Hyperemia	8 (4%)	7 (7%)
Vitreous Haze	7 (3%)	4 (4%)
Foreign Body Sensation In Eyes	7 (3%)	2 (2%)
Vitritis	6 (3%)	8 (9%)
Vitreous Floaters	6 (3%)	5 (5%)
Eye Pruritus	6 (3%)	5 (5%)
Conjunctival Hyperemia	5 (2%)	2 (2%)
Ocular Discomfort	5 (2%)	1 (1%)
Macular Fibrosis	5 (2%)	2 (2%)
Glaucoma	4 (2%)	1 (1%)
Photopsia	4 (2%)	2 (2%)

(continued)

Table 1: Ocular Adverse Reactions Reported in ≥ 1% of Subject Eyes and Non-Ocular Adverse Reactions Reported in ≥ 2% of Patients

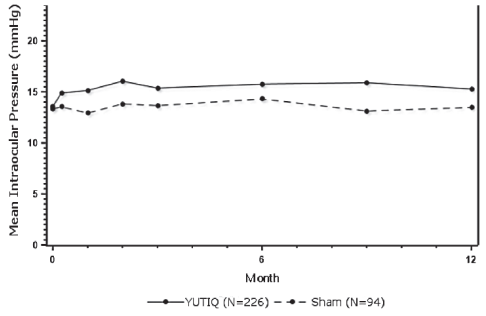
Ocular		
ADVERSE REACTIONS	**YUTIQ (N=226 Eyes) n (%)**	**Sham Injection (N=94 Eyes) n (%)**
Vitreous Hemorrhage	4 (2%)	0
Iridocyclitis	3 (1%)	7 (7%)
Eye Inflammation	3 (1%)	2 (2%)
Choroiditis	3 (1%)	1 (1%)
Eye Irritation	3 (1%)	1 (1%)
Visual Field Defect	3 (1%)	0
Lacrimation Increased	3 (1%)	0
Non-ocular		
ADVERSE REACTIONS	**YUTIQ (N=214 Patients) n (%)**	**Sham Injection (N=94 Patients) n (%)**
Nasopharyngitis	10 (5%)	5 (5%)
Hypertension	6 (3%)	1 (1%)
Arthralgia	5 (2%)	1 (1%)

1. Includes cataract, cataract subcapsular and lenticular opacities in study eyes that were phakic at baseline. 113 of the 226 YUTIQ study eyes were phakic at baseline; 56 of 94 sham-controlled study eyes were phakic at baseline.

Table 2: Summary of Elevated IOP Related Adverse Reactions

ADVERSE REACTIONS	YUTIQ (N=226 Eyes) n (%)	Sham (N=94 Eyes) n (%)
IOP elevation ≥ 10 mmHg from Baseline	50 (22%)	11 (12%)
IOP elevation > 30 mmHg	28 (12%)	3 (3%)
Any IOP-lowering medication	98 (43%)	39 (41%)
Any surgical intervention for elevated IOP	5 (2%)	2 (2%)

Figure 1: Mean IOP During the Studies



8. USE IN SPECIFIC POPULATIONS. 8.1 Pregnancy. Risk Summary. Adequate and well-controlled studies with YUTIQ have not been conducted in pregnant women to inform drug associated risk. Animal reproduction studies have not been conducted with YUTIQ. It is not known whether YUTIQ can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. YUTIQ should be given to a pregnant woman only if the potential benefit justifies the potential risk to the fetus. All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the United States general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. **8.2 Lactation.** Risk Summary. Systemically administered corticosteroids are present in human milk and can suppress growth, interfere with endogenous corticosteroid production. Clinical or nonclinical lactation studies have not been conducted with YUTIQ. It is not known whether intravitreal treatment with YUTIQ could result in sufficient systemic absorption to produce detectable quantities of fluocinolone acetonide in human milk, or affect breastfed infants or milk production. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for YUTIQ and any potential adverse effects on the breastfed child from YUTIQ. **8.4 Pediatric Use.** Safety and effectiveness of YUTIQ in pediatric patients have not been established. **8.5 Geriatric Use.** No overall differences in safety or effectiveness have been observed between elderly and younger patients.

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DIGITAL EXCLUSIVES

The Evolution of Gene Therapy Technologies
By Gustavo De Moraes, MD, PhD, MPH, and Christian Sundstrom

READ IT NOW

Uveitis for Rural Retina Gurus
By Christopher G. Fuller, MD, and Steven Yeh, MD

READ IT NOW

DEPARTMENTS

JULY/AUGUST 2022
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NEI RESEARCHERS DISCOVER NEW GENETIC EYE DISEASE

Researchers from the National Eye Institute (NEI) have identified a novel macular dystrophy. The scientists' findings on the disease, which is yet to be named, have been published online in *JAMA Ophthalmology*.[1]

Macular dystrophies usually cause central visual loss because of mutations in several genes, including *ABCA4*, *BEST1*, *PRPH2*, and *TIMP3*. As a point of comparison, in the study the researchers referenced Sorsby fundus dystrophy, a genetic eye disease specifically linked to *TIMP3* variants. Patients with Sorsby fundus dystrophy usually develop symptoms in adulthood and often have sudden changes in visual acuity due to choroidal neovascularization (CNV). *TIMP3* is a protein that helps regulate retinal blood flow and is secreted from the retinal pigment epithelium (RPE). All *TIMP3* gene mutations reported are in the mature protein after it has been "cut" from RPE cells in a process called "cleavage."

However, the researchers found two patients that had *TIMP3* variants not in the mature protein, but in the short signal sequence the gene uses to cut the protein from the cells. The variant prevents cleavage, which traps the protein in the cell and creates RPE toxicity, the researchers noted in an NEI news release.

The research team followed these findings with clinical evaluations and genetic testing of the patients' family members to verify that the new *TIMP3* variants are connected to this atypical maculopathy.

"In this case, we had seen a couple of families who had a similar maculopathy, and when we went to look at their genetic testing results, both had a variance of uncertain significance in *TIMP3* in the beginning of the protein," Rob Hufnagel, MD, PhD, senior author and director of the Ophthalmic Genomics Laboratory at NEI, said in an interview with *Retina Today*. "These hadn't been recognized before as disease-associated, so when we started looking at the pattern of disease and inheritance and where these variants were located, we made the hypothesis that they were affecting the signal peptide of *TIMP3*. And then we sought to do functional studies to demonstrate that they were indeed pathogenic and would disrupt the normal function of *TIMP3*."

The researchers determined that those affected with the novel macular dystrophy had scotomas and changes in their maculas indicative of disease but, for now, have preserved central vision and no CNV.

"It's similar to other macular dystrophies and similar to the *TIMP3*-related Sorsby fundus dystrophy in that it primarily affects the macula where central vision is mediated. And we do see similar macular atrophy and degeneration of the photoreceptor and RPE layer in the macula, specifically. There are some atrophic lesions just outside that region as well," Dr. Hufnagel said. "How it differs so far from Sorsby fundus dystrophy is that, in our patients, we've not seen CNV, which can lead to bleeding via hemorrhaging of those new vessels. And we also don't see as much thickening of the Bruchs membrane. So, we're trying to understand whether this is something that's perhaps specific to these two families and to these variants, or maybe we're still uncovering the spectrum of these conditions."

NEI's Ophthalmic Genomics Laboratory gathers and manages specimens and diagnostic data from patients who have been recruited into multiple studies within the NEI clinical program to facilitate research of rare eye diseases, including Sorsby fundus dystrophy. Dr. Hufnagel said having such an integrated clinical laboratory with clinical care can be very important for providing answers to affected patients.

"We were able to see the patient in our clinic with our wonderful clinical team of ophthalmologists and genetic counselors. The clinical lab was able to perform the analyses to establish the pattern in this new type of variant in *TIMP3*, and then perform functional studies," Dr. Hufnagel said. This information helps to educate patients, he added.

Dr. Hufnagel said that discovering novel disease mechanisms may help patients that have been looking for the correct diagnosis and will hopefully lead to new therapies.

The study was funded by the NEI Intramural Research Program. ■

1. Guan B, Huryn LA, Hughes AB, et al. Early-onset TIMP3-related retinopathy associated with impaired signal peptide. [Preprint published online June 9, 2022] *JAMA Ophthalmol*.

(Continued on page 13)


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IN THE VBS HOT SEAT: iOCT, WET AMD, AND ROP

Vit-Buckle faculty tackled tough debates on the latest technologies and treatment approaches.

BY GRANT A. JUSTIN, MD; YUXI ZHENG, MD; AND NITA VALIKODATH, MD, MS

Debates are a long-standing tradition at the Vit-Buckle Society's (VBS) annual meeting. This year, experts put on a spirited show defending their stance on techniques and technologies that are forcing many to rethink their in-office and OR strategies.

DEBATE 1: INTRAOPERATIVE OCT

The first discussion was kicked off by Dilraj S. Grewal, MD, from Duke University, arguing that intraoperative OCT (iOCT) is necessary, and Katherine E. Talcott, MD, from Cleveland Clinic, stating that iOCT is useless. Dr. Grewal revisited the evolution of surgical microscopes, which now can incorporate heads-up display and iOCT. This new technology offers a "Google Street View" and "takes the guesswork out of surgery," he stated. Dr. Grewal emphasized several advantages of iOCT, including better tissue visualization. He described a case of optic disc maculopathy for which iOCT was helpful in visualizing platelet rich plasma. In addition, iOCT offers unique depth feedback, such as the proximity of instruments to intraocular tissues. iOCT can also help surgeons obtain more accurate volumetric measurements, which is useful during subretinal delivery. Furthermore, iOCT can be valuable for training surgical fellows. In the future, real-time feedback may be possible when iOCT is integrated with artificial intelligence. He concluded that iOCT is necessary for further innovation in retina.

Dr. Talcott argued that iOCT does not change clinical decision making in the OR for most bread-and-butter cases. To drive home her point, she walked the audience through a typical OR day with cases such as a non-clearing vitreous hemorrhage in proliferative diabetic retinopathy, macular hole, traumatic subluxed intraocular lens, and retinal detachment. In these cases, iOCT did not change her surgical plan; instead, it caused longer operating times. She also pointed out other disadvantages, such as increased cost and lack of reimbursement. She stated that iOCT images make for great presentations but are not practical for everyday use.

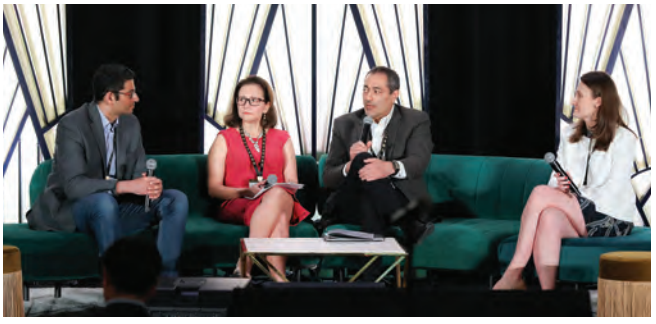

Image courtesy of Kevin Caldwell.

Figure. Dilraj S. Grewal, MD, (left), and Katherine E. Talcott, MD, (right) discuss the pros and cons of intraoperative OCT with session moderators Sandra R. Montezuma, MD, (middle left) and Tarek S. Hassan, MD (middle right). Image courtesy of Kevin Caldwell.

In the discussion that followed, some attendees and moderators agreed that iOCT can be a distraction because the surgeon must monitor it during each case and using iOCT successfully has a learning curve. Others admitted that iOCT comes in handy for complex cases, such as pediatric retinal detachments, or high-precision cases like macular holes. Ultimately, the room consensus was that current systems are not well-equipped to accommodate iOCT but as technology evolves, it will become cheaper, easier to use, and allow for faster surgeries. In the future, robotic-assisted surgery may be employed, and iOCT will be necessary in these cases.

DEBATE 2: WET AMD THERAPIES

The next debate focused on changes to our wet AMD armamentarium, highlighting the port delivery system (PDS) with ranibizumab (Susvimo, Genentech/Roche) and gene therapy versus standard anti-VEGF therapy.

Ashley M. Crane, MD, of the Retina Vitreous Associates of Florida, presented on the PDS and outlined its implantation procedure and refill process. She noted possible complications, including dislocation of the implant, and the device's black box FDA warning of a threefold higher risk of endophthalmitis. The risk is associated with conjunctival erosion.

Still, 95% of patients did not require supplemental treatment during the 24-week period. Critically, 92% of patients preferred the PDS over intravitreal injections, she stated.

Next, Robert L. Avery, MD, of California Retina Consultants, discussed how gene therapy is poised to revolutionize the treatment of AMD. The benefit of a gene therapy treatment is that it is one and done, Dr. Avery said. One study found that treatment with Regenxbio's RGX-314 gene therapy candidate led to a 97% reduction in the need for anti-VEGF injections at 2 years. He discussed a patient who required 13 injections in the year prior to treatment with RGX-314—and zero rescue injections after treatment.

Finally, Esther Lee Kim, MD, of Orange County Retina, rocked the house with her lecture on the continued use of anti-VEGF injections. She began by emphasizing that anti-VEGF therapy is the standard and provides excellent visual acuity gains. We have given millions of injections with a < 0.1% risk of endophthalmitis, she said. Further, injections don't require a trip to the OR, and they provide good durability with 45% of patients treated with either aflibercept (Eylea, Regeneron) or faricimab (Vabysmo, Genentech/Roche) able to extend to injections every 16 weeks.

After her impassioned presentation, the audience overwhelmingly agreed that anti-VEGF injections remain the treatment of choice.

DEBATE 3: MANAGING RETINOPATHY OF PREMATURITY

The final debate addressed retinopathy of prematurity (ROP) treatments. Safa Rahmani, MD, MS, a pediatric retina surgeon at Northwestern University, first defended laser photocoagulation for ROP, followed by Eric Nudleman, MD, PhD, a pediatric retina surgeon at Shiley Eye Institute at the University of California San Diego Health, who argued for the use of anti-VEGF therapy.

Dr. Rahmani noted that laser photocoagulation for ROP is an effective treatment with easy follow-up and no surprise reactivations. She emphasized the 30-year history of success with lasers, stating that the Early Treatment for Retinopathy of Prematurity study is already 2 decades old. Laser treatment is still the current standard, she said. For patients who are at risk for poor follow-up, performing adequate laser treatments is often enough, she added, while anti-VEGF injections come with a risk for reactivation. Dr. Rahmani highlighted other negatives of using anti-VEGF injections, such as the possibility of systemic side effects of anti-VEGF therapy in developing infants.

Dr. Nudleman then defended the use of intravitreal anti-VEGF injections for the treatment of ROP, highlighting advantages such as its rapid response, potential for larger visual field with reduced myopia, and its ability to be performed bedside. He also acknowledged the disadvantages of late recurrence and systemic side effects. In theory, anti-VEGF injections could have neurodevelopmental systemic risks, he admitted. However, he noted that studies have not shown any difference in these risks between groups that did and did not use anti-VEGF agents. He then brought up the increased risk of adverse effects of anesthesia required for laser photocoagulation in the smallest, sickest infants. He ended by saying that if infants have persistent avascular retina, you can always laser when the patient is older.

These talks were followed by a lively discussion of the importance of laser as a more permanent option for ROP, which should be considered for patients at-risk for loss to follow-up. Still, some argued that many patients may not even need laser after anti-VEGF therapy. Audience members expressed their preference for laser versus anti-VEGF therapy. Dr. Nudleman added that he uses anti-VEGF agents initially in the inpatient setting and follows patients closely to see if they need additional laser. He noted that about 75% of patients eventually need laser photocoagulation, but 25% of them can revascularize. Another great pearl by session moderator Sandra R. Montezuma, MD, from the University of Minnesota, was that you can minimize the risks of anti-VEGF treatments by using the SAFER mnemonic: **S**horter needle (32-gauge, 4 mm), using **A**ntiseptic iodine, **F**ollow-up after the procedure, **E**xtra attention to personal protective equipment, and **R**eturn in 1 to 2 weeks.

After a great discussion of the nuances of choosing laser versus anti-VEGF injections, there was overwhelming support for the use of anti-VEGF therapy in infants with ROP.

THE PATH FORWARD

Active audience participation that followed each debate made clear the importance of collaboration—and keeping an open mind (Figure). iOCT is still in its infancy, as are many AMD therapies and ROP approaches. While these therapies and technologies did not win this year, advances in the field may lead to very different outcomes in the years to come. ■

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WEST COAST CONFERENCE VIBES


The annual Pacific Retina Club was chock-full of case presentations, panel discussions, and top-notch education.

BY TIMOTHY J. PEIRIS, MD, AND BRIAN A. LEE, MD

The 8th annual Pacific Retina Club, organized by David Sarraf, MD; SriniVas R. Sadda, MD; and H. Richard McDonald, MD, provided attendees with a wonderful blend of case presentations, cutting-edge educational sessions, and lively discussion (Figure). Here, we outline some of the noteworthy happenings from the event.

CASES GALORE

Held at the University of California Los Angeles on April 1-2, the event was no joke, kicking off with more than 50 clinical case presentations that kept the audience on its toes with discussions of genetic, infectious, inflammatory, and toxic cases.

Medical students, residents, and fellows presented first with mystery cases, but it proved difficult to trick the panelists. Phototoxicity and toxicity from anastrozole, didanosine (Videx, Bristol-Myers Squibb), pentosan polysulfate sodium (Elmiron, Janssen Pharmaceuticals), deferoxamine (Desferal, Novartis), and latanoprost were discussed. The audience was captivated by the range of infectious cases, such as a case of tuberculosis that took an unusual turn with an ovarian mass. The trainee session was capped by a debate about whether a patient's choroidal thickness changes were due to uveitis from a herpetic infection or steroid administration.

In the afternoon, David S. Boyer, MD, discussed a case of sterile endophthalmitis that cropped up after switching from prefilled syringes to vials; he noted the decreasing frequency of endophthalmitis with prefilled syringes compared with vial injections.

The audience and panelists were stumped by a case, presented by Paul Bernstein, MD, PhD, of diffuse retinal pigment epithelial atrophy. He finally revealed that it was caused by ingestion of potassium iodide pills—used to protect the thyroid from radioactive iodine in the event of a nuclear emergency. The session concluded with a presentation on the importance of using automatically segmented maps to highlight ganglion cell layer loss.

The highlight of the day was the Alexander R. Irvine Lecture given by Jay S. Duker, MD, who discussed the past, present, and future of OCT. The award was presented by Dr. McDonald.

Figure. The conference organizers were honored to be joined by many colleagues to help them provide exceptional education. Pictured here are (left to right): H. Richard McDonald, MD; Carl D. Regillo, MD; David R. Chow, MD; Baruch D. Kuppermann, MD, PhD; Steven D. Schwartz, MD; and Tarek S. Hassan, MD.

PANELS, EDUCATION, AND ANTICS

The second day of the conference started with no less energy than the first. K. Bailey Freund, MD, and Dr. Sadda led things off by moderating a host of basic science lectures. Nadia Waheed, MD, MPH, discussed progression modeling of geographic atrophy, while Christine A. Curcio, PhD, touched on progression modeling of hyperreflective foci in AMD. This was followed by Dr. McDonald leading an action-packed surgical panel, which included J. Michael Jumper, MD; Colin McCannel, MD; Gaurav K. Shah, MD; and Homayoun Tabandeh, MD. The cases were presented in a rapid-fire style, with some panelists only having time to answer with a quick sentence or two before Dr. McDonald cried out, "Correct!" and proceeded to the next image.

The tumor panel that followed, moderated by William F. Mieler, MD, was similarly engaging, and Amani A. Fawzi, MD, kicked off a star-studded panel on retinal imaging with her presentation, "Predicting progression of diabetic retinopathy in OCTA." This was followed by a fascinating talk by David Brown, MD, who discussed increased choroidal thickness seen in NASA astronauts during spaceflight.

PACIFIC RETINA CLUB

Richard Spaide, MD, bookended the imaging session with amazing new OCT and 3D images of the vitreous. Another imaging panel moderated by Dr. Duker led into an illuminating debate regarding a series of cases with subtle OCT findings.

The pediatric surgery panel, moderated by Dr. Jumper, provided attendees with the latest on difficult pediatric retina cases and choices regarding prophylactic barrier laser in Stickler syndrome. Conference organizers Drs. Sadda and Sarraf presented their work regarding OCT biomarkers for progression of intermediate AMD and non-neovascular fluid in AMD, respectively.

The uveitis session was moderated by Sunil Srivastava, MD, and included Emmett Cunningham, MD, PhD, MPH; Quan Nguyen, MD, MSc; and University of California Los Angeles' very own Dr. Edmund Tsui, MD. Carl D. Regillo, MD, presented 2-year data from the phase 3 faricimab trials for treating diabetic macular edema in the diabetes session.

A highlight of the retinal vascular session, moderated by Michael Ip, MD, and Dr. Tabandeh, was a talk by Mathieu Bakhoum, MD, PhD, in which he discussed retinal ischemic perivascular lesions, an imaging biomarker of cardiovascular disease. Dr. Bakhoum presented data linking subtle deflections and characteristic deformations in the outer nuclear layer to cardiovascular pathology. The day closed out with a surgical panel moderated by Steven D. Schwartz, MD, and a discussion of the latest in wet AMD trials moderated by Dr. Boyer and Susan Bressler, MD.

Camaraderie among the faculty and trainees was evident throughout the event. The two days were filled with spirited debate, abrupt exclamations, and plenty of good humor. Dr. Sarraf was not shy to challenge his fellow faculty on naming the 80s songs that played during CME questions, and he channeled Will Smith when he proclaimed to a presenter on stage, "Keep Dr. Sadda's name out of your mouth!" (met with a chorus of applause and cheers).

There were many introductions and reunions among the fellows and attendings, some of whom had only communicated via email during the pandemic. By the time the organizers brought the 8th annual Pacific Retina Club to a close, the only thought on our minds was: We can't wait for next year! ■

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(Continued from page 8)

Pharma Updates from Eyewire+

The first half of the year has been busy for industry. Here's a roundup of significant pharmaceutical news breaks.

Apellis submitted a New Drug Application to the FDA for its investigational, targeted C3 therapy, pegcetacoplan, for the treatment of geographic atrophy (GA) secondary to AMD. The application is based on phase 3 clinical trial data showing clinically meaningful reduction of GA lesion growth across a population of > 1,500 study participants. A decision from the FDA is expected in August.

Bausch + Lomb was granted a permanent, product-specific code, J3299, by the United States Centers for Medicare and Medicaid Services for its 1 mg triamcinolone acetonide (Xipere), effective for provider billing on July 1.

Biogen and Samsung Bioepis launched the first biosimilar drug ranibizumab-nuna (Byooviz) in the United States. This biosimilar is FDA-approved for the treatment of wet AMD, macular edema following retinal vein occlusion, and myopic choroidal neovascularization and is now commercially available through major US distributors.

EyePoint Pharmaceuticals and **OcuMension Therapeutics** received approval from China's Center for Drug Evaluation of the National Medical Products Administration for 0.18 mg fluocinolone acetonide intravitreal implant (Yutiq) to treat chronic noninfectious uveitis affecting the posterior segment of the eye.

In June, **Novartis** announced the FDA approval of 6 mg brolucizumab-dbll (Beovu) for the treatment of diabetic macular edema. Approval is based on positive 1-year data from phase 3 clinical trials showing noninferior visual acuity gains compared with aflibercept (Eylea, Regeneron) and significant reduction in central subfield thickness among patients treated with brolucizumab-dbll.

OcuMension Therapeutics, partner to **Alimera Sciences**, received approval from the National Medical Products Administration in China to begin a randomized, multicenter phase 3 clinical trial of its 0.19 mg fluocinolone acetonide intravitreal implant (Iluvien). The goal of the trial will be to gather data supporting approval for the company to market the drug in China for the same indication as in the United States (eg, diabetic macular edema previously treated with corticosteroids).

In June, **Ocuphire** was issued a new patent from the United States Patent and Trademark Office for its late-stage oral drug candidate for the treatment of diabetic eye disease, APX3330. This patent has a longer expiry date (up to the year 2038) and broadens coverage of the drug to include the treatment of chronic pain and inflammation in patients with diabetes. Topline phase 2b data on APX3330 for the treatment of diabetic retinopathy and diabetic macular edema is expected later this year, according to Mina Sooch, MBA, founder and CEO of the company.

To find more eye care news, scan the QR code or visit *Eyewire+* online at eyewire.news.

JAYANTH SRIDHAR, MD

Please share with us your background.

I was born and raised in Miami and am one of five children. My parents were Indian immigrant physicians (oncology and pediatrics) who dedicated themselves 100% to us kids. My father passed away when I was 12, and my mother worked full-time. She is my inspiration and the reason I decided to follow in my oldest sister's footsteps and enroll in a combined BS/MD program at the University of Miami.

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

As a third-year medical student, I struggled to find my place in the world. Heading into clinical rotations, I thought I would discover a passion for medical oncology, but it simply was not a good fit for my personality. On a whim, I signed up for a spring elective in ophthalmology at the Miami Veterans Administration Hospital. I was immediately hooked by the beauty of the surgeries and the elegant design of the eye.

I completed my residency at the Bascom Palmer Eye Institute, where I discovered my passion for the retina. The first ophthalmologists I worked with as a student were first-year residents, Ryan F. Isom, MD, and D. Wilkin Parke III, MD. Drs. Isom and Parke were senior retina fellows when I was deciding on a subspecialty and were instrumental in guiding me to my primary research mentor, Harry W. Flynn Jr, MD. The examples set by Dr. Flynn as a clinician, surgeon, mentor, and researcher still serve as my gold standard to this day.

Who are your mentors?

There have been so many wonderful people throughout my career who I still lean on for guidance, but for the sake of brevity I will be leaving some out. My Miami mentors include Dr. Flynn; Steven J. Gedde, MD; Audina M. Berrocal, MD; and Thomas A. Albini, MD. My mentors from Wills Eye Hospital, Julia A. Haller, MD; Allen C. Ho, MD; Carl D. Regillo, MD; and Arunan Sivalingam, MD, are a constant presence in my life and frequently are the victims of my rapid-fire texting.

I believe mentors also include the peers and friends who make you stronger, and in my case that would be Ella Leung, MD, and Ajay E. Kuriyan, MD. Finally, I would not be half the physician or person I am today without Nika Bagheri, MD, a whiz clinician and surgeon who I am lucky enough to call my best friend and wife.

Describe your current position.

I am a clinician and surgeon at the Bascom Palmer Eye Institute in Miami. My practice is primarily with adult patients, and I enjoy the challenges of complex surgical scenarios, especially when it requires collaborating with my superlative anterior segment colleagues on combination, multi-step procedures that would be impossible to perform in most practice settings.

I also serve as a mentor to several medical students, in addition to my responsibilities as the associate residency program director, and run my own educational podcast, *Straight From the Cutter's Mouth: A Retina Podcast*.

What has been the most memorable experience of your career thus far?

At the risk of turning this into a humble brag, receiving "Professor of the Year" this past academic year by our amazing ophthalmology residents. This is an honor given annually at Bascom Palmer that is completely at the discretion of the residents, and it was so shocking and humbling that for once in my life I was left speechless. Teachers do not teach for awards, but to see students succeed; to feel their appreciation, love, and respect is a special feeling that cannot be put into words.

What advice can you offer to individuals who are just now choosing their career paths after finishing fellowship?

Stay positive and open-minded. There are so many different practice models, career options, professional development opportunities, and research interests that exist in our field. Be fluid and flexible, ignore the noise, and lean on your mentors and friends when making big decisions. Finally, constantly reevaluate and make sure your clinical, surgical, and academic career remains in line with your core values. ■

JAYANTH SRIDHAR, MD

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MANAGE MYOPIC TRACTION MACULOPATHY WITH EASE

These guidelines can help you care for patients in the clinic and the OR.

BY BARBARA PAROLINI, MD

Myopic traction maculopathy (MTM) is a pathology that affects 9% to 34% of eyes with high myopia (refractive error > 6.00 D and/or axial length > 26.5 mm).[1-3] In highly myopic eyes, different tractional forces act on the retina and fovea. Forces that are perpendicular to the retinal plane can cause maculoschisis or retinal detachment (RD). Forces that are tangential to the retinal plane can cause lamellar macular holes (LMHs) and full-thickness macular holes (FTMHs).

MTM is a spectrum of various clinical pictures. The recently introduced MTM staging system describes the proposal of pathogenesis, the natural evolution, and the prognosis of MTM, and offers potential guidelines for management (Figure).[4] The system defines the evolution of the disease in a direction perpendicular to the retina (Stages 1–4) and tangential to the retina and the fovea (Stages A–C). Outer LMHs may occur in Stage 2, 3, and 4, while the presence of epiretinal abnormalities is possible in every stage. The retina can evolve from Stage 1 to 4 and from pattern A to C simultaneously or separately. The mean time taken to evolve from one stage to the next ranges from weeks to 18 months.

MTM stages might show a spontaneous improvement.[5] However, my team found that, when the eyes are observed for a long time, let's say more than 2 years, even after spontaneous resolution, the MTM may begin to evolve again.

THE BEST MANAGEMENT

According to our studies, to obtain the best efficacy:safety ratio, eyes in the early stages of MTM that have an intact fovea and good vision should be observed because progression is slow.[4,5] For more advanced cases, treatment is required. Forces perpendicular to the retinal plane, causing maculoschisis and RD, can be counteracted by placing a macular buckle (MB), which pushes the sclera toward the retina. Forces tangential to the retinal plane, causing LMH or FTMH, can be counteracted by pars plana vitrectomy (PPV), which creates a force pointing toward the center of the fovea. PPV can also counteract the forces perpendicular to the retinal plane exerted when the vitreous pulls the retina anteriorly.

THE FINAL PROFILE OF THE RETINA AND THE SCLERA SHOULD BE AS FLAT AND HORIZONTAL AS POSSIBLE, RESEMBLING A NONMYOPIC MACULA.

The suggested management strategies customized per stage are as follows[6]:

Stage 1A: Observation and follow-up in 1 year
Stage 1B: PPV only if there is a significant drop in vision (but not recommended)
Stage 1C: PPV and internal limiting membrane (ILM) peeling

Stage 2A: Observation and follow-up in 6 months
Stage 2B: MB, PPV afterward only if the residual LMH prevents significant visual improvement (but not recommended)
Stage 2C: Combined MB and PPV

Stage 3A: MB
Stage 3B: MB, PPV afterward only if the residual LMH prevents significant visual improvement (but not recommended)
Stage 3C: Combined MB and PPV

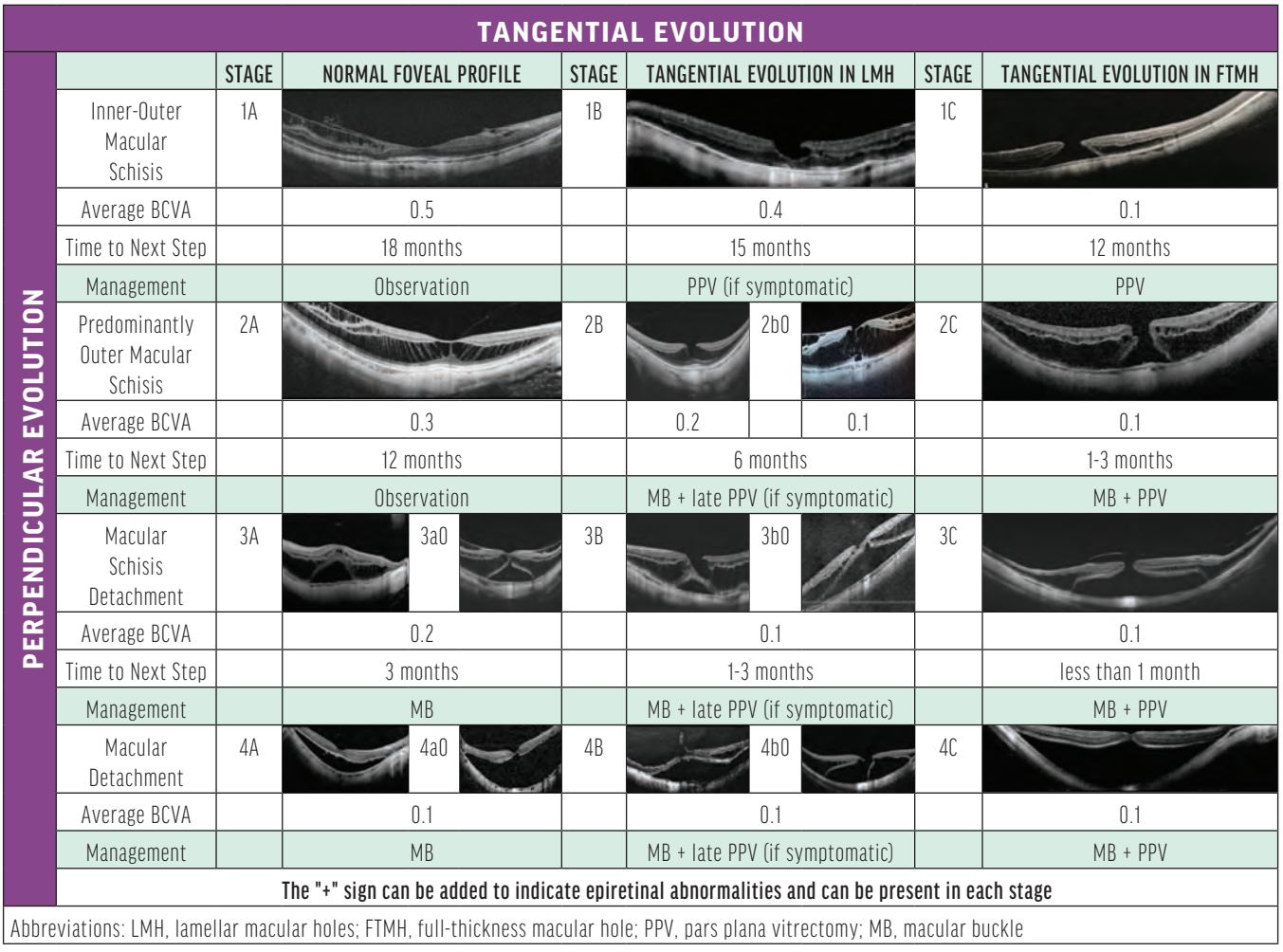

Figure. In the MTM staging system, the four rows represent the evolution of the disease in a direction perpendicular to the retina from inner/outer schisis to complete MD. The columns represent the evolution in a direction tangential to the retina and the fovea from normal fovea to FTMH. The outer LMH is marked as 0 and may occur in Stages 2, 3, and 4. The presence of epiretinal abnormalities is marked as "+" and is possible in every stage. Reprinted with permission from Parolini B et al.[4]

Stage 4A: MB
Stage 4B: MB, PPV afterward only if the residual LMH prevents significant visual improvement (but not recommended)
Stage 4C: MB and PPV (combined simultaneously or sequentially by attaching the retina first with MB and then treating the macular hole in a second step on the attached retina)

Possible complications of MB are superficial extrusion of the lateral arm of the MB (5%), diplopia (1%), temporary foveal detachment (1%), and temporal choroidal hemorrhage (0.5%).[6,7]

Possible complications of PPV are temporary foveal detachment, worsening of the retinal stage, iatrogenic FTMH (20%), RD relapse, and proliferative vitreoretinopathy; other complications include cataract, vitreous hemorrhage, choroidal hemorrhage, retinal tears, and secondary glaucoma or hypotony.[8-11]

An advantage of using an MB to solve the schisis and RD secondary to MTM is avoiding the use of silicone oil. The use of standard or heavy silicone oil in highly myopic eyes inevitably leads to secondary glaucoma.

The surgical technique with an MB aims to counteract the pull on the retina exerted by the elongation of the sclera. The buckling side of the device is placed behind the posterior pole to push the sclera anteriorly. Different models of MB have been proposed.[7] Surgery may be performed under general or local anesthesia. For local anesthesia, we prefer sub-Tenon anesthesia delivered with a blunt cannula to avoid the potential risk of scleral perforation with retrobulbar injections in highly myopic eyes.

Surgical Steps

1. Perform a superotemporal peritomy.
2. Place a traction thread around the lateral and superior rectus muscles.

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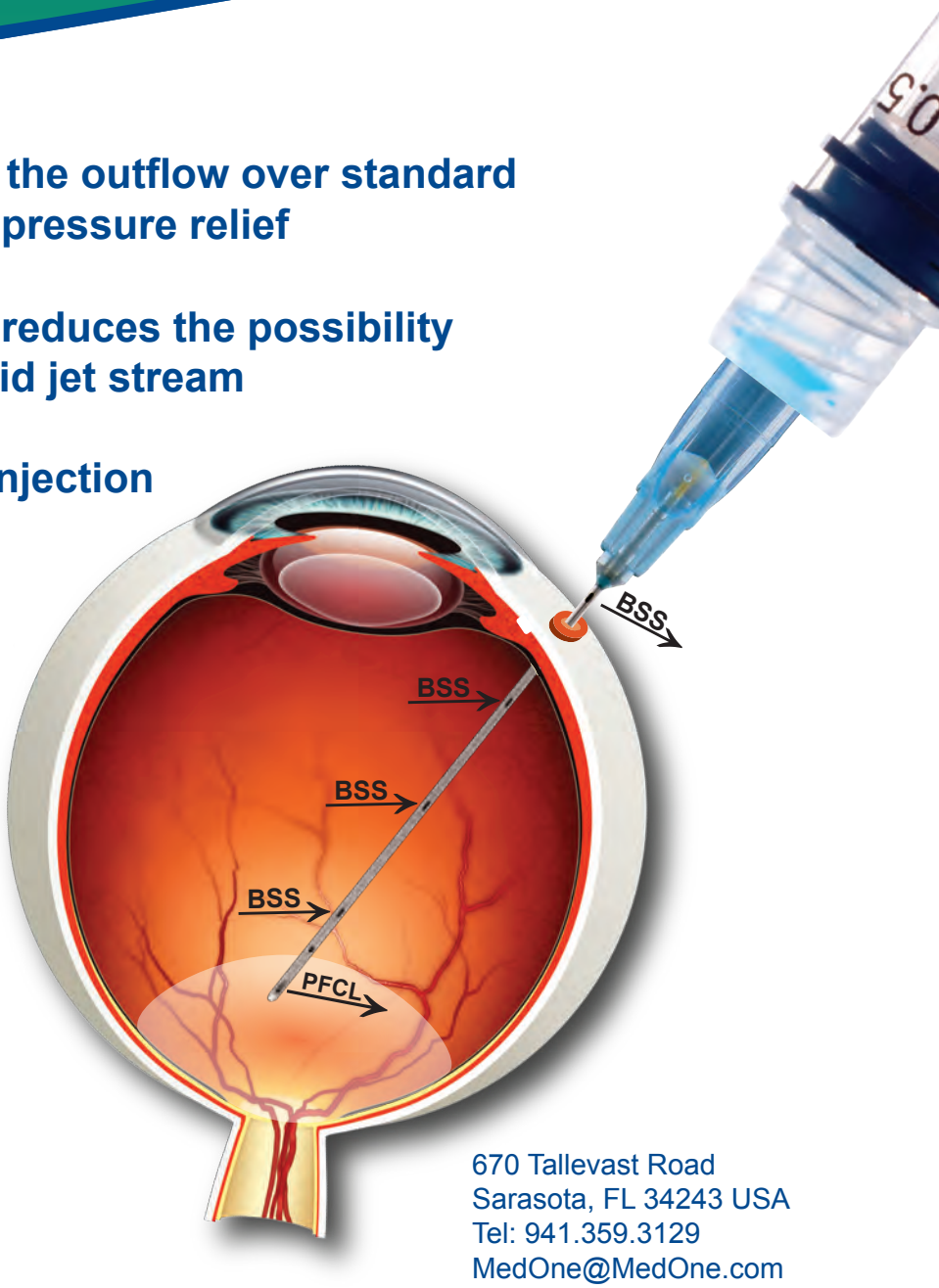

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CASE EXAMPLES

Case No. 1: A 53-year-old female presented with myopic traction maculopathy (MTM) Stage 4C (Figure 1A and B). Her BCVA was 0.05 with a spherical equivalent of -25.0 D and an axial length of 38 mm. The patient underwent a combined pars plana vitrectomy (PPV), macular buckle (MB), and internal limiting membrane (ILM) peel and ILM flap on the associated full-thickness macular hole (FTMH), with SF_6 gas injection. Face-down positioning was advised for 3 days postoperatively. One month after surgery, the retina was attached, and the hole was closed (Figure 1C and D). BCVA was 0.2 with a spherical equivalent of -23.0 D. The patient underwent cataract surgery and achieved a final BCVA of 0.6 with a spherical equivalent of -3.0 D at 9 months after surgery.

Case No. 2: A 47-year-old male presented with MTM Stage 3A (Figure 2A). His BCVA was 0.05 with a spherical equivalent of -22.0 D and an axial length of 31.7 mm. Microperimetry showed a large scotoma (Figure 2B). The patient underwent a 30-minute MB-only procedure. One month after surgery, the retina was attached (Figure 2C) and remained attached until the 12-month follow-up visit. His BCVA improved to 0.7 with a spherical equivalent of -19.0 D. Microperimetry showed the disappearance of the scotoma postoperatively (Figure 2D).

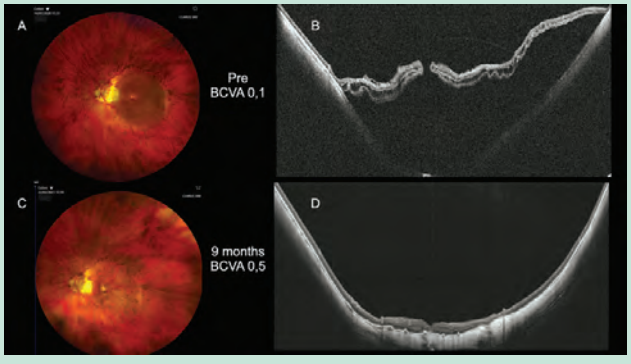

Figure 1. MTM Stage 4C (A, B). One month after surgery, the patient's retina was attached, and the hole was closed (C, D).

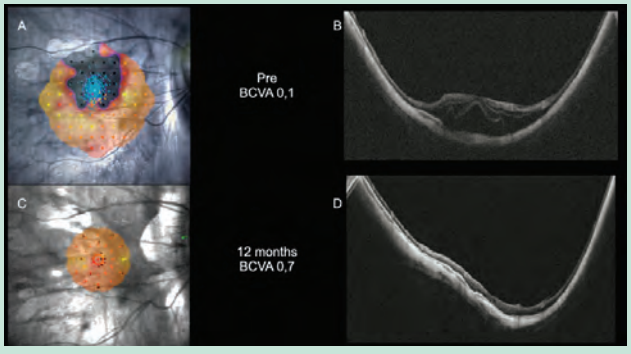

Figure 2. MTM Stage 3A (A). Microperimetry showed a large scotoma (B). One month after surgery, the patient's retina was attached (C), and microperimetry showed the disappearance of the scotoma (D).

3. Insert a chandelier light.
4. Perform an anterior chamber paracentesis to lower the IOP and help the insertion of the buckle.
5. Position the MB behind the posterior pole.
6. Use the panoramic viewing system and transillumination to check that the MB is centered behind the macula.
7. Once satisfied with the position of the MB, mark the position of the arm under the microscope. This is the most crucial, difficult, and time-consuming part of the surgery. The surgeon must hold the arm of the buckle without moving it relative to the eye while the assistant surgeon cleans the area of blood and peribulbar tissue and marks the position of the MB arm.
8. Use a Ti-Cron 6-0 suture (Medtronic) to fix the arm to the sclera.
9. Check the position of the MB after suturing.
10. Remove the chandelier light and traction sutures and close the conjunctiva.

ADDITIONAL GUIDELINES

Surgeons should avoid excessive indentation of the sclera. The final profile of the retina and the sclera should be as flat and horizontal as possible, resembling a nonmyopic macula.

Intraoperative OCT can assist in centering the MB and setting the right amount of indentation, although the procedure can be completed without intraoperative OCT.

When these guidelines are followed, surgery has a good prognosis. In my experience, the patient's BCVA improves by an average of 2 lines. It is particularly important to highlight this achievement because an anatomic—not a functional—improvement is expected after surgery on highly myopic eyes with MTM.[6] ■

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PODCASTS: A NEW APPROACH TO LEARNING

Retina specialists have several ways to stay up to date, including tuning in to their favorite podcast.

BY ANNE X. NGUYEN; FANGFANG SUN; SUNIL RUPARELIA; HAOCHEN XU; CHRISTOPHER LE; RENAUD DUVAL, MD; AND ISABELLE HARDY, MD

Asynchronous learning, also known as e-learning or mobile learning, has become increasingly popular in medical education.[1] In addition, the COVID-19 pandemic generated a need to rapidly adapt educational environments, creating a surge in remote teaching modalities such as virtual conference sessions, online classes, recorded lectures, blogs, and podcasts.[2-5]

The field of medicine has witnessed dramatic increases in the uptake of educational podcasts, especially within the field of retina.[6] In a survey of the three largest retina societies in the United States (the American Society of Retina Specialists, the Retina Society, and the Macula Society), 41.1% of respondents reported listening to at least one medical podcast on a weekly basis.[7]

Podcasts can offer a variety of benefits to retina specialists and trainees. Research-focused podcasts provide updates to specialists on the latest advances in their field, while education-focused podcasts provide an overview of common presentations encountered in retina clinics. These episodes may allow specialists to refresh their diagnostic skills and trainees to glean knowledge to support their learning. Additionally, some podcasts, such as *Straight from the Cutter's Mouth: A Retina Podcast*, have partnered with a society (AAO, in this case) to grant continuing medical education credits to their listeners. Should this trend continue, it will surely impact the accessibility and delivery of continuing education in the future.

While podcasts can be incredibly useful, listeners may find it daunting to identify a podcast that suits their needs.[8] This article reviews the currently available retina-specific podcasts to help trainees and retina specialists navigate this new medium for medical education.

THE SEARCH

To find all the podcasts specific to retina, we used the keywords "retina" and "rétine" in the following podcast hosting platforms: Anchor, Apple Podcasts/iTunes, Breaker, Castbox, Eyetube, Google Podcasts, Overcast, Player FM, Pocket Casts, Podbean, RadioPublic, Spotify, and Stitcher. In addition, we searched for "retina podcast" in Google to ensure completeness of the results. We included podcasts that were free, had a primary focus on retina (> 50% of content focused on medical retina, surgical retina, or both), and were recorded in English, French, or Spanish. Each identified podcast was analyzed based on its lifetime, number of episodes, release schedule, year of activity, affiliation, geographic region, language, number of hosts, and host status (ophthalmologist or not).

RESULTS

As of December 1, 2021, 18 podcasts were available for retina specialists—14 of which were active at the time of data collection (Table). Four focused on medical retina, two on surgical retina, and twelve included both medical and surgical retina. The lifetime of these podcasts varied between 11 weeks and 19 years, with the average podcast lasting approximately 4 years. Podcasts had between one and 298 episodes, with an average of 50 episodes in any given podcast. The podcasts were released between 2006 and 2021, and release schedules varied between simultaneous release and sporadic release.

Most podcasts are affiliated with an organization, whether that be a society, academic institution, or retina trade publication. Nine podcasts were based in the United States, seven in Europe, one in Mexico, and one in Canada. Fourteen

TABLE. RETINA PODCAST NAMES AND CHARACTERISTICS

Name	Language	Type	Format	Target	Affiliation	Geographic Region	Schedule	Status (Years of Activity)	Retina Focus
ASRS's Retina Health for Life	English	Educational, technology, innovation	Conversation	General public	American Society of Retina Specialists	United States	Frequent	Active (2020-2021)	Surgical, medical
Brightfocus Chats: Macular Degeneration	English	Educational	Conversation	General public	BrightFocus Foundation	United States	Monthly	Active (2011-2021)	Surgical, medical
Canal Retina	Spanish	Educational	Conversation	General public	Retimur	Spain	Monthly	Active (2019-2021)	Medical
Desprendimiento de Retina	Spanish	Educational	Monologue	General public, ophthalmologists	None	Spain	Sporadic	Active (2021)	Surgical
eOphthalmology Review	English	Educational	Conversation, Monologue	Ophthalmologists	Johns Hopkins University School of Medicine	United States	Sporadic	Inactive (2011-2018)	Surgical, medical
Eyes on Retina	English	Educational	Conversation	General public	Boehringer Ingelheim	Germany	Sporadic	Active (2020-2021)	Medical
Health on the Net – Conferences & Events on Retina	English	Educational	Conversation, Monologue	Ophthalmologists	Health On the Net	Switzerland	All at once	Inactive (2016)	Surgical, medical
In-Focus Podcast Series	English	Educational	Interview	General public, ophthalmologists	Retina International	Ireland, Switzerland	Sporadic	Active (2021)	Surgical, medical
Innovation Technologique Liliane Bettencourt - Collège de France	French	Educational, research	Monologue	General public, ophthalmologists	Collège de France	France	Sporadic	Inactive (2016-2016)	Medical
New Retina Radio	English	Educational, research	Conversation	Ophthalmologists	Eyetube/*Retina Today*	United States	Frequent	Active (2016-2021)	Surgical, medical
Punto Retina	Spanish	Educational	Conversation	General public, ophthalmologists	Asociación Mexicana de Retina	Mexico	Monthly	Active (2021)	Surgical
Retina Journal Podcast	English	Research	Monologue	Ophthalmologists	*The Journal of Retinal and Vitreous Diseases*	United States	All at once	Active (2021)	Surgical, medical
Retina Synthesis	English	Educational	Conversation	General public	Retina Synthesis	United States	Frequent	Active (2021)	Surgical, medical
Retina UK	English	Educational	Monologue	Ophthalmologists	Retina UK	United Kingdom	Frequent	Active (2006-2021)	Medical
Retinal Physician Insider	English	Educational	Conversation	General public, ophthalmologists	*Retinal Physician*	United States	Monthly	Active (2020-2021)	Surgical, medical
Revealing Retina	English	Educational	Conversation	Ophthalmologists	None	United States	Frequent	Inactive (2007-2019)	Surgical, medical
Straight from the Cutter's Mouth: A Retina Podcast	English	Educational, research	Conversation	Ophthalmologists	Jayanth Sridhar, MD; AAO (continuing medical education)	United States	Weekly	Active (2016-2021)	Surgical, medical
The Retina Channel Podcast	English	Research	Conversation	Ophthalmologists	None	Canada	Monthly	Active (2017-2021)	Surgical, medical

IN A SURVEY OF THE THREE LARGEST RETINA SOCIETIES IN THE UNITED STATES (THE AMERICAN SOCIETY OF RETINA SPECIALISTS, THE RETINA SOCIETY, AND THE MACULA SOCIETY), 41.1% OF RESPONDENTS REPORTED LISTENING TO AT LEAST ONE MEDICAL PODCAST ON A WEEKLY BASIS.

podcasts were recorded in English, three in Spanish, and one in French. Twelve podcasts were hosted by a single individual, and 10 podcasts were hosted by ophthalmologists. All 18 podcasts serve educational purposes: five discussed research and one elaborated on topics related to technology and innovation. Eight podcasts were specifically designed for ophthalmologists, five for the general public, and five for both. Fourteen podcasts were conversational (interview style), and four contained monologues.

DISCUSSION

This study provides a comprehensive review of podcasts available to the retina community. All 18 retina podcasts were created with the purpose of educating listeners, whether they are medical experts (ophthalmologists, optometrists, and other health care professionals) or the general public. Host factors were analyzed to determine the demographic characteristics of those currently responsible for creating podcast content for retina specialists.

While podcasts are becoming increasingly popular as a medium for education, our results suggest that retina podcasts are still lacking, with only 18 retina podcasts across 13 podcasting platforms. Of the podcasts directed toward medical experts, very few offer continuing medical education credits for the time and effort spent listening. Future podcast creators may wish to address this gap to continue to expand the use of podcasts and incentivize podcast listening in ophthalmology continued education. ■

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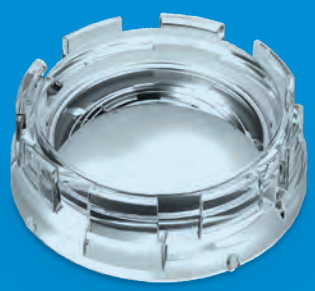

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THE UPS AND DOWNS OF GENE THERAPY RESEARCH

Many clinical trials are underway for inherited retinal diseases—and each is teaching us something new.

BY MARC MATHIAS, MD

The field of gene therapy and genetic testing has risen to the forefront of the quest to find treatments for inherited retinal diseases (IRDs). Access to no-cost genetic testing programs, such as the My Retina Tracker Program (Foundation Fighting Blindness) and Invitae's ID Your IRD Program (sponsored by Spark Therapeutics), has increased patient identification for gene therapy trials. In addition, greater access to these programs and increasing patient awareness have led many patients to ask about enrollment in current or future clinical trials. In this environment, it is important that we remain up to date on the current state of gene therapy studies.

APPROACHES, VECTORS, AND DELIVERY

The term *gene therapy* encompasses a broad range of therapeutic options, and both gene-dependent and gene-agnostic approaches (such as optogenetics) are under investigation for the treatment of IRDs.

Gene augmentation refers to the replacement of a mutated copy of a particular gene and is most commonly used in autosomal recessive conditions. Gene editing uses various tools, such as CRISPR/Cas9, to modify the host genome and can be used for both recessive and dominant diseases.[1] Antisense oligonucleotides (AONs) are small, single-strand oligonucleotide polymers that can bind to host RNA and can either "knockdown" mRNA or affect alternative splicing.[2] Compared with the first two methods, which may involve only one procedure, AON approaches are expected to require repeat dosing at regular intervals to have a sustained therapeutic effect.

Vectors for delivery of genetic material can be either viral or nonviral, although viral approaches are more common. Viral vectors use a capsid to infect host target cells and deliver the genetic material. The workhorse for ocular gene therapy is the adeno-associated virus (AAV). Although there are many advantages to AAV vectors, one major disadvantage is their small genetic payload capacity, around 4,800 kilobases.[3] Many genes that cause common IRDs, such as *ABCA4* and *MYO7A*, exceed the payload capacity of the AAV vector.

Several companies are pursuing a dual-vector approach that will use an AAV vector but split the DNA material into two smaller parts. The full-length gene is then reconstructed within the host cell. Preclinical programs using this dual-vector approach are underway for both Usher 1B due to *MYO7A* and Stargardt disease due to *ABCA4*.[4]

Non-viral approaches using DNA nanoparticles are under development and may reduce immunogenicity compared with viral capsids.[5]

There are several approaches to delivering gene therapy; transvitreal subretinal delivery is the most common. This requires a standard pars plana vitrectomy with delivery of the gene therapy product to the subretinal space through localized bleb formation. The bleb can be created outside the fovea or involve the fovea with subfoveal detachment. The

AT A GLANCE

- A variety of gene therapy approaches, including vector-based gene augmentation, antisense oligonucleotides, and gene editing, are under investigation.
- Lessons learned from past and current trials will help guide future study designs.
- Challenges that require further study include the development of clinically meaningful outcome measures, gene therapy–associated uveitis, and late sequelae of gene therapy.

gene therapy product has the highest transduction in the area of the localized bleb formation, and foveal detachment may be desirable in some IRD conditions to treat the central cone cells. However, this has the potential for iatrogenic injury to the foveal structures.

To minimize mechanical disruption of the fovea, lateral-spreading vectors are being developed to allow for more efficient transduction of foveal cone cells through peripheral bleb formation.[6] These vectors have the unique ability to spread through the retina to more distant sites to deliver the desired genetic material. Delivery through intravitreal injection may have some advantages, including more widespread transduction to central and peripheral retinal cells, decreased morbidity through an office-based procedure, and treatment of diseases where the risk of retinal detachment may be increased (eg, X-linked retinoschisis). However, the vector must be able to efficiently cross the internal limiting membrane and effectively transduce cells in the outer retina and retinal pigment epithelium.

Delivery to the suprachoroidal space has some potential advantages, including more widespread transduction of retinal cells, avoidance of mechanical iatrogenic trauma from subretinal bleb formation, and segregation of the therapeutic away from anterior segment structures.[7] However, challenges similar to those for intravitreal delivery exist such as effective transduction of target cells in the outer retina and retinal pigment epithelium across Bruch's membrane, as well as potentially increased exposure to the immune system outside of the blood–retina barrier. Suprachoroidal delivery is being evaluated for anti-VEGF gene therapy in wet AMD and diabetic macular edema but has not yet been used in any human studies for IRDs.

CURRENT STATE OF IRD CLINICAL TRIALS

More than 20 gene therapy trials are underway for IRDs, including retinitis pigmentosa (RP), Leber congenital amaurosis (LCA), achromatopsia, choroideremia, and X-linked retinoschisis (Table). Although many of these trials use gene augmentation, ProQR is developing therapies based on AON technology, and Editas is using CRISPR-based therapy for the treatment of *CEP290*-related disease. Other genes in various stages of preclinical evaluation include *CRB1*, *PDE6C*, *NPHP5*, *LCA5*, *RDH12*, *NMNAT1*, and *BEST1*.

In the past year, several trials have not met their primary endpoint. In 2021, Biogen announced that its clinical products BIIB112 for the treatment of *RPGR*-associated X-linked RP and BIIB111 for the treatment of choroideremia did not meet their primary endpoints in late-stage clinical trials. In addition, ProQR announced in early 2022 that its lead late-stage product QR-110 did not meet its primary endpoint for the treatment of *CEP290*-mediated LCA10. However, the knowledge and insights gained from these trials provide important stepping-stones for the design of

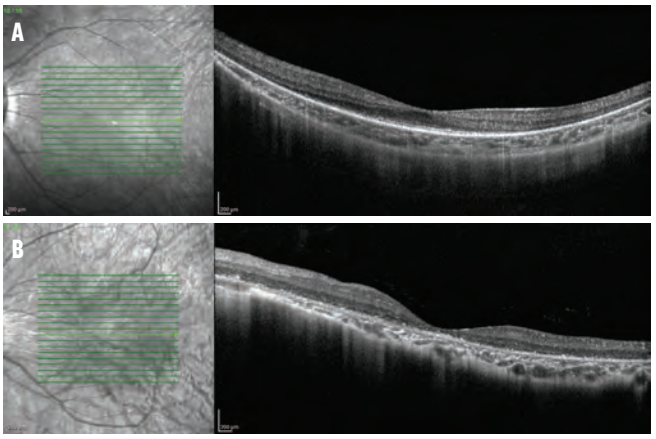

Figure. Patients with earlier stages of X-linked RP who still have intact central cone cells would likely respond well to treatment (A), whereas others with significant central degeneration of the cone cells may not be good gene therapy candidates (B).

future studies. In addition, signs of potential efficacy in some of these trials, even though the primary endpoints were not met, highlight the need for careful study design and appropriate and meaningful outcome measures.

The success of future IRD trials depends on carefully chosen functional and structural endpoints. A better understanding of the natural progression of IRDs can help to guide the development of those meaningful and practical outcome measures.[8] Multiple natural history studies that are underway, such as the rate of progression of *USH2A*-related retinal degeneration (RUSH2A), the rate of progression in *EYS*-related retinal degeneration (Pro-EYS), and the rate of progression in Stargardt disease (ProgSTAR), can facilitate future study designs.[9,10] So far, these studies are suggesting that earlier treatment may be desirable before there is significant photoreceptor and outer retinal degeneration (Figure).

The role of inflammation in ocular gene therapy is also gaining more attention. Acute and chronic gene therapy-associated uveitis is well reported. Although most cases are mild and transient, severe and more chronic cases have been described. Most current clinical trials use various combinations of topical, oral, and periocular steroids to suppress the immune response.

Our knowledge of the molecular mechanisms of immunogenicity is expanding. The immune response may be activated against viral capsid proteins, vector DNA (including inverted terminal repeat sequences, promoter, and transgene), or impurities in the vector preparation.[11] Research has suggested that toll-like receptors may play an important role. Activation of inflammatory pathways could induce retinal damage or reduce transduction efficiency. As we begin to better understand these pathways, researchers may look toward targeted therapies or, in some cases, steroid-sparing agents to mitigate the immune response.

Understanding the long-term effects of ocular gene therapy is crucial; for example, recent reports have described the

TABLE. ACTIVE GENE THERAPY TRIALS FOR IRDs

Condition	Delivery	Phase	Product	Gene	Sponsor
LCA	Intravitreal	2/3*	QR-110	*CEP290*	ProQR
	Subretinal	1/2	EDIT-101	*CEP290*	Editas
		1/2	SAR439483	*GUCY2D*	Atsena
LCA/RP	Subretinal	1/2	AAV-RPE65	*RPE65*	MeiraGTx
RP	Subretinal	1/2	OCU400	*NR2E3*	Ocugen
Autosomal recessive RP	Subretinal	2/3	QR-421a	*USH2A*	ProQR
		1/2	AAV-PDE6A	*PDE6A*	STZ Eyetrial
		1/2	AAV-PDE6B	*PDE6B*	Coave Therapeutics
Autosomal dominant RP	Intravitreal	1/2	QR-1123	*RHO P23H*	ProQR
XLRP	Subretinal	2/3	AGTC-501	*RPGR*	AGTC
		3	AA5-RPGR	*RPGR*	MeiraGTx/Janssen
		2/3*	BIIB112	*RPGR*	Biogen
	Intravitreal	1/2	4D-125	*RPGR*	4DMT
ACHM	Subretinal	2	AGTC-402	*CNGA3*	AGTC
		2	AGTC-401	*CNGB3*	AGTC
		1/2	AAV-CNGA3	*CNGA3*	MeiraGTx/Janssen
		1/2	AAV-CNGB3	*CNGB3*	MeiraGTx/Janssen
		1/2	AAV-CNGA3	*CNGA3*	STZ Eyetrial
Choroideremia	Intravitreal	1/2	4D-110	*CHM*	4DMT
	Subretinal	3*	BIIB111	*CHM*	Biogen
		1/2	AAV-REP1	*CHM*	University of Alberta
X-linked retinoschisis	Intravitreal	1/2	AAV-RS1	*RS1*	National Eye Institute

*Did not meet primary endpoints.
Abbreviations: ACHM, achromatopsia; IRDs, inherited retinal diseases; LCA, Leber congenital amaurosis; RP, retinitis pigmentosa; XLRP, X-linked retinitis pigmentosa.

development of perifoveal and nummular atrophy in patients treated with voretigene neparvovec-rzyl (Luxturna, Spark Therapeutics).[12] The mechanisms of this atrophy are currently under investigation and are not completely understood.

OUTLOOK

Despite the challenges, the future of gene therapy for IRDs remains bright. Knowledge gained from natural history studies, preclinical gene therapy studies, and past and current clinical trials can help guide the future of IRD therapy. ■

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THE ROLE OF GENETIC COUNSELORS IN IRD PATIENT CARE

A team-based approach can help you better diagnose and educate patients undergoing genetic testing.

BY REBECCA PROCOPIO, MS, CGC

Primary Findings: Negative. A patient's genetic testing report returned with a non-diagnostic result. However, under the heading of *Additional Findings*, I noticed two variants of uncertain significance in *MKKS*. Knowing that these variants are associated with autosomal recessive Bardet Biedl syndrome (BBS), I recognized the real meaning of the report. I was also reminded of just how valuable genetic counselors and inherited retinal disease (IRD) specialists can be for patients and clinicians who are seeking answers.

Although a thorough history was obtained at our initial visit, the patient disclosed the key to unlocking the meaning of this unclear report during our review of the results. He stated that he was born with extra fingers and has a learning disability. These features, with his history of retinitis pigmentosa and obesity, were consistent with a diagnosis of BBS. Because this phenotypic information was initially missing from the documents provided to the laboratory, it did not report the *MKKS* variants as primary findings.

Genetic testing has the power to diagnose and provide prognostic guidance; still, a laboratory's ability to accurately report genetic findings depends on the inclusion of relevant information and history. As this patient's genetic counselor, I adhered to a carefully curated process of obtaining patient history, selecting the appropriate test, and reviewing the results. The time I took to build rapport with the patient is what ultimately led to clarity for him and his care team.

Genetic counseling sessions are an environment in which patients should feel confident discussing their medical and ocular history in detail. These sessions are also a dedicated space for patients to receive information about their genetic testing—why it's being ordered and what it might reveal—as well as a space for them to provide information to their counselors. In some cases, this information is critical enough to turn a negative report into a positive result.

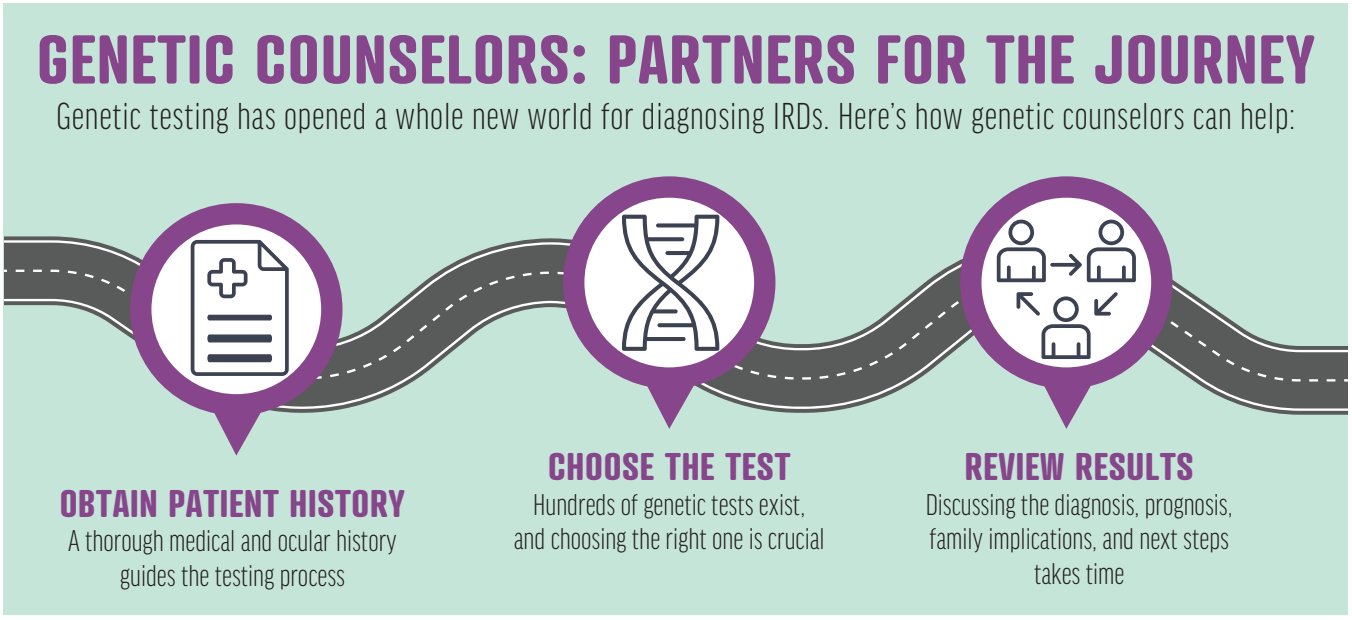
TESTING IS KEY

Medical care is moving in the direction of precision health, and the integration of genetic testing into daily practice is already here. Rapidly evolving technologies, including next-generation sequencing, have made genetic diagnosis faster and cheaper than ever before.[1] A new breed of genetic testing for IRDs has gained momentum: the no-charge, or sponsored, gene panel. These panels contain more than 300 genes associated with IRDs and are paid for by pharmaceutical companies, providing patients with high quality, comprehensive testing free of charge.

However, the innumerable benefits of a genetic diagnosis and the convenience of performing sponsored IRD panels can overshadow the potential risk for ethical and personal dilemmas. Receiving genetic information is different from regular test results, as it is deeply complex and intertwined with the patient's identity. Even though patients do not have to pay for this type of testing, the service is not truly "free" in every sense. Pharmaceutical companies pay for this testing

AT A GLANCE

- A laboratory's ability to accurately report genetic findings depends on a thorough patient history.
- It is essential to choose the best test for each patient with respect to the differential diagnosis, privacy preferences, and information desired.
- There are many benefits to working with genetic counselors, including cost savings, better patient management, and increased patient satisfaction.



in exchange for patient data, which can limit a patient's privacy. The results could leave a patient vulnerable to insurance discrimination if it reveals a predisposition for a new medical condition. True biological relationships, including consanguinity and nonpaternity, may also come to light. Patients should be made aware of these nuances prior to testing, and providers should have a conversation with the patient to ensure informed consent.

Complicating matters further, hundreds of genetic tests exist with numerous options for sponsored IRD panels. It is essential to choose the test that is best for each patient with respect to the differential diagnosis, preferences for privacy, and the level of information desired. Genetic tests vary in panel content, coverage, reporting, and turnaround time.

Returning results is also a process that should include careful education and counseling. A genetic testing result should be reviewed thoroughly, using databases and resources to assess the relevance of the findings. Using the patient's clinical history to guide the conversation, as in the example of our patient with BBS, is critical. Patients must understand what a genetic test means for their own diagnosis and management, and they should be counseled on who else in their family may be at risk. Genetic counselors are careful to explain variants of uncertain significance and negative results in the context of evolving interpretations and information.

A TEAM APPROACH

Genetic counselors guide families through the entire genetic testing process, including: obtaining a detailed medical and family history, critically assessing genetic testing options, interpreting results, and reviewing the report. They also assist in identifying genotype-specific clinical trials and can assess baseline eligibility for interested families.

There are many benefits to working with genetic counselors, including cost savings, better patient management, and increased patient satisfaction.[2,3] As part of the care team, genetic counselors provide education and optimum test selection for providers. They serve to empower both patients and physicians to use genetic testing technology in the safest and most beneficial manner.

As I prepare to see the patient with BBS for follow-up with his updated genetic testing report in hand, I am reminded that, although sponsored genetic testing panels have increased access to genetic diagnosis, they do not diminish the need for careful and thorough clinical evaluation. Retina clinics caring for individuals with IRDs have a unique opportunity to provide multidisciplinary specialty care that includes genetic counselors.[4] For example, at Wills Eye Hospital, we have developed a model where a genetic counselor is available to any subspecialty service and functions as an independent care provider.

Genetic counseling is vital to providing high-quality, comprehensive care and should be offered to patients receiving genetic testing. ■

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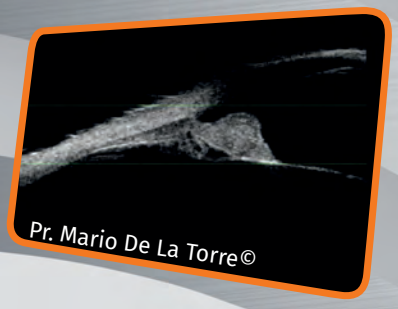
IMAGING EXCELLENCE



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INDICATIONS

VABYSMO (faricimab-svoa) is a vascular endothelial growth factor (VEGF) inhibitor and angiopoietin-2 (Ang-2) inhibitor indicated for the treatment of patients with Neovascular (Wet) Age-Related Macular Degeneration (nAMD) and Diabetic Macular Edema (DME).

IMPORTANT SAFETY INFORMATION

Contraindications

VABYSMO is contraindicated in patients with ocular or periocular inflammation, in patients with active intraocular inflammation, and in patients with known hypersensitivity to faricimab or any of the excipients in VABYSMO.

Warnings and Precautions

- Endophthalmitis and retinal detachments may occur following intravitreal injections. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay, to permit prompt and appropriate management.
- Increases in intraocular pressure have been seen within 60 minutes of an intravitreal injection.
- There is a potential risk of arterial thromboembolic events (ATEs) associated with VEGF inhibition.

Adverse Reactions

The most common adverse reaction (≥5%) reported in patients receiving VABYSMO was conjunctival hemorrhage (7%).

You may report side effects to the FDA at (800) FDA-1088 or www.fda.gov/medwatch. You may also report side effects to Genentech at (888) 835-2555.

Please see Brief Summary of VABYSMO full Prescribing Information on the following page.

*Dosing Information:

In nAMD, the recommended dose for VABYSMO is 6 mg (0.05 mL of 120 mg/mL solution) IVT Q4W for the first 4 doses, followed by OCT and visual acuity evaluations 8 and 12 weeks later to inform whether to extend to: 1) Q16W (weeks 28 and 44); 2) Q12W (weeks 24, 36, and 48); or 3) Q8W (weeks 20, 28, 36, and 44).

In DME, the recommended dose for VABYSMO is 6 mg (0.05 mL of 120 mg/mL solution) IVT Q4W for ≥4 doses until CST is ≤325 µm (by OCT), followed by treat-and-extend dosing with 4-week interval extensions or 4- to 8-week interval reductions based on CST and visual acuity evaluations through week 52. Alternatively, VABYSMO can be administered IVT Q4W for the first 6 doses, followed by Q8W dosing over the next 28 weeks.

Although VABYSMO may be dosed as frequently as Q4W, additional efficacy was not demonstrated in most patients when VABYSMO was dosed Q4W vs Q8W. Some patients may need Q4W dosing after the first 4 doses. Patients should be assessed regularly and the dosing regimen reevaluated after the first year.

CST=central subfield thickness; IVT=intravitreal; OCT=optical coherence tomography; Q4W=every 4 weeks; Q8W=every 8 weeks; Q12W=every 12 weeks; Q16W=every 16 weeks.

References: 1. VABYSMO [package insert]. South San Francisco, CA: Genentech, Inc; 2022. **2.** Beovu® (brolucizumab) [package insert]. East Hanover, NJ: Novartis; 2020. **3.** Eylea® (aflibercept) [package insert]. Tarrytown, NY: Regeneron Pharmaceuticals, Inc; 2021. **4.** LUCENTIS® (ranibizumab) [package insert]. South San Francisco, CA: Genentech, Inc; 2018. **5.** SUSVIMO™ (ranibizumab injection) [package insert]. South San Francisco, CA: Genentech, Inc; 2022.

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THE WINDOW TO CHANGE

VABYSMO™
faricimab-svoa injection 6 mg

VABYSMO™ (faricimab-svoa) injection, for intravitreal use

This is a brief summary. Before prescribing, please refer to the full Prescribing Information

1 INDICATIONS AND USAGE

VABYSMO is a vascular endothelial growth factor (VEGF) and angiopoietin 2 (Ang-2) inhibitor indicated for the treatment of patients with:

1.1 Neovascular (wet) Age-Related Macular Degeneration (nAMD)

1.2 Diabetic Macular Edema (DME)

4 CONTRAINDICATIONS

4.1 Ocular or Periocular Infections

VABYSMO is contraindicated in patients with ocular or periocular infections.

4.2 Active Intraocular Inflammation

VABYSMO is contraindicated in patients with active intraocular inflammation.

4.3 Hypersensitivity

VABYSMO is contraindicated in patients with known hypersensitivity to faricimab or any of the excipients in VABYSMO. Hypersensitivity reactions may manifest as rash, pruritus, urticaria, erythema, or severe intraocular inflammation.

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis and Retinal Detachments

Intravitreal injections have been associated with endophthalmitis and retinal detachments *[see Adverse Reactions (6.1)]*. Proper aseptic injection techniques must always be used when administering VABYSMO. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay, to permit prompt and appropriate management *[see Dosage and Administration (2.6) and Patient Counseling Information (17)]*.

5.2 Increase in Intraocular Pressure

Transient increases in intraocular pressure (IOP) have been seen within 60 minutes of intravitreal injection, including with VABYSMO *[see Adverse Reactions (6.1)]*. IOP and the perfusion of the optic nerve head should be monitored and managed appropriately *[see Dosage and Administration (2.6)]*.

5.3 Thromboembolic Events

Although there was a low rate of arterial thromboembolic events (ATEs) observed in the VABYSMO clinical trials, there is a potential risk of ATEs following intravitreal use of VEGF inhibitors. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause).

The incidence of reported ATEs in the nAMD studies during the first year was 1% (7 out of 664) in patients treated with VABYSMO compared with 1% (6 out of 662) in patients treated with aflibercept *[see Clinical Studies (14.1)]*.

The incidence of reported ATEs in the DME studies during the first year was 2% (25 out of 1,262) in patients treated with VABYSMO compared with 2% (14 out of 625) in patients treated with aflibercept *[see Clinical Studies (14.2)]*.

6 ADVERSE REACTIONS

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

- Hypersensitivity *[see Contraindications (4)]*
- Endophthalmitis and retinal detachments *[see Warnings and Precautions (5.1)]*
- Increase in intraocular pressure *[see Warnings and Precautions (5.2)]*
- Thromboembolic events *[see Warnings and Precautions (5.3)]*

6.1 Clinical Trial 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 other clinical trials of the same or another drug and may not reflect the rates observed in practice.

The data described below reflect exposure to VABYSMO in 1,926 patients, which constituted the safety population in four Phase 3 studies *[see Clinical Studies (14.1, 14.2)]*.

Table 1: Common Adverse Reactions (≥ 1%)

Adverse Reactions	VABYSMO		Active Control (aflibercept)	
	AMD N=664	DME N=1262	AMD N=622	DME N=625
Conjunctival hemorrhage	7%	7%	8%	6%
Vitreous floaters	3%	3%	2%	2%
Retinal pigment epithelial tear[a]	3%		1%	
Intraocular pressure increased	3%	3%	2%	2%
Eye pain	3%	2%	3%	3%
Intraocular inflammation[b]	2%	1%	1%	1%
Eye irritation	1%	1%	< 1%	1%
Ocular discomfort	1%	1%	< 1%	< 1%
Vitreous hemorrhage	< 1%	1%	1%	< 1%

[a]AMD only
[b]Including iridocyclitis, iritis, uveitis, vitritis

Less common adverse reactions reported in < 1% of the patients treated with VABYSMO were corneal abrasion, eye pruritus, lacrimation increased, ocular hyperemia, blurred vision, eye irritation, sensation of foreign body, endophthalmitis, visual acuity reduced transiently, retinal tear and rhegmatogenous retinal detachment.

6.2 Immunogenicity

The immunogenicity of VABYSMO was evaluated in plasma samples. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to VABYSMO in immunoassays. The detection of an immune response is highly dependent on the sensitivity and specificity of the assays used, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to VABYSMO with the incidence of antibodies to other products may be misleading.

There is a potential for an immune response in patients treated with VABYSMO. In the nAMD and DME studies, the pre-treatment incidence of anti-faricimab antibodies was approximately 1.8% and 0.8%, respectively. After initiation of dosing, anti-faricimab antibodies were detected in approximately 10.4% and 8.4% of patients with nAMD and DME respectively, treated with VABYSMO across studies and across treatment groups. As with all therapeutic proteins, there is a potential for immunogenicity with VABYSMO.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate and well-controlled studies of VABYSMO administration in pregnant women.

Administration of VABYSMO to pregnant monkeys throughout the period of organogenesis resulted in an increased incidence of abortions at intravenous (IV) doses 158 times the human exposure (based on C_{max}) of the maximum recommended human dose *[see Animal Data]*. Based on the mechanism of action of VEGF and Ang-2 inhibitors, there is a potential risk to female reproductive capacity, and to embryo-fetal development. VABYSMO should not be used during pregnancy unless the potential benefit to the patient outweighs the potential risk to the fetus.

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

Data

Animal Data

An embryo fetal developmental toxicity study was performed on pregnant cynomolgus monkeys. Pregnant animals received 5 weekly IV injections of VABYSMO starting on day 20 of gestation at 1 or 3 mg/kg. A non-dose dependent increase in pregnancy loss (abortions) was observed at both doses evaluated. Serum exposure (C_{max}) in pregnant monkeys at the low dose of 1 mg/kg was 158 times the human exposure at the maximum recommended intravitreal dose of 6 mg once every 4 weeks. A no observed adverse effect level (NOAEL) was not identified in this study.

8.2 Lactation

Risk Summary

There is no information regarding the presence of faricimab in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. Many drugs are transferred in human milk with the potential for absorption and adverse reactions in the breastfed child.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for VABYSMO and any potential adverse effects on the breastfed child from VABYSMO.

8.3 Females and Males of Reproductive Potential

Contraception

Females of reproductive potential are advised to use effective contraception prior to the initial dose, during treatment and for at least 3 months following the last dose of VABYSMO.

Infertility

No studies on the effects of faricimab on human fertility have been conducted and it is not known whether faricimab can affect reproduction capacity. Based on the mechanism of action, treatment with VABYSMO may pose a risk to reproductive capacity.

8.4 Pediatric Use

The safety and efficacy of VABYSMO in pediatric patients have not been established.

8.5 Geriatric Use

In the four clinical studies, approximately 60% (1,149/1,929) of patients randomized to treatment with VABYSMO were ≥ 65 years of age. No significant differences in efficacy or safety of faricimab were seen with increasing age in these studies. No dose adjustment is required in patients 65 years and above.

17 PATIENT COUNSELING INFORMATION

Advise patients that in the days following VABYSMO administration, patients are at risk of developing endophthalmitis. If the eye becomes red, sensitive to light, painful, or develops a change in vision, advise the patient to seek immediate care from an ophthalmologist *[see Warnings and Precautions (5)]*.

Patients may experience temporary visual disturbances after an intravitreal injection with VABYSMO and the associated eye examinations *[see Adverse Reactions (6)]*. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

VABYSMO™ [faricimab-svoa]
Manufactured by:
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U.S. License No.: 1048

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CRISPR: BEYOND GENE EDITING

A deep dive into the science behind the latest advances that are poised to change how we treat inherited retinal diseases.

BY LUCIE Y. GUO, MD, PHD; LEI STANLEY QI, PHD; SUI WANG, PHD; STEPHEN J. SMITH, MD; LOH-SHAN LEUNG, MD; AND VINIT B. MAHAJAN, MD, PHD

Clustered, regularly interspaced, short palindromic repeats (CRISPR), an ancient feature of bacteria's adaptive immune system, refers to DNA sequences in bacteria left behind after viral infections; when bacteria encounter those viruses again, their CRISPR-associated (Cas) proteins recognize and bind to these sequences in the virus.

This system has been harnessed for precise gene targeting in human cells by using two components: a Cas9 nuclease that cuts DNA and a programmable guide RNA (gRNA) that directs Cas9 to specific loci within the genome. When Cas9 and gRNA are delivered into the same cell, they generate a double-stranded break (DSB) in the DNA, which can then be repaired by the cell's intrinsic DNA repair machinery to delete a gene (ie, knockout) or add additional code to the DNA using the cell's homology-directed repair (HDR) machinery. The main advantages of CRISPR technology are its efficiency, programmability, and precision.

The eye is at the forefront of the gene therapy and genome editing fields, with its surgical accessibility, relative immune privilege,[1] and the unquestionable effect of blinding diseases. The first in vivo CRISPR clinical trial, BRILLIANCE, is underway to investigate the treatment of Leber congenital amaurosis with EDIT-101 (Editas Medicine). More recently, molecular engineering has expanded the powers of CRISPR/Cas beyond gene editing (Figure).

CONTROLLING GENE DOSAGE

By inactivating the DNA-cutting ability while keeping its other functionalities intact, a nuclease-dead Cas9 (dCas9) maintains its precise genome-targeting capability without causing DNA damage.[2] dCas9 proteins can be fused to a variety of modulator proteins to enable expanded capabilities, such as tuning the level of gene expression.

This type of CRISPR-based gene activation can be therapeutically useful for inherited retinal diseases (IRDs) that involve mutations in genes with functionally equivalent homologs that are normally expressed in other cell types. For example, retinitis pigmentosa (RP) involves mutations in the *rhodopsin* gene in rod cells, but increasing expression of a cone-opsin gene in rod cells could indirectly compensate for genetically defective *rhodopsin*. One group tested dCas9 fused to an activator to increase the expression levels of a cone-opsin gene and showed that delivery by an adenoviral-associated viral (AAV) vector slowed retinal degeneration in a mouse model of RP.[3] CRISPR-based activation of functionally equivalent genes could be particularly useful for the replacement of large genes in common IRDs, such as

AT A GLANCE

- The eye is at the forefront of the gene therapy and genome editing fields, with its surgical accessibility, relative immune privilege, and the effect of blinding genetic diseases.
- CRISPR/Cas has revolutionized our ability to edit the human genome.
- New CRISPR tools are now available for gene regulation, epigenetic editing, and multiplexed genome targeting.

ABCA4 or *MYO7A*, that exceed the packaging limitations of AAVs.

CRISPR BASE EDITING

In the early days of CRISPR/Cas9 technology, correcting a point mutation relied on the rate of HDR following the formation of a DSB by the Cas9 nuclease. However, the rates of HDR can be quite low, especially in non-dividing cells such as photoreceptors, which leaves most cells uncorrected. Furthermore, the DSB that is created by the Cas9 nuclease may generate undesired genomic mutations or occur at an off-target location.

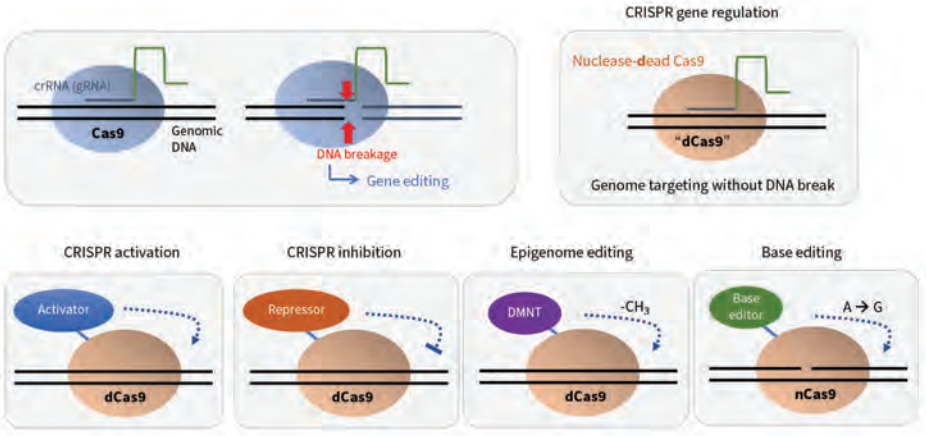


Figure. In addition to traditional gene editing, CRISPR/Cas systems now include regulated gene expression, base editing, prime editing, and other novel approaches.

CRISPR base editing involves the fusion of a base editor (an enzyme that can directly convert one specific DNA base pair to another base pair) to a Cas9 enzyme that is engineered to avoid DSBs in DNA. In a mouse model of Leber congenital amaurosis, a CRISPR base editing system corrected the pathogenic mutation in the *RPE65* gene, restoring therapeutically relevant gene levels and rescuing the function and survival of cone photoreceptors on a long-term basis.[4,5]

Although base editing only corrects single-gene mutations, it may prove to be useful for many IRDs. A cross-sectional study examined more than 12,000 alleles that are too large for AAV vector delivery (eg, *ABCA4*, *CDH23*, *MYO7A*, *CEP290*, *USH2A*, and *EYS*) and concluded that 53% of pathogenic alleles are correctable with existing base editing technology, and 76% of patients who received diagnoses through a genetic service possessed an allele amenable to base editing.[6]

CRISPR PRIME EDITING

Prime editors are one of the latest additions to the CRISPR genome engineering toolkit. Prime editors use an engineered reverse transcriptase enzyme fused to a Cas9 nickase, which only generates a break in one DNA strand. Prime editing systems use a prime editing gRNA that contains both the sequence directing the Cas9 nickase to its desired genomic target and another sequence that specifies the desired sequence change. The new sequence is reverse-transcribed by the nearby enzyme and used as a template for correcting the host genetic sequence.

In a proof of concept study, a prime editing system was delivered by dual AAV vectors in the rd12 model of RP and precisely corrected the pathogenic point mutation and improved optomotor response measurements in mice.[7]

MULTIPLEXED GENOME TARGETING

Given the large number of human diseases that are polygenic, the ability to target multiple genes simultaneously holds clinical promise. Editing multiple sites with Cas9 is challenging, but the discovery of the Cas12 system has expanded the possibilities for multiplexing. Cas12 can take an array of gRNAs, cut them into individual gRNAs, and simultaneously target multiple sites in the genome. This opens the possibility of treating more complex retinal diseases, including those caused by mutations in two or more genes. Furthermore, a nuclease-dead Cas12 (dCas12) can be used for multiplex gene regulation, but the low efficiency of the protein hindered its applications. Recently, an engineered version of dCas12, hyperCas12a, enabled simultaneous activation of multiple genes in mouse retina.[8,9]

THE FUTURE FOR CRISPR GENE THERAPY

With nearly 300 different genes that cause retinal diseases, and new mechanisms being uncovered at a rapid pace, there is ample opportunity to apply CRISPR technology for gene editing and gene regulation. But there are also challenges. For one, the high genetic heterogeneity of IRDs makes personalized therapy a daunting task. At the 2022 American Society of Gene & Cell Therapy meeting, Francis Collins, MD, PhD, the acting White House chief science advisor and former National Institutes of Health director, paid tribute to the global scientific effort that generated the first draft of the human genome sequence in 2003 and highlighted the tour-de-force from the Telomere-to-Telomere consortium that finally completed the full human genome in 2022. The Human Genome Project has identified more than 7,000 human genetic disorders, most of which have no treatment and cannot be treated by an ex vivo therapy approach. In his keynote speech, he said that "delivery is the real challenge" and called for greater progress in making in vivo genome editing scalable to treat more patients.

Our toolkits for sophisticated genome engineering are growing, with potential for providing new waves of

(Continued on page 37)

MYSTERY CASES: RARE AND IN YOUR CHAIR

Test your diagnostic acumen with these unusual cases.

While one patient may walk through your door with a classic clinical picture, leading to an easy diagnosis, another may present with signs and symptoms that have you phoning a friend. The mystery cases presented here can help to hone your diagnostic skills and prepare for even the most surprising retinal conditions.

- Rebecca Hepp, Editor-in-Chief

MYSTERY CASE NO. 1

By Meera D. Sivalingam, MD; Taku Wakabayashi, MD, PhD; and Yoshihiro Yonekawa, MD

An 11-year-old boy with a history of microcephaly and developmental delay was referred for retinal screening. His VA was 20/40 in each eye. Fundus examination and widefield fluorescein angiography (FA) demonstrated avascular peripheral retina and geographic chorioretinal atrophy in the inferior midperiphery of each eye (Figure 1). OCT showed well-preserved inner and outer retina laminations in the central macula, but the outer retina became attenuated leading up to the inferior area of atrophy (Figure 2).

What do you think is the diagnosis? See the discussion below to find out.

MYSTERY CASE NO. 2

By Taku Wakabayashi, MD, PhD; Meera D. Sivalingam, MD; and Yoshihiro Yonekawa, MD

A 13-year-old boy presented with decreased vision in the left eye. VA was 20/20 OD and 20/200 OS. The fundus examination of the right eye was unremarkable, while the left eye showed an optic disc anomaly (Figure 3). FA showed hyperfluorescence around the disc and midperiphery corresponding to areas of chorioretinal atrophy. Retinal nonperfusion was also observed in the temporal periphery. OCT showed peripapillary serous subretinal fluid. Brain MRI and MRA did not show evidence of Moyamoya disease.

What is causing this patient's decreased vision? Find out in the discussion below.

MYSTERY CASE NO. 3

By Natasha Ferreira Santos da Cruz, MD; Carlos Ernesto Mendoza Santiesteban, MD; and Audina M. Berrocal, MD

An 8-year-old boy was referred to the office with problems with his night vision. The patient's mother reported that the child prefers brighter rooms. The patient had a normal birth history and no past ocular or family history. On initial examination, the patient's BCVA was 20/25 OD and 20/30 OS. The anterior segment examination was normal in each eye. The fundus examination revealed diffuse and discrete whitish flecks with macular sparing in each eye (Figure 4). OCT imaging located the lesions in the zone of interaction between the photoreceptor inner and outer segment and the apical retinal pigment epithelium (RPE, Figure 5). Fundus autofluorescence imaging showed small flecks of hyperautofluorescence in each eye, which may correlate to the spots on the fundus photographs. Full-field electroretinogram (ERG) testing demonstrated diminished scotopic responses that markedly improved to normal after prolonged dark adaptation.

What is causing this child's night vision problems? See the discussion below to find out.

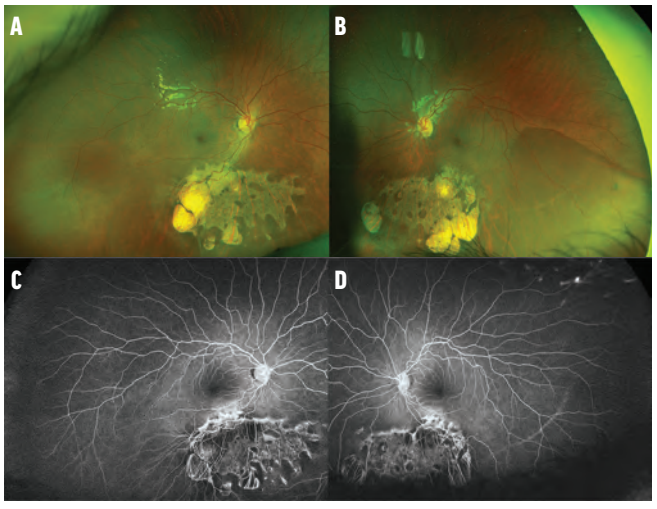


Figure 1. Widefield imaging of the right (A) and left (B) eyes shows peripheral avascular retina, retinal dragging, and midperipheral chorioretinal atrophy. Widefield FA of the right (C) and left (D) eyes highlights peripheral avascular retina and the chorioretinal atrophy. There is no neovascularization.

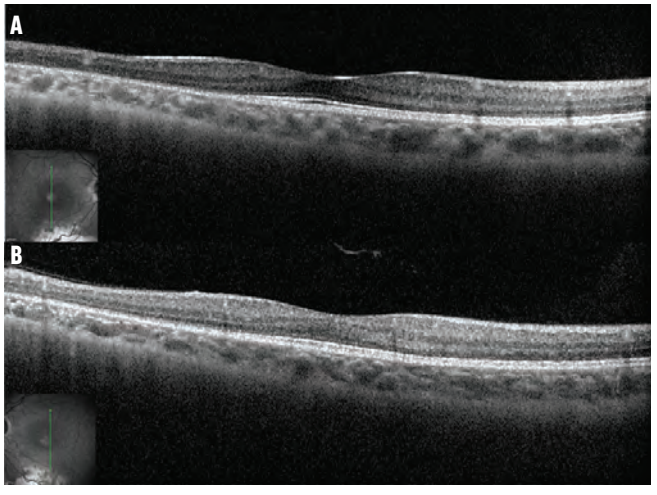


Figure 2. Spectral-domain OCT of the right (A) and left (B) eyes shows that overall microanatomy of the macula is intact, except for the start of outer retinal attenuation approaching the area of atrophy inferiorly.

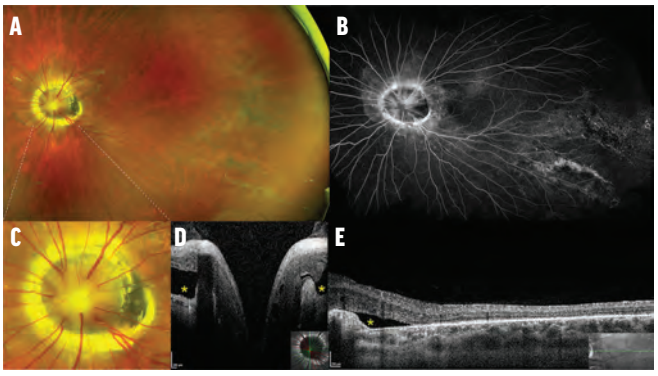


Figure 3. Fundus imaging shows an enlarged disc with radiating retinal vasculature (A). FA highlights the retinal vascular pattern, nonperfusion, and areas of chorioretinal atrophy (B). A magnified image helps depict the optic disc (C). Vertical OCT of the disc shows peripapillary subretinal fluid (D, yellow asterisks). Horizontal OCT shows a thin macula without foveal microanatomy (E).

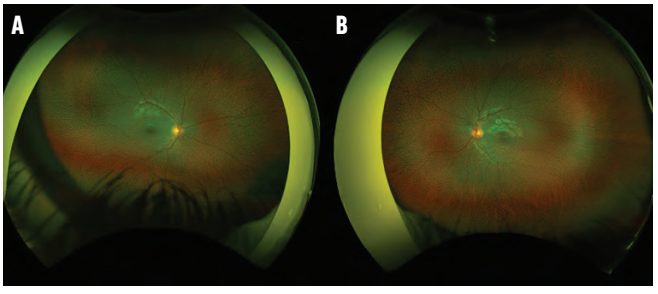


Figure 4. The patient's fundus photographs document diffuse, discrete, macula-sparing whitish flecks in the right (A) and left (B) eyes.

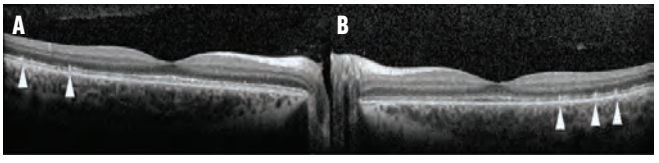


Figure 5. OCT imaging shows the lesions in the zone of interaction between the photoreceptor inner and outer segment and the apical RPE (white arrows) in the right (A) and left (B) eyes.

WE ASKED, YOU ANSWERED

Retina specialists took to social media to sleuth out the answers to these mystery cases. How well did you do?

Case No. 1 Social Media Poll Results:

- 37% *KIF11*-Related Familial Exudative Vitreoretinopathy
- 32% Norrie Disease
- 12% Incontinentia Pigmenti
- 19% Coats Disease

Case No. 2 Social Media Poll Results:

- 24% Coloboma
- 23% Papillorenal Syndrome
- 18% Juxtapapillary Staphyloma
- 35% Morning Glory Disc Anomaly

DISCUSSION

Case No. 1: *KIF11* Vitreoretinopathy

Genetic testing in this patient revealed a heterozygous mutation in *KIF11* (c.128_131dup), which was predicted to result in a frameshift and premature protein termination. The findings have been stable during subsequent follow-up visits.

Familial exudative vitreoretinopathy (FEVR) is a group of inherited retinal diseases characterized by abnormal retinal vascular development. Early stages are often asymptomatic and characterized by peripheral avascular retina and anomalous retinal vasculature. More advanced stages result in neovascularization, exudation, and tractional retinal detachment. FEVR is caused by genetic mutations in the Wnt signalizing pathway. The classic genes are *NDP*, *FZD4*, *TSPAN12*, and *LRP5*, but in recent years, researchers have identified additional genes implicated in FEVR-like syndromes.[1,2]

Clinicians are encouraged to identify the genetic etiology because there are different systemic consequences. For our patient described above, the *KIF11* mutation causes a FEVR-like phenotype with microcephaly, developmental delay, and chorioretinal atrophy. It is a part of a syndrome called microcephaly with or without chorioretinopathy, lymphedema, or intellectual disability, or MCLID.[1,2]

Case No. 2: Morning Glory Disc Anomaly (MGDA)

Also known as morning glory syndrome, this congenital anomaly of the optic disc is characterized by an enlarged, funnel-shaped excavation of the optic disc (megalopapilla), glial tufts within the disc, and peripapillary chorioretinal pigmentary changes.[3] An aberrant radial disposition of retinal vessels originating from the disc is also characteristic.

The diagnosis of MGDA is primarily made by the characteristic optic disc findings. Possible concomitant ophthalmic comorbidities include strabismus, retinal detachment (serous or rhegmatogenous), persistent fetal vasculature, cataract, aniridia, microphthalmos, peripheral retinal nonperfusion, and peripapillary choroidal neovascularization.[4] MGDA is typically unilateral, but bilateral involvement is also reported. Visual prognosis is often limited with a VA ranging between 20/200 and counting fingers in the affected eye, although some eyes retain good vision.

It is important to rule out Moyamoya disease in patients with MGDA because this association is common and can be life threatening. Other systemic associations may include basal encephalocele, PHACES syndrome, Aicardi syndrome, Chiari malformation type I, neurofibromatosis type 2, and CHARGE syndrome.

Case No. 3: Biallelic *RDH5* Mutation in Fundus Albipunctatus

This patient's genetic testing was positive for two variants in the *RDH5* gene, p.Arg54Ter and p.Arg191Gln, confirming the diagnosis of fundus albipunctatus. After 1 year of follow-up, the patient's retinal findings have remained stable.

Fundus albipunctatus is a rare autosomal recessive form of congenital stationary night blindness that is characterized by night blindness from childhood, stationary or slow progression of rod abnormalities, and progressive cone abnormalities in older age. Patients usually complain of delayed dark adaptation after exposure to bright light with normal visual acuity and color perception.[5-7]

The disease is characterized by numerous small white dots from the midperipheral to peripheral retina, without vascular or optic nerve abnormalities. The deposits are localized between the outer limiting membrane and the outer aspect of the RPE on OCT.[8,9] The shape and number of spots will vary with age and may even fade entirely.[10] The presumed accumulation of cisretinol and cisretinyl esters in the RPE due to 11-cis-retinol dehydrogenase deficiency may be responsible for the formation of the white dots seen in *RDH5* mutation-associated fundus albipunctatus.[11]

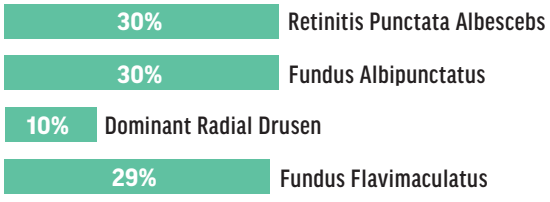
The differential diagnoses of flecked retinal disorders include retinitis punctata albescens, vitamin A deficiency, dominant radial drusen, benign familial fleck retina, fundus flavimaculatus, and fleck retina of Kandori; however, a much wider array of diseases correspond to the vague definition of fleck retina syndromes. The extension of flecks to the retinal periphery, lack of drusen on the macula and the nasal side of the optic disc, and the absence of high-density autofluorescent deposits exclude dominant radial drusen and fundus flavimaculatus.

Although benign retinal flecks show normal results in a full-field ERG, prolonged or overnight dark adaptation should be performed to differentiate fundus albipunctatus and retinitis punctata albescens. The ERG result normalizes or improves after prolonged dark adaptation for patients with fundus albipunctatus, while the result remains abnormal even with prolonged dark adaptation for patients with retinitis punctata albescens.[12]

The case presented here highlights the importance of considering fundus albipunctatus in the differential diagnosis of retinal flecks disease. For patients suspected to have this condition, appropriate genetic analysis and electrophysiological findings appear to be crucial elements of a proper diagnosis. ■

WE ASKED, YOU ANSWERED

Case No. 3 Social Media Poll Results:



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(Continued from page 33)

first-in-class gene therapies. The retina stands as a critical testing ground for translating these innovative tools into therapeutics not only for IRDs, but also for forging new paths to tackle other diseases of mankind. ■

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OCT BIOMARKERS IN UVEITIC MACULAR EDEMA

Noninvasive indicators of disease severity and prognosis may help guide management.

BY AUMER SHUGHOURY, MD, AND THOMAS A. CIULLA, MD, MBA


Macular edema (ME) is the most common cause of vision loss in intraocular inflammatory disease and is a common feature of active uveitis.[1,2] However, the diagnosis and management of uveitic ME (UME) can be challenging, owing in part to its often subtle examination findings and variable effects on visual acuity. Inconsistent correlations between UME severity, response to treatment, and visual prognosis can complicate the development of individualized treatment plans and make it difficult to provide patients with accurate prognostic counseling.

OCT has revolutionized the field of ophthalmology by providing a simple, noninvasive modality for reliably studying the microscopic cross-sectional structure of the retina in vivo. Several OCT biomarkers have been proposed as measures of disease severity and visual prognosis in UME, such as microscopic patterns of ME, central subfield thickness (CST), ellipsoid zone (EZ) integrity, and disorganization of retinal inner layers (DRIL).

Research continues to enhance our understanding of the correlations between these OCT biomarkers, baseline BCVA, and visual prognosis.[3-5] Here, we provide a brief overview of the use of these various biomarkers as indicators of visual function and long-term prognosis in UME.

PATTERNS

Three major patterns of ME have been described based on their OCT appearance (Figure 1).[6,7] The most common pattern, cystoid ME (CME), is characterized by clearly

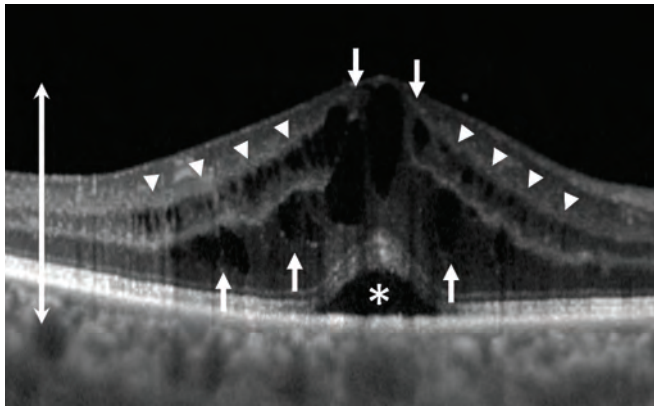

Figure 1. This OCT image demonstrates all three major patterns of ME in one unlucky patient. CME (arrows) appears as large, clearly defined, cystoid spaces. Diffuse ME (arrow heads) appears as small, sponge-like, low-reflective areas. Serous retinal detachment (asterisk) appears as a clean separation of the neurosensory retina from the retinal pigment epithelium. ME is also associated with increased central retinal thickness (double-headed arrow).

AT A GLANCE

- Several OCT biomarkers have been proposed as measures of disease severity and visual prognosis in uveitic macular edema.
- Tracking central subfield thickness at baseline and across treatment sessions may hold some value in clinical prognostication and patient counseling.
- Recent research suggests that foveal disorganization of retinal inner layers could be a valuable biomarker for BCVA in uveitic macular edema in addition to ellipsoid zone integrity and central subfield thickness.

defined, large, low-reflective intraretinal spaces.[7] Diffuse ME is characterized by generalized increased retinal thickness with small, sponge-like, low-reflective spaces. Serous retinal detachment is a clean separation of the neurosensory retina from the retinal pigment epithelium.[7] Correlations between each of these OCT patterns and baseline BCVA, response to treatment, and long-term visual prognosis in UME have been widely studied.[8]

CENTRAL SUBFIELD THICKNESS

One of the simplest objective OCT measures of the degree of ME is retinal thickness.[9] The most useful measure of retinal thickness as a biomarker of visual prognosis is CST, calculated by OCT software as the average thickness (in microns) across a 1-mm diameter circular area centered around the fovea (from the internal limiting membrane to the inner third of the retinal pigment epithelium on Cirrus OCT (Carl Zeiss Meditec), to Bruchs membrane on the Spectralis OCT (Heidelberg Engineering), or to the EZ on the Stratus OCT (Carl Zeiss Meditec). CST serves as a reliable, objective measure of the severity of vision-threatening ME and can be tracked over time.[10]

Increased CST has been shown to correlate negatively with baseline BCVA and visual prognosis in ME.[11] However, early studies of CST in UME demonstrated only a weak correlation between macular thickness and visual acuity.[6,12,13] More recently, data from 128 eyes enrolled in the Multicenter Uveitis Steroid Treatment (MUST) trial suggested a moderately negative correlation between CST and BCVA at baseline, as well as between change in CST and change in BCVA at 6 months.[14]

MUST trial data also demonstrated a 6.5-letter increase in BCVA on average for every 100-µm reduction in CST following therapy,[14] whereas other studies showed that eyes with UME that achieved at least a 20% decrease in CST tended to demonstrate an increase in BCVA of at least 10 to 15 letters.[14,15] Notably, some research has suggested that CST may be more strongly correlated with visual acuity in CME compared with other patterns of UME.[13]

A recent pooled analysis of 198 UME patients enrolled in the PEACHTREE and AZALEA trials examined the use of suprachoroidal injection of a triamcinolone acetonide corticosteroid formulation (CLS-TA, Clearside Biomedical) in ME and found only a moderately negative correlation between CST and BCVA at baseline, with CST accounting for 14.6% of the variation in baseline BCVA.[11] There was also a moderately negative correlation in the change from baseline to 24 weeks between BCVA and CST, although change in CST accounted for only 17.5% of the total variation in the change in BCVA.[11] Further analysis of the same pooled cohort suggested that CST changes may precede BCVA improvement by up to 6 weeks (3 weeks vs 9 weeks, respectively) following treatment of UME, with earlier CST response significantly associated with better visual prognosis.[5]

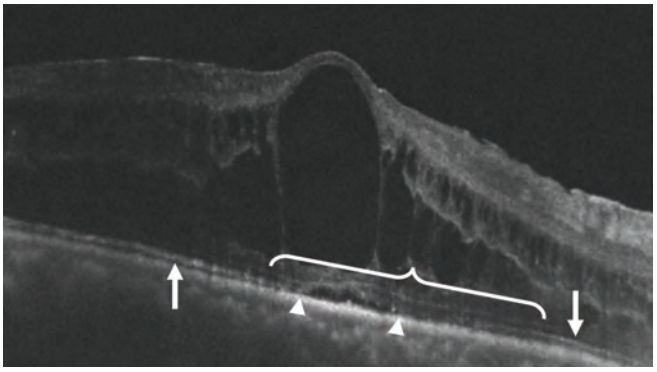

Figure 2. The intact EZ (arrows) loses its integrity (bracket) within the area of UME. Note the mild serous retinal detachment (between arrow heads) causing significant EZ disruption. Overlying large central cystoid spaces and diffuse ME are also seen.

These findings suggest that tracking CST at baseline and across treatment sessions may hold some value in clinical prognostication and patient counseling. However, because correlations between CST and BCVA are at best moderate and fail to account for a large portion of BCVA variability, evaluation of other biomarkers such as those representing severity of retinal tissue damage or structural derangement may provide more information than analysis of CST alone.[16]

EZ INTEGRITY

The EZ corresponds anatomically to the photoreceptor inner segment–outer segment junction and is thought to represent the mitochondria of photoreceptor inner segments.[17] The evaluation of its reflectivity and integrity on OCT imaging serves as an important biomarker of photoreceptor health.[17,18]

Loss of EZ integrity is associated with decreased visual acuity in a large number of retinal diseases (Figure 2). In UME, the degree of central subfield EZ disruption at baseline was associated with poorer baseline BCVA and poorer response to treatment in the pooled AZALEA/PEACHTREE trial UME cohort, although it may account for less than 30% of the total variation in BCVA, on average.[5,11] A smaller study by Grewal et al analyzed 56 eyes from the VISUAL-1 trial of UME and found EZ integrity on OCT to be weakly associated with BCVA when averaged across all visits.[19] Finally, degree of EZ disruption has been associated with intensity of corticosteroid therapy required to treat UME.[20] These findings suggest that EZ analysis may be helpful in predicting clinical response to treatment; however, as with CST, EZ analysis alone is not sufficient for accurate prognostication in UME.

DRIL

Precise organization of the inner retina is critical to physiologic visual function. Complex interactions between bipolar cells and networks of horizontally and vertically oriented amacrine cells in the inner retinal layers are responsible for

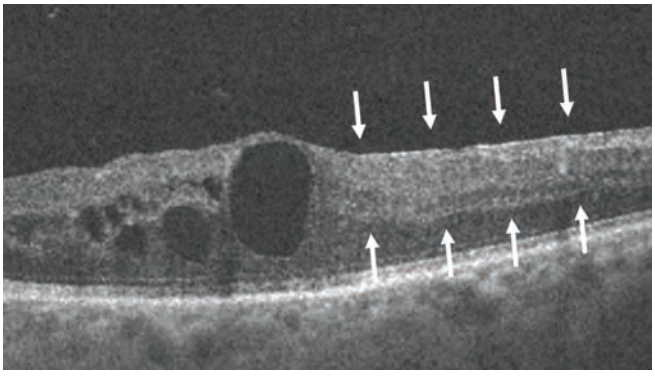

Figure 3. This OCT image demonstrates DRIL in UME. Note the loss of clearly delineated boundaries between the inner retinal layers (between arrows) adjacent to the large central cystoid space.

processing photoreceptor signals and relaying the visual image to the brain.[21] Macular or foveal disruption of these intricate networks may profoundly impact visual acuity.[22] DRIL, an OCT biomarker of retinal disease, appears as loss of clearly delineated boundaries between the ganglion cell–inner plexiform layer complex, the inner nuclear layer, and the outer plexiform layer (Figure 3).[23]

DRIL has been robustly associated with poorer baseline BCVA and visual prognosis in diabetic ME, even after treatment and resolution of edema.[22,24] One study found that the volume of retinal tissue between the inner and outer plexiform layers as determined by OCT imaging predicted 80% of the variance in baseline BCVA compared with 14% predicted by CST; this validates retinal tissue integrity with preserved axonal connections as an indicator of visual function.[25] DRIL may also be a sign of inner retinal ischemia or inflammatory neurodegeneration.[19]

Few studies have assessed DRIL as a biomarker in UME. Grewal et al first reported a significant association between baseline BCVA and both the horizontal and vertical retinal area of foveal DRIL in UME.[19] Liu et al similarly found that the transverse and vertical diameter of DRIL on baseline OCT imaging was associated with worse baseline BCVA and poorer final BCVA, while baseline macular thickness was not correlated with improvement in BCVA at 6 months.[26] While more research is necessary, these findings suggest that DRIL may ultimately prove to be a robust and useful biomarker of disease severity and prognosis in UME.

MORE WORK AHEAD

Continued research clarifying the precise significance of these biomarkers and others in the diagnosis and management of retinal disease may prove them to be invaluable for guiding the management of UME. Integration of such biomarkers into machine-learning algorithms may ultimately provide the key to developing personalized therapeutic strategies and accurate prognostic guidance in the management of uveitis and other retinal diseases. ■

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A PRIMER ON PEDIATRIC UVEITIS

Here's the latest on diagnosing, treating, and following these patients.

BY MONIQUE MUNRO MD, FRCSC; POOJA BHAT, MD; AND ANN-MARIE LOBO-CHAN, MD



Pediatric uveitis accounts for approximately 5% to 15% of all uveitis patients, and, while rare compared with adult uveitis, it presents unique challenges.[1,2] If ocular inflammation is not identified promptly and treated effectively, irreversible damage may occur.[1-8] Unfortunately, delayed presentations are more frequent in pediatric patients, given that patients may be asymptomatic, may be unaware symptoms are abnormal, or may be preverbal. Diagnosing and monitoring uveitis in a child requires an experienced examiner, and examination under anesthesia (EUA) is often necessary.[6,9]

Treatment in these developing patients also carries significant weight beyond the already challenging side effects common in adults. Here, we discuss updates in the care for pediatric patients with uveitis.

CAUSES

As with its adult counterpart, pediatric uveitis may be secondary to infectious or noninfectious causes and is classified based on the location of ocular involvement. Anterior uveitis is the most common presentation for pediatric uveitis, and the differential diagnosis is slightly more focused compared with adult uveitis.

Noninfectious uveitis accounts for the majority of pediatric uveitis in Europe and the United States.[3] Noninfectious causes include juvenile idiopathic arthritis (JIA)-associated uveitis (the most common cause in the United States and Northern Europe), juvenile-onset spondyloarthropathies, postinfectious autoimmune uveitis, tubulointerstitial nephritis and uveitis, systemic lupus erythematosus, Behçet disease, and sarcoidosis, including early-onset sarcoidosis and Blau syndrome.[6,7,10,11]

Infectious uveitis is more common in children than in adults, and entities such as toxoplasmosis, toxocariasis, and viral infections (eg, herpes simplex virus) should be considered.[6,7] While rare, masquerade syndromes also need to be considered, including retinoblastoma and other local tumors; leukemia and other systemic malignancies; inherited retinal diseases such as retinitis pigmentosa; juvenile xanthogranuloma; chronic retinal detachment; and intraocular foreign bodies.[5,12]

NEW DIAGNOSTICS

Genetic testing is more prevalent in medicine, and HLA class I and II gene polymorphisms have been observed in association with pediatric uveitis. For example, HLA-DRB1*11 and HLA-DRB1*13 are associated with JIA, and HLA-DR2 and HLA-DR15 are associated with pars planitis.[13]

Biomarkers would be a valuable tool to monitor pediatric patients and avoid repeat EUA. Various biomarkers have been studied for early diagnosis and classification of patients with JIA-associated uveitis. For example, research has shown that the Th1:Th2 ratio, anti-interleukin (IL)-10, and IL-13 are higher in JIA-associated uveitis patients compared with JIA patients without ocular inflammation.[13,14]

TREATMENTS: NEW AND OLD

Evidence suggests that early and aggressive treatment improves visual outcomes in pediatric patients with uveitis. Physicians must be comfortable with systemic immunomodulating therapies because pediatric autoimmune uveitis

AT A GLANCE

- Evidence suggests that early and aggressive treatment improves visual outcomes in pediatric patients with uveitis.
- Noninfectious uveitis accounts for the majority of pediatric uveitis in Europe and the United States.
- Pediatric patients with uveitis should be frequently examined until remission is achieved, and frequent follow-up is necessary due to the increased risk for flares in these patients.

frequently has a chronic course with a high risk for relapse that can lead to significant ocular morbidity. Even low-grade residual inflammation can cause significant damage to a pediatric eye long-term.[8,12] Due to this risk, the goal is to achieve inactive uveitis (defined as grade 0 cells in the anterior chamber according to the Standardization of Uveitis Nomenclature criteria) with steroid-sparing medications and to eventually reach drug-free remission.[13,15] However, this goal is difficult to attain because the side effects of immunomodulating medications in developing pediatric patients are a significant concern.[13,16] This is further complicated by the fact that few medications are approved for pediatric uveitis.

Corticosteroids

The current approach for treating acute pediatric uveitis includes topical and oral corticosteroids. While a stepwise approach is commonly used in adult uveitis patients, steroids must be used sparingly in pediatric patients because long-term systemic side effects, such as growth retardation, weight gain, and hyperglycemia, can have deleterious effects on children.[9,16] If a corticosteroid therapy fails or if a patient has chronic uveitis, a systemic disease associated with a chronic uveitis, or frequent recurrent uveitis with ocular sequelae, early initiation of corticosteroid-sparing immunomodulatory therapy is advised. These medications broadly include antimetabolites, T-cell inhibitors, alkylating agents, and biologics.[13]

NSAIDs

Although it is worth noting NSAIDs as treatment options in uveitis, they are not typically the drug of choice for the majority of pediatric uveitis due to severity and chronicity. Of the NSAIDs, naproxen and tolmetin are the medications most frequently used in pediatric uveitis.

Antimetabolites

Methotrexate is the most frequently used immunomodulating medication in pediatric uveitis and is generally the first line of therapy in chronic autoimmune uveitis.[13] Methotrexate can be administered subcutaneously or orally; however, the bioavailability of methotrexate is reduced in the oral form. Side effects include renal, liver, and gastrointestinal toxicity, and the medication should be taken with folic acid supplements.

Azathioprine is another antimetabolite but has been used less frequently due to a combination of factors, including its unfavorable side effect profile, lower efficacy, and limited data on pediatric dosage.[13]

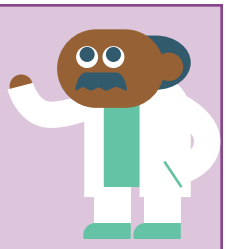
Biologic Response Modifiers

Biologic medications include anti-tumor necrosis factor alpha (TNF-α), anti-IL-1, anti-B-cell, and anti-T-cell inhibitors.

Adalimumab, an anti-TNF-α drug, is the only biologic agent FDA-approved for noninfectious uveitis in children. It is a fully humanized monoclonal antibody that is administered subcutaneously every 2 weeks and, arguably, could be given more frequently in refractory cases.[12] In the SYCAMORE trial, researchers found that adalimumab was associated with a lower rate of treatment failure than placebo in patients with active JIA-associated uveitis on a stable dose of methotrexate.[17] Adalimumab is also effective in cases of early onset, chronic, anterior uveitis refractory to topical therapy and methotrexate.

Infliximab is another commonly used TNF-α inhibitor drug administered as an intravenous infusion. When used to treat pediatric uveitis, it demonstrates efficacy in both retrospective and prospective studies. A meta-analysis demonstrated the efficacy of adalimumab and infliximab in the treatment of chronic pediatric uveitis with adalimumab showing some superiority to infliximab. However, the dose of infliximab can be escalated to elicit a response.[11,12,16] These

CURRENT STRATEGIES



These recommendations by the American College of Rheumatology and the Arthritis Foundation for immunomodulatory therapy in juvenile idiopathic arthritis may be leveraged for other forms of chronic uveitis in children:[1]

- Subcutaneous methotrexate is superior to oral methotrexate for starting treatment.
- For severe disease, a combination of methotrexate and a biologic is recommended for initial treatment.
- Other tumor necrosis factor alpha (TNF-α) inhibitors are superior to etanercept in chronic anterior uveitis.
- TNF-α inhibitor dose intervals should be shortened in cases of inadequate response to standard dosing.
- A second TNF-α inhibitor should be employed if a patient fails on the first one.
- Abatacept and tocilizumab can be employed in patients who fail methotrexate and two TNF-α inhibitors.
- All effective medications should be continued for 2 years before tapering therapy.

In addition, a review by Maleki et al found that, in the acute uveitis setting, topical and systemic corticosteroids should be used first with the addition of methotrexate or another antimetabolite if chronic uveitis or a systemic condition is present. If this fails, TNF-α inhibitors should be added. Should this fail, medications such as rituximab, tocilizumab, abatacept, or other emerging therapies may be tried.[2]

1. Onel KB, Horton DB, Lovell DJ, et al. 2021 American College of Rheumatology guideline for the treatment of juvenile idiopathic arthritis: recommendations for nonpharmacologic therapies, medication monitoring, immunizations, and imaging. *Arthritis Rheumatol*. 2022;74(4):570-585.
2. Maleki A, Anesi SD, Look-Why S, Manhapra A, Foster CS. Pediatric uveitis: A comprehensive review. *Surv Ophthalmol*. 2022;67(2):510-529.

STEROIDS MUST BE USED SPARINGLY IN PEDIATRIC PATIENTS BECAUSE LONG-TERM SYSTEMIC SIDE EFFECTS [...] CAN HAVE DELETERIOUS EFFECTS ON CHILDREN.

two medications have similar side effect profiles and are generally well tolerated.

Abatacept binds to CD80/CD86 on antigen presenting cells and prevents T-cell activation.[13] It is approved for children 2 years of age and older with polyarticular JIA, but the efficacy in pediatric uveitis is limited.[12] Tocilizumab is a humanized recombinant anti-IL-6 receptor antibody that inhibits T-cell activation and immunoglobulin secretion. Tocilizumab was studied in JIA-associated uveitis patients refractory to both methotrexate and anti-TNF-α medications in the APTITUDE trial.[18] Unfortunately, this trial did not meet the phase 2 primary endpoint. Tocilizumab's efficacy in autoimmune uveitis is currently being evaluated in the STOP-Uveitis and JIA-associated uveitis (JIA-U) trials.[19,20]

Rituximab targets the CD20 B-cell marker and causes B-cell apoptosis. Promising results have been shown in JIA-associated uveitis, but it is used less frequently due to the unfavorable efficacy profile and lack of robust data compared with other medications.[21]

Emerging Treatments

Janus kinase inhibitors have been recently evaluated in adults for the treatment of uveitis, and a study evaluating baricitinib in pediatric JIA-associated uveitis or chronic anterior ANA-positive uveitis is currently underway.[22]

FOLLOW-UP

Pediatric patients with uveitis should be seen frequently until remission is achieved, and frequent follow-up is necessary due to the increased risk for flares in these patients. Once in remission, the interval between follow-up visits can be extended, between 8 and 12 weeks, depending on the medications used and clinical stability.[13] If activity cannot be assessed in a clinical setting, an EUA must be pursued. High-risk blood monitoring tests should be performed at regular intervals and will depend upon the medication regime.

Ocular complications and sequelae to monitor for include cataracts, band keratopathy, glaucoma, synechiae, hypotony, cystoid macular edema, epiretinal membrane formation, retinal detachment, and neovascularization.

In addition to a thorough ophthalmic examination, a physical examination by a pediatrician and pediatric rheumatologist should be pursued to evaluate and monitor for associated systemic disease findings. ■

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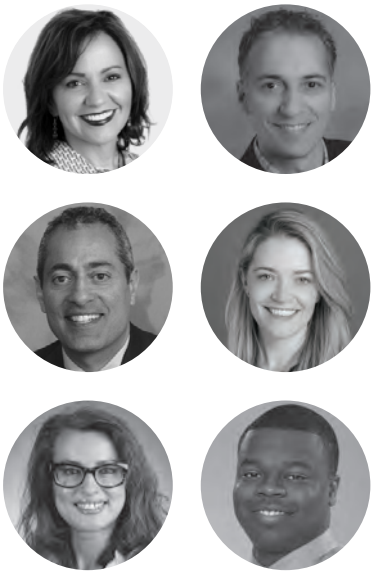

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ICROP3 UPDATES: REACTIVATION AND REGRESSION



Revisiting the classification has led to significant changes to help you better diagnose, monitor, and treat this condition.

BY M. ELIZABETH HARTNETT, MD, FACS, FARVO; M. MARGARITA PARRA, MD; AND MELISSA CHANDLER, BS

The committee for the International Classification of Retinopathy of Prematurity, third edition (ICROP3), included 34 international pediatric ophthalmologists and retina specialists who met to revisit the retinopathy of prematurity (ROP) classification.[1] ICROP3 was intended to assist research and clinical trials and provide consensus statements on ROP management but not to provide guidance on management. The main goals of the ICROP3 committee were to address earlier components of the classification that were subjective and open to interpretation; discuss imaging innovations that allow identification and comparison of levels of disease severity; explain the new understanding of ROP pathophysiology with therapies that interfere with VEGF bioactivity and introduce the conditions of regression and reactivation; and recognize patterns of ROP in other regions of the world using the revised classification[1]

Much has changed since the original ICROP in 1984, including the increased use of telemedicine screening and global education on ROP management.[2] In countries that recognized ROP as retrolental fibroplasia in the 1950s,[3] there have been technologic advances in neonatology, oxygen monitoring, and regulation that allow extremely premature infants to survive. In emerging nations, ROP occurs in more developmentally mature infants and can present in a severe and rapidly progressive form.[4,5]

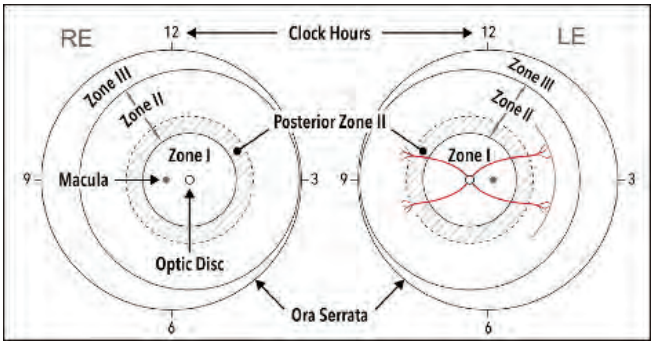

Figure 1. This diagram outlines the different zones evaluated in ROP screening. Reprinted with permission from Chiang MF, et al.[1]

In addition, agents that regulate cell signaling through a VEGF receptor by inhibiting angiogenesis reduce abnormal angiogenesis into the vitreous (stage 3 ROP) and allow angiogenesis to extend retinal vascularization into the periphery toward the ora serrata.[6-10] These processes are included in events of regression, a new term presented in ICROP3.[1] However, reactivation, also described in ICROP3, can occur, especially after anti-VEGF treatment, and this was not commonly seen with laser therapy for ROP in the past.[1]

ZONE, STAGE, PLUS DISEASE

The parameters for describing ROP remain the same: zone, stage, plus disease, and, less often considered for assessing treatment-warranted acute ROP, extent of stage.

Zone defines the retinal area that has been vascularized during development. A zone I fundus is the least vascularized and is associated with the most severe disease. A zone III fundus is the most vascularized. In ICROP3, posterior zone II is a circular area of vascularization centered on the optic nerve with a radius that is approximately 1.5 times the disc–macula distance (Figure 1). The zone II designation is still an estimate because the fovea is not developed in the premature infant.

In addition, zone I secondary to notch was described for eyes with 1 or 2 clock hours of zone I ROP in the horizontal meridian when other clock hours were in zone II (Figure 2).

Incomplete vascularization within a zone was a description before the development of ROP stages. Progressive stage 4 ROP, more common following laser therapy or cryotherapy for threshold ROP in the past, is seen less often with early laser treatment for stage 1 ROP.[11] When progressive stage 4 ROP occurs following laser therapy, the features of concern for a tractional retinal detachment (RD) are vitreous condensation over the ridge or optic nerve, haze, plus disease, or condensation over the ridge to an extent greater than 6 clock hours.[12] These features were distinct from persistent or new stage 3 ROP that warranted laser of skipped areas or antiangiogenic therapy.[12] Exudative RDs can also occur following laser therapy, are associated with a convex

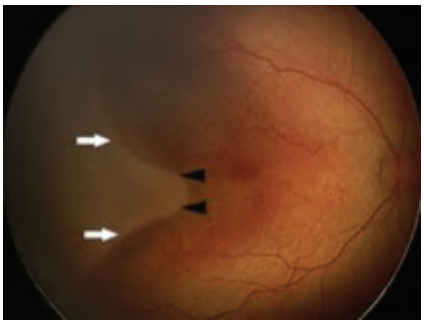

Figure 2. A notch between the vascular arcades (arrows, zone I). Reprinted with permission from Chiang MF, et al.[1]

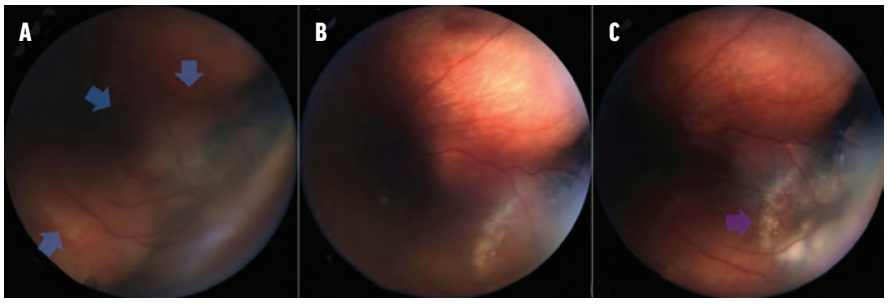

Figure 3. A female infant born at 25 weeks gestational age and 800 g birth weight was treated with laser photocoagulation at 44 4/7 weeks PMA. She presented with progressive stage 4 ROP and an inferotemporal exudative RD (blue arrow) at 55 4/7 PMA (A). During close observation, an improvement in the subretinal fluid occurred (B) with resolution of the RD at 62 3/7 weeks PMA (C). Note the exudation with resolution of subretinal fluid (purple arrow).

appearance, and often resolve with the appearance of exudates (Figure 3). After anti-VEGF therapy, reactivation can occur followed by progressive stage 4 ROP at the previous regressed ridge, at a new reactivated one, and/or at the optic nerve (Figure 4).

Stage 5 ROP was subclassified into 5A having an open funnel, 5B having a closed funnel with a view to the posterior eye, and 5C having a closed funnel with anterior segment involvement, including anterior lens displacement, anterior chamber shallowing, and corneal opacification.

Plus disease, classically described as dilation and tortuosity of the retinal veins and arterioles, now encompasses a spectrum of vascular changes graded by their zone 1 appearance. This acknowledges that clinicians have varying levels of comfort in diagnosing plus disease, although there was strong agreement regarding the normal and severe ends when committee members were asked to grade retinal images.

Aggressive ROP (A-ROP) is rapid development of pathologic neovascularization and severe plus disease without progression through the typical stages. A-ROP expands the earlier aggressive posterior ROP to include aggressive forms that occur in larger preterm infants and extend beyond the posterior retina with more peripheral vascular abnormalities.

REGRESSION

Regression, previously known as *involution* or *resolution*, is the lessening of severity of treatment-warranted ROP and can occur spontaneously (Figure 5) or after treatment but appears to have a more rapid course after anti-VEGF therapy (Figure 6) than laser treatment. Regression in plus disease involves reduction of vascular dilation and tortuosity, although tortuosity may persist or lessen when other conditions, such as cardiac diseases or pulmonary hypertension, are present. Other features of regression include involution of the tunica vasculosa lentis, improved pupillary dilation, media clarity, resolution of intraretinal hemorrhages, and thinning and whitening of the neovascular tissue. An aspect unique to ROP is vascularization into the peripheral avascular retina (VPAR) that can be complete or incomplete. When incomplete, the area devoid of vascularization is called *persistent avascular retina*.

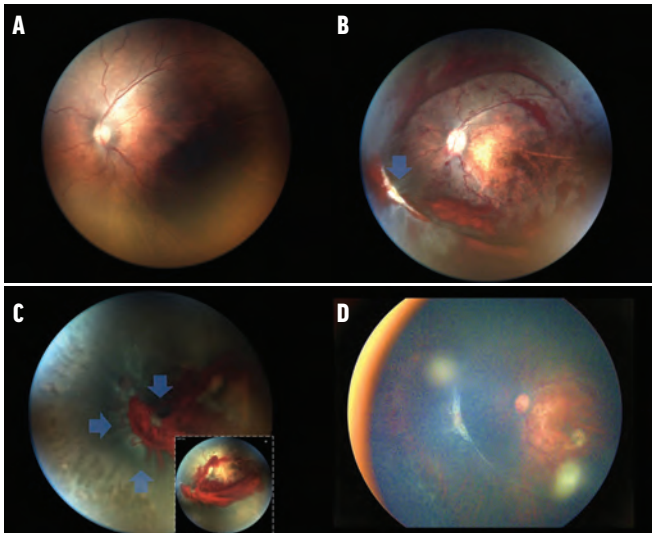

Figure 4. A female infant with a history of intraventricular hemorrhage, born at 26 2/7 weeks gestational age and 610 g birth weight, presented at 35 6/7 weeks PMA with type 1 ROP in the left eye. An injection of 0.25 mg bevacizumab (Avastin, Genentech/Roche) in a volume of 0.01 mL into the vitreous was performed. ROP regression occurred at 40 4/7 weeks (A). Reactivation occurred, and laser photocoagulation was performed to the peripheral avascular retina at 59 6/7 weeks PMA. A vitreous hemorrhage and nasal vitreoretinal tractional RD developed and worsened over the next 7 weeks into progressive stage 4 ROP (B, C; blue arrow). A lens-sparing vitrectomy was performed to segment the nasal vitreoretinal traction. An examination under anesthesia at 83 weeks PMA showed reduced nasal traction and no further extension (D).

REACTIVATION

Reactivation is generally seen following anti-VEGF therapy and may be less commonly appreciated following spontaneous regression. Before anti-VEGF therapy, early stages of ROP could regress, with more peripheral stages developing later as part of the natural history of the disease. Since the adoption of anti-VEGF agents, reactivation can occur much later than in the natural history of ROP. Current recommendations are to monitor infants after anti-VEGF injection until they are 65 weeks postmenstrual age (PMA).[13] Following anti-VEGF therapy, new lines or ridges, dilation, or tortuosity of retinal vasculature, or new extraretinal neovascularization is described by the term *reactivated* at the most anterior ridge. Zone I reactivation can occur with lacy vessels and hemorrhages.

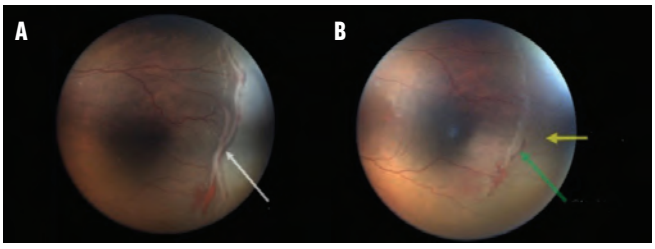

Figure 5. A female infant, born at 22 6/7 weeks gestational age and 660 g birth weight, presented with stage 3, zone II ROP (white arrow) without plus disease at 34 3/7 weeks PMA (A). At 39 5/7 weeks PMA (B), note the regressing ROP (green arrow) and VPAR (yellow arrow).

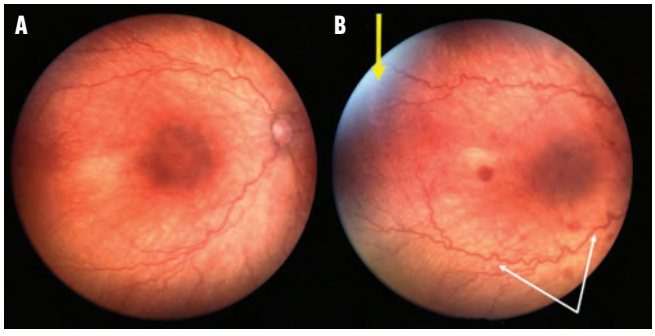

Figure 7. A female infant, born at 24 6/7 weeks gestational age and 555 g birth weight, had regressed ROP at 41 weeks PMA after treatment with 0.25 mg bevacizumab in a volume of 0.01 mL (A). Reactivated ROP occurred at 50 weeks PMA (B) with reactivated stage 2, zone II (yellow arrow) and greater dilation and tortuosity of retinal vasculature (white arrows).

Reactivation does not need to progress through the sequence of stages of acute-phase ROP. Reactivation typically occurs at the site of the original ridge, at the new junction and stage of vascular and avascular retina, or elsewhere in the vascularized retina (Figure 7).

What remains unclear is whether the appearance of angiogenesis at the vascular–avascular junction is the initiation of VPAR or reactivation of extraretinal neovascularization. This is an important consideration for future research because additional treatment with anti-VEGF injections may have detrimental effects on the neural retina or the developing infant from anti-VEGF agents that leak into the circulation.[14,15] Likewise, laser therapy might reduce visual field that would have developed with further VPAR.

ICROP3 also described long-term sequelae such as late tractional, rhegmatogenous, and, rarely, exudative RDs; retinoschisis; persistent avascular retina that may be prone to thinning holes and lattice-like changes; macular anomalies; retinal vascular changes and folds; and glaucoma—some of which are more apparent by fluorescein angiography or OCT.

BETTER GUIDANCE

The ICROP3 provides clearer guidance for future advances in the clinical management of and research on ROP based on advances in technology, pathophysiology, imaging, and an increased incidence of ROP worldwide, especially in emerging countries. ■

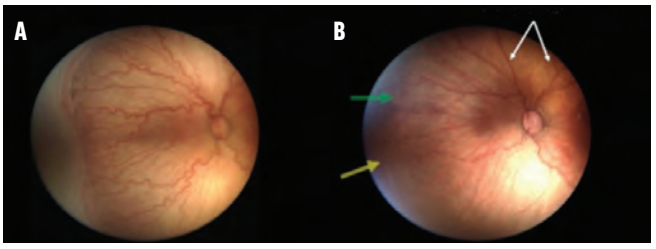

Figure 6. A female infant born at 25 6/7 weeks gestational age and 400 g weight had type 1 ROP with stage 3 disease at 34 4/7 weeks PMA. An intravitreal injection of 0.25 mg bevacizumab in a volume of 0.01 mL was given (A). At 50 weeks PMA (B), there was a faint line representing the regressed ridge (green arrow) and reduced vascular tortuosity and dilation (white arrows). In addition, VPAR occurred (yellow arrow).

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TWO SISTERS, TWO SYSTEMS, ONE VIEW

Two experts offer their clinical experience with the OCULUS HD Disposable Lenses for vitreoretinal surgery.

BY *RETINA TODAY*

Recent advances in lens technology and retinal imaging systems have given vitreoretinal surgeons novel viewing capabilities. *Retina Today* recently interviewed Audina (Nina) M. Berrocal, MD, FASRS, and María H. Berrocal, MD, to learn about their respective experiences with the OCULUS HD Disposable Lens for the BIOM® (see the *OCULUS HD Disposable Lens Portfolio*) and its version LenZ (both from OCULUS Surgical, Inc.) for use with the RESIGHT® Surgical Microscope (Carl Zeiss Meditec). Here, these surgeons and sisters describe their technological preferences for achieving the clearest, most efficient clinical treatments.

OUR PRACTICES AND OR SETUPS

Dr. María Berrocal: The majority of my surgical cases are diabetic detachments, macular holes and puckers, and retinal detachments. My OR setup includes a LuxOR Revalia Ophthalmic Microscope (Alcon) and the NGenuity 3D Visualization System (Alcon). For wide-angle viewing, I use the OCULUS BIOM® non-contact viewing system with the OCULUS HD Disposable Lenses.

Dr. Nina Berrocal: My practice is eclectic. It spans complex cases to very straightforward ones: Retinopathy of prematurity, permanent keratoprosthesis, suprachoroidal detachments, buphthalmic eyes in children, trauma in children, multiple detachments in the pediatric population, gene therapy, and the run-of-the-mill macular holes, epiretinal membranes, and rhegmatogenous detachments.

Recently, I transitioned my OR to exclusively using the NGenuity 3D system with both the Constellation Vision System (Alcon) and the EVA Phaco-Vitrectomy System (DORC), plus the ZEISS Rescan 700 iOCT (Carl Zeiss Meditec). I use the OCT in the Rescan as needed. My ideal combination now is the NGenuity with the OCULUS LenZ HD Disposable Lens with the RESIGHT®. The HD LenZ Disposable Lenses make the surgical view as clear and sharp as I need it to be.

THE LENSES WE PREFER FOR VITRECTOMY SURGERY

Dr. María Berrocal: I prefer the single-use, disposable vitrectomy lenses—the OCULUS HD Disposable Lens and the HD Optic Set for BIOM® (OCULUS Surgical, Inc.)—because their angle of viewing is very large (approximately 130º), and their clarity is exquisite. One of the main problems with reusable lenses is that they get easily scratched from repeated autoclaving and wiping. The quality of the OCULUS HD Disposable Lenses is never compromised. Interestingly, I think the resolution of structures and the depth of focus afforded by these HD Lenses are much better than any other lenses.

The HD Lens' wide-viewing angle coupled with the NGenuity 3D system has several advantages when performing this type of surgery. I can see the eye on a very large screen, and I can magnify the operating area significantly. Using the HD Disposable Lens with the NGenuity 3D system allows me to view the entire periphery, which has not always been the case with microscope-only viewing. This pairing gives me maximum magnification plus a full field of view. I appreciate that the HD Disposable Lenses work with my microscope of choice.

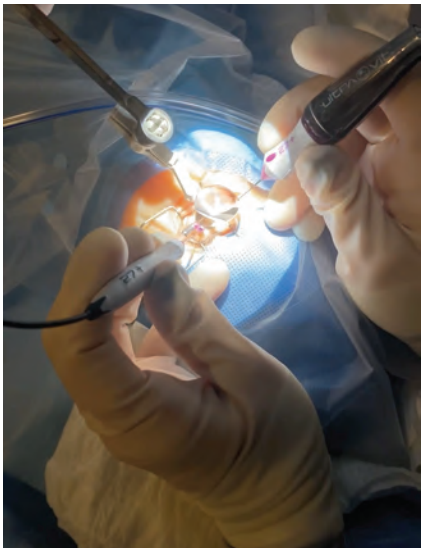

Image courtesy of Audina (Nina) M. Berrocal, MD, FASRS.

Figure. A complex retinal surgery performed with the Versa HD Lens from OCULUS Surgical, Inc.

The primary benefit of the OCULUS HD Disposable Lenses is that it is never in direct contact with the cornea and therefore will not cause corneal damage. I am able to see all the way to the ora serrata by manipulating the HD Disposable Lens. Often, I can see the entire retina without having to depress the sclera. I can even use the HD Disposable Lens with the NGenuity 3D system to correct macular holes and puckers without having to use a contact lens for viewing.

Dr. Nina Berrocal: I am in love with the LenZ and the HD Lenses by

THE OCULUS HD DISPOSABLE LENS PORTFOLIO

By Ariel Finkelstein, VP of Business Development, OCULUS Surgical, Inc.

The versatility and adaptability of the OCULUS HD Disposable Lens portfolio (OCULUS Surgical, Inc.) gives the surgeon the ability to choose the right tools to achieve the best surgical outcomes (Figure). This lens portfolio provides viewing solutions compatible with most microscope systems available on the market.

Figure. The HD Disposable LenZ (top) and Versa HD Lens (bottom) from OCULUS Surgical, Inc.

OCULUS. I remember the day I realized the difference between these and traditional vitrectomy lenses. I was operating on a tough case, using a glass lens from ZEISS RESIGHT®, and my view was hazy. I asked my assistant to change to the HD LenZ and voilà, my view of the surgical field was super clear. With both the LenZ and the Versa HD Lens, I have the clearest image I can get with every case, and I can use these lenses for macular work.

WHY WE RECOMMEND THE OCULUS HD LENSES TO COLLEAGUES

Dr. María Berrocal: If you want to achieve the best possible view in vitreoretinal surgery, I believe the OCULUS HD Lenses are the best choice. An unobstructed view is important, especially in eyes that have some cataract or corneal opacities that limit the view of the fundus.

Furthermore, I have found other lenses to be too large in deep-set eyes or those with a prominent nose or brow. I do not have this problem when I use the Versa HD Lens from OCULUS in these challenging eyes, because it is narrow. I can position the instruments wherever I want, even at a steep angle, without the lens becoming an impediment. Even in children, the OCULUS HD Lens is so thin that it gives me easy access to the eye and a good view of the fundus without the risk that my hands or instruments will move it. I am using the OCULUS HD Lens in about 80% of my surgeries.

Another reason I prefer the OCULUS HD Lenses is that they really enhance my depth of focus when I use a 3D imaging system. I often record my surgeries in 3D for teaching purposes, and the view through theses HD lenses is unsurpassed. I feel they are a great benefit for surgical videos.

Dr. Nina Berrocal: I think every vitreoretinal surgeon should try the OCULUS HD Lenses. Their performance reminds me of the sharpness, wide field, and clarity that I would get with the contact AVI wide-field lenses (Advanced Visual Instruments). The Versa HD LenZ is fantastic for pediatric eyes, for long myopic eyes, and for those cases in which the nose is prominent. It allows me to complete the case with efficiency (Figure).

CASE EXAMPLES

Dr. María Berrocal: I recently operated on a diabetic who had retinal detachment. This woman was in her late 80s and very thin, and her eye was extremely deep set. I started the procedure with the HD BIOM® Lens, but I was having a lot of difficulty moving the instruments around to repair the detachment. I kept moving the lens as I was moving the instruments, so I switched to the Versa HD Lens, and I was able to complete the case without having any loss of view or time.

Dr. Nina Berrocal: I recently operated on a child with a retinal detachment in a myopic eye with an axial length of 32 mm. The Versa HD Lens allowed me to do the case easily. I did not need long instruments, and I was able to use one lens efficiently.

CONCLUSION

No matter the microscope system a surgeon chooses, the benefits of using OCULUS HD Disposable Lenses in vitreoretinal surgery remain the same: Exceptional clarity that is never compromised, a 130º field of view, a precise depth of field, a range of surgical applications, and no risk of cross-contamination.

For these reasons, Drs. Nina and María Berrocal, who use two different microscope systems, agreed that they continue to use the OCULUS HD Lenses in the majority of their surgeries, and they continue to be pleased with their results. In their experience, these lenses offer exceptional clarity, a large and precise field of view, and a range of surgical applications with little risk of cross-contamination. ■

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WHEN RADIATION RETINOPATHY BECOMES A BLOODY MESS



Fundus autofluoresence can help you document acute and chronic hemorrhage associated with this treatment complication.

BY NICHOLAS E. KALAFATIS, MD; ZEYNEP BAS, MD; AND CAROL L. SHIELDS, MD

Proliferative radiation retinopathy (PRR) is characterized by findings of ischemic retinopathy, such as microaneurysms, hemorrhage, hard exudation, and nerve fiber layer infarctions, as well as retinal neovascularization.[1] Bianciotto et al studied 3,841 eyes treated with plaque radiotherapy for uveal melanoma and found that PRR occurred in 6% of patients assessed 5 years post-radiotherapy and 7% of patients assessed 10 and 15 years post-radiotherapy.[2]

Various risk factors have been linked to the likelihood of developing PRR, including history of diabetes mellitus, tumor close to the optic disc, and increasing basal tumor diameter (> 10 mm). As a result, patients with irradiated uveal melanoma are monitored closely for radiation complications, and anti-VEGF therapy and prophylactic panretinal photocoagulation (PRP) are administered every 4 months for 2 years after initial radiation treatment.

Hemorrhagic findings in PRR can present in the intraretinal, preretinal, or vitreous layers.[2] Preretinal hemorrhage tends to occur in the subhyaloid region that occupies the potential space between the posterior hyaloid (vitreous) face and the superficial retina. Subhyaloid hemorrhage can result from a variety of conditions, including diabetic retinopathy (50%), Valsalva retinopathy (20%), traumatic choroidal rupture (10%), retinal artery macroaneurysm (7%), and retinal vein occlusion (3%), among others.[3] A finding of subhyaloid hemorrhage has not been well-documented on fundus autofluorescence (FAF), but those that have been reported demonstrate regions of hyperautofluorescence of chronic yellow hemorrhage and regions of hypoautofluorescence of acute red hemorrhage.[4]

The management of subhyaloid hemorrhage depends on the size and location of the hemorrhage, as well as the underlying cause. Herein, we describe an interesting presentation of subhyaloid hemorrhage following plaque radiotherapy of choroidal melanoma and correlate the FAF findings with the acute and chronic hemorrhagic features.

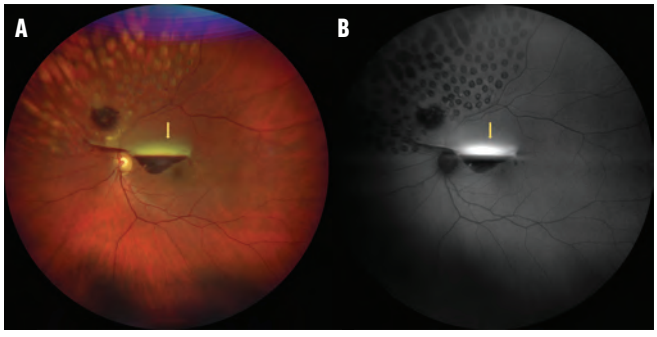

Figure 1. Fundus imaging of the left eye revealed a boat-shaped subhyaloid hemorrhage in the macula. Dehemoglobinized blood (yellow arrow) can be seen superior to fresh blood with clear separation between layers (A). FAF of the left eye demonstrated hyperautofluorescence of the dehemoglobinized subacute subhyaloid blood (yellow arrow) and hypoautofluorescence of the fresh blood (B).

CASE REPORT

A 45-year-old White male presented with a history of choroidal melanoma in the left eye, measuring 10 mm in basal diameter and 2.5 mm in thickness. He was treated with iodine-125 plaque radiotherapy using an apex dose of 70 centigray (cGy) and rate of 57.89 cGy/hour. Prophylactic PRP was administered to the region of radiotherapy, as well as prophylactic intravitreal bevacizumab (Avastin, Genentech/Roche) every 4 months for 2 years.

Medical history included chronic controlled hypertension and hyperlipidemia. Five years post-radiotherapy, retinal neovascularization elsewhere (NVE) was discovered in the region of the treatment, consistent with PRR, and additional sector PRP was added. One year after that treatment, he developed a blind spot in his central vision and was noted to have a new subhyaloid hemorrhage in the treated eye.

On examination, BCVA was 20/20 OU. The anterior segment of each eye was unremarkable and there was no iris neovascularization. The right fundus was normal. The left fundus showed a flat retina with the tumor completely regressed to a barely visible flat scar, with surrounding PRP.

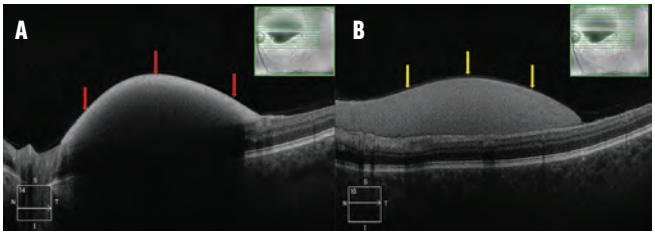

Figure 2. OCT of the left eye demonstrated subhyaloid hemorrhage. Cross-sectional capture of fresh hemorrhage (A, red arrows) versus old hemorrhage (B, yellow arrows), both with relatively homogeneous optical density (B), was obtained.

There was new subhyaloid hemorrhage located near the foveola with fresh red blood (inferior) and chronic yellow, dehemoglobinized blood (superior; Figure 1A). The superotemporal retinal vein was sclerosed.

FAF showed dramatic marked hyperautofluorescence of the chronic dehemoglobinized yellow blood and marked hypoautofluorescence of the fresh red blood (Figure 1B). OCT confirmed preretinal, optically dense debris in a dome-shaped configuration representing fresh red hemorrhage (Figure 2A) and similar, but less dense preretinal debris representing chronic yellow hemorrhage (Figure 2B). Fluorescein angiography of the retinal NVE showed leakage along the superotemporal vascular arcade. The patient was treated with an intravitreal injection of bevacizumab and returned 1 month later for additional PRP.

DISCUSSION

In this case, the yellow dehemoglobinized blood was displaced superiorly above fresh red blood with clear delineation between the two layers—an interaction that is often seen between two fluids that do not homogenize. The loss of hemoglobin in chronic hemorrhagic blood results in a lower mean corpuscular hemoglobin concentration and lower density,[5] so it is possible for a slow, insidious leak of blood to show separation, such that degraded blood floats above continuously deposited fresh blood.

The characteristics of subhyaloid hemorrhage on FAF have rarely been documented in the literature, although the temporary hyperautofluorescence in dehemoglobinized blood has been related to the degree of fluorescence in the breakdown products of heme.[4] Heme is structurally considered a porphyrin ring, which is composed of multiple methyl groups and double bonds, with an iron molecule at its core.[6] As blood is broken down, the iron molecule separates, and the conjugated double bonds exhibit the highest level of hyperautofluorescence, with degradation of these double bonds leading to lower and lower levels of autofluorescence.[4,7] Bilirubin, a yellowish pigment that is a breakdown product of heme, also exhibits hyperautofluorescence when bound to albumin and likely contributes to the weak hyperautofluorescence seen in chronic hemorrhage.[4,8] This phenomenon would explain the findings of hyperautofluorescence in subacute subhyaloid hemorrhage and its slow conversion to hypoautofluorescence in chronic cases.

CLINICAL TAKEAWAY

A pathophysiologic explanation for findings of retinal hemorrhage on FAF has rarely been discussed. Subhyaloid hemorrhage is a sequela of various retinal pathologies, including PRR, that warrants quick and appropriate management. An understanding of FAF patterns in cases of hemorrhage can assist in the characterization and management. While fresh hemorrhage will appear hypoautofluorescent, newly dehemoglobinized hemorrhage will initially appear brightly hyperautofluorescent followed by diminishing autofluorescence over time. A timeline of the hemorrhage can be drafted, and the delivery of treatment can be given accordingly. ■

Support provided in part by the Eye Tumor Research Foundation, Philadelphia, PA (CLS). The funders had no role in the design and conduct of the study, in the collection, analysis and interpretation of the data, and in the preparation, review or approval of the manuscript. Carol L. Shields, MD, has had full access to all the data in the study and takes responsibility for the integrity of the data.

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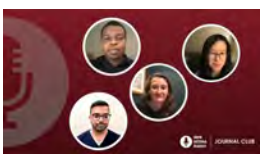
Basil Williams, MD; Karen Jeng-Miller, MD, MPH; M. Ali Khan, MD; and Katherine Talcott, MD



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Zeba A. Syed, MD, and Jose Pulido, MD, MS, MBA, MPH

CODING ADVISOR

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PROTECT YOUR REVENUE

Take the coding quiz and test your expert coding knowledge.

BY JOY WOODKE, COE, OCS, OCSR

The ultimate goal for coding and reimbursement in the retina practice is to appropriately maximize reimbursement by producing clean claims and providing audit-proof documentation. This can be achieved by a commitment to developing expert-level knowledge. Start with building an exceptional foundation and continue growing each year.

MASTER THE FUNDAMENTALS

You can develop a solid coding foundation by understanding a few essential topics in retina coding. These areas should be continually reviewed to build a solid foundation of coding knowledge.

- Evaluation and management (E/M) and eye visit codes
- Modifiers
- Correct coding initiative bundles
- Testing services
- Global periods
- ICD-10 coding rules
- Payer policies

Coding is a team sport, and each person in the practice contributes to appropriate documentation and correct coding. Although the physician is ultimately responsible, staff provide an important supporting role and, everyone should receive ongoing education related to their individual roles. Each step of the patient encounter and revenue cycle management provides an opportunity to contribute expert coding knowledge.

TEST YOUR KNOWLEDGE

Take this quiz based on specific coding scenarios to test your knowledge and see how much you know!

Questions

1. An established patient was seen for a follow-up evaluation of an epiretinal membrane in the left eye and proliferative retinopathy in each eye with previous panretinal photocoagulation. Fluorescein angiography and OCT were performed. The plan was to continue to observe and schedule a follow-up visit in 6 months. Based on the multiple problems and testing, would this be moderate level of medical decision making (MDM) and E/M level 4, CPT code 99214?

2. In the global period of a pars plana vitrectomy in the right eye, a laser to repair a retinal tear was performed in the left eye. Which modifier should you use?

3. When can CPT codes 92133 and 92134 be unbundled with modifier -59, distinct procedure scheduled when performed on the same day?

4. How frequently can CPT code 92134 be billed for a patient receiving monthly intravitreal injections?

5. We billed Medicaid for an office visit because the patient was 14 days status-post; we used CPT code 67228 and received a denial with the explanation that the visit was considered postoperative. Doesn't this laser treatment have a 10-day global period?

6 We received the results from a Medicare audit and one of our intravitreal injections was denied as not medically necessary. The ICD-10 codes H35.3122 (nonexudative AMD, intermediate, left eye) and H35.321 (exudative AMD, right eye) were linked to CPT code 67028-LT. Why was the claim denied?[1]

Answers

1. The final determination for the level of E/M is based on the level of the three MDM components: problem, data, and risk. To meet an overall MDM as moderate, two of three components must meet or exceed that level. In this case, two or more stable chronic illnesses would be a moderate level problem. Additionally, the level of risk would be low with a final MDM of low, and CPT code 99213 would be appropriate.

Fundamental: For E/M code selection, consider the level of MDM for each category, then determine the final E/M MDM based on meeting or exceeding two or three categories.[2]

2. Append modifier -79, unrelated procedure by the same physician in the postoperative period, along with the appropriate anatomical modifier (ie, -RT or -LT).

Fundamental: Master modifiers, including surgical modifiers -58 and -78.[3]

3. CPT codes 92133 and 92134 are mutually exclusive and should never be unbundled. Bill the test that contributes most to the MDM on the day of the encounter.

Fundamental: Review National Correct Coding Initiative edits and the scenarios in which it is appropriate to unbundle.[4]

4. The answer depends on the insurance payer policy. For the Medicare Administrative Contractor, Novitas, its two policies for OCT, L35038 and A57600, state "No more than one (1) examination per month will be considered medically reasonable and necessary to manage the patient with retinal conditions undergoing active treatment, or in conditions suggestive of rapid deterioration."[4] For patients not on active treatment "no more than one (1) examination every two (2) months" or "in conditions suggestive of rapid deterioration."[5] Note: 1 month is defined in A57600 as every 28 days. Policies for other contractors can be found at aao.org/lcds.

Fundamental: Confirm payer-published policies for retina services provided to identify documentation requirements, frequency edits, and covered diagnoses.

5. Medicare has a 10-day global period for CPT code 67228, but some payers, including Medicaid plans, may still recognize it as a 90-day global period and a major surgery.

Fundamental: Identify the global period for all retinal procedures per insurance payer and create an internal reference guide for correct coding.[6]

6. Link only the ICD-10 code that supports medical necessity to the injection. Reporting nonexudative AMD as a diagnosis for an intravitreal injection may lead to a denial as not medically necessary.

Fundamental: The appropriate ICD-10 to CPT code link is crucial as it supports the medical necessity for the service reported.

HOW DID YOU DO?

Knowing how to bill for retina services correctly and efficiently is crucial in any retina practice. For more information on the *Fundamentals of Retina Coding*, visit aao.org/retinapm or explore the *Retina Coding: Complete Reference Guide*, available at aao.org/store. ■

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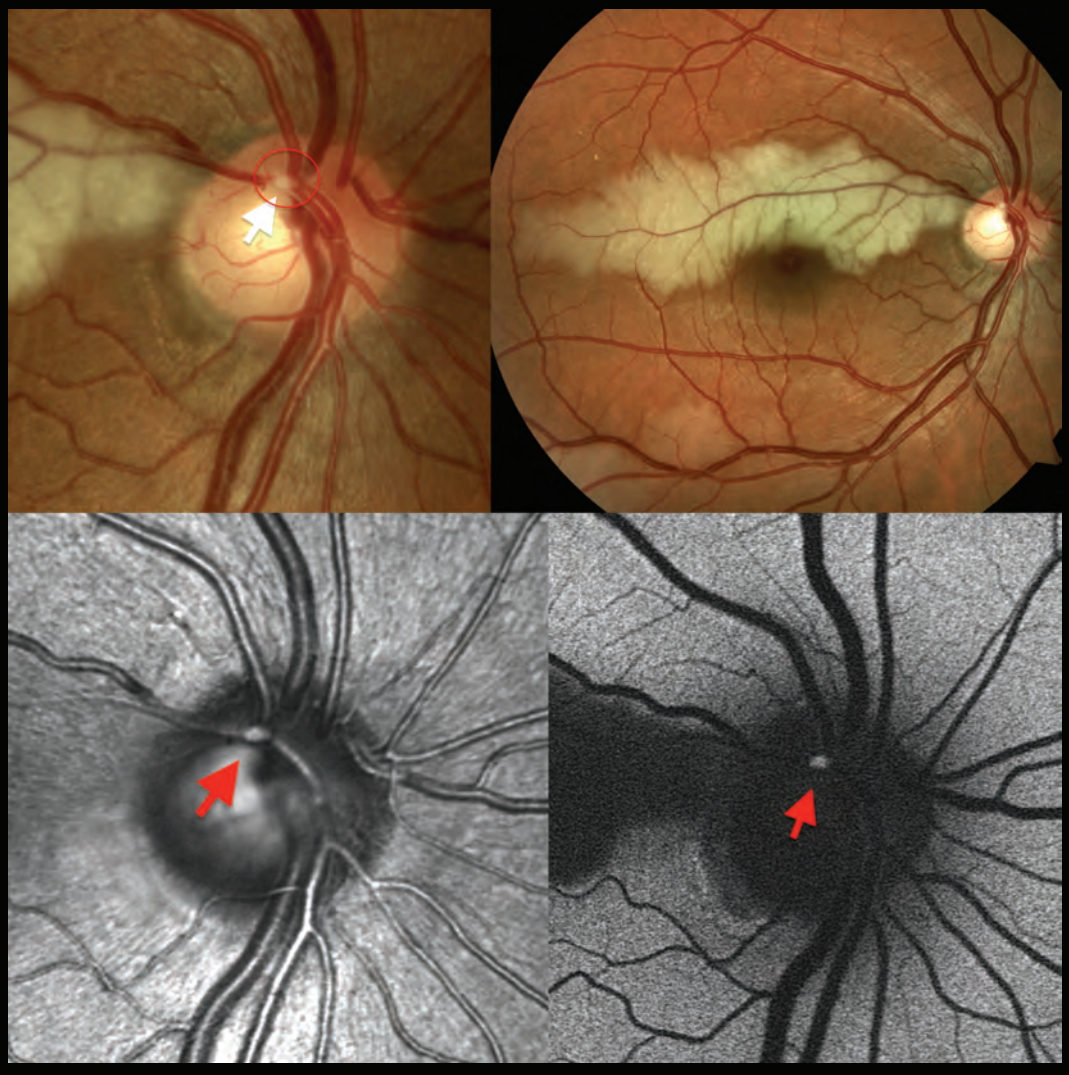
For more coding tips, scan the QR code or visit *Retina Today* online at retinatoday.com



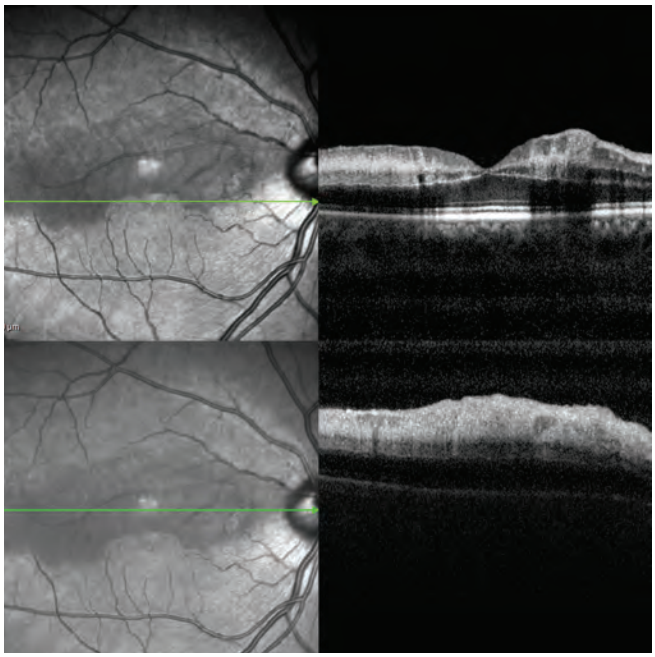
BRANCH RETINAL ARTERY OCCLUSION SECONDARY TO CALCIFIC EMBOLI

An unusual ocular finding may be the first sign of cardiovascular disease.

BY ISIL SAYMAN MUSLUBAS, MD, FEBO; MUMIN HOCAOGLU, MD, FEBO; SERRA ARF, MD; AND MURAT KARACORLU, MD, MSC, FEBO

A 31-year-old man presented with sudden painless vision loss in his right eye. VA was 20/25 OD and 20/20 OS. On ocular examination, the anterior segment of each eye and the left fundus were normal. The right fundus examination revealed a superior branch retinal artery occlusion with calcific emboli appearing as a whitish plaque at the optic disc. Infrared reflectance imaging and fundus autofluorescence of the right optic disc confirmed calcific emboli (Main Figure). Spectral-domain OCT revealed hyperreflectivity and increased thickness of the inner layers of the superior retina (Figure, next page).

The patient was referred to a cardiologist to rule out unrecognized cardiovascular disease, where he was diagnosed with atrial septal defect and mitral calcific valve stenosis.



DISCUSSION

A calcific retinal embolism is an unusual but serious complication of calcific cardiac valve disease. It may be the first clinical manifestation of underlying cardiovascular pathology, so it is important to refer the patient to a cardiologist whenever this finding is noted. ■

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If you have an image or images you would like to share, email Dr. Nagpal.
Note: Photos should be 400 dpi or higher and at least 10 inches wide.

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GIUSEPPE QUERQUES, MD, PHD

When did you know you wanted to pursue a career in ophthalmology?

I became interested in medicine in high school. Later, I enrolled in a medical university and was fascinated by the ophthalmologic pathophysiology. I was not exposed to the ophthalmology clinic until my fourth year of university, when I performed my first ocular fundus examination on a patient with a peripheral hemorrhage due to diabetic retinopathy. My assistant did not recognize the hemorrhage and congratulated me on the diagnosis. At that moment, I realized that I wanted to become an ophthalmologist and a retinal specialist.

One of your main areas of research is retinal imaging. What drew you to this aspect of the field?

Retinal imaging plays a pivotal role in establishing the diagnosis and treatment options for retinal pathologies. I am most interested in how retinal imaging helps advance medical knowledge and helps retina specialists improve patient care. Retinal diseases are numerous and many share common findings; thus, it is not always easy to distinguish them. A multimodal imaging approach allows us to precisely classify and diagnose most retinal diseases. This aspect of our clinical practice fostered my desire to investigate retinal imaging tools in depth.

What are some new technological and/or therapeutic advances that you have found particularly exciting?

The intersection between advanced imaging technology, such as high-resolution OCT, OCT angiography (OCTA), and ultra-widefield fluorescein angiography, and the ever-expanding number of treatment modalities makes caring for our patients very interesting. The aim of my group's recent studies is to better diagnose and classify retinal diseases and tailor patients' treatments.

Because of the large number of patients diagnosed with dry AMD, I would be enthusiastic to develop a treatment that could stop or slow down macular atrophy. Research protocols to treat dry AMD patients with subthreshold laser and photobiomodulation are in progress, and I am curious to verify their effectiveness.

Your team pioneered changes to the field's understanding of the staging of macular neovascularization (MNV) in 2013. How has the growth of OCTA affected that line of research?

OCTA represents an essential tool in the diagnosis of MNV and in monitoring its evolution, including treatment-naïve nonexudative forms and quiescent MNV that we first described in 2013. OCTA shows an anatomically detailed visualization of MNV, allowing a staging and deeper investigation of these lesions. Moreover, OCTA, associated with high-resolution OCT, provides information about MNV activity, with the ambition of predicting short-term exudation. In addition, as a dye-free noninvasive imaging modality, OCTA is suitable to be performed frequently and is thus an essential tool in the follow-up of MNV. Moreover, the application of OCTA in research and clinical practice is likely to grow with the introduction of new algorithms to better visualize the periphery.

Figure. Dr. Querques with his wife and daughter seaside during the holidays in Puglia, Italy.

What are you hoping to accomplish in 2022?

Conducting research and educating ophthalmology residents and fellows will always be the focus. However, I would like to take some time to have fun at home with my wife and daughter (Figure), who are the highlights of my life outside work, and to pursue my hobbies, such as skiing and my passion for cars and motorcycles. ■

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susvimo™

ranibizumab injection 100 mg/mL For Ocular Implant

SUSVIMO™ (ranibizumab injection) for intravitreal use via SUSVIMO ocular implant. This is a brief summary. Before prescribing, please refer to the full Prescribing Information.

WARNING: ENDOPHTHALMITIS

The SUSVIMO implant has been associated with a 3-fold higher rate of endophthalmitis than monthly intravitreal injections of ranibizumab. Many of these events were associated with conjunctival retractions or erosions. Appropriate conjunctiva management and early detection with surgical repair of conjunctival retractions or erosions may reduce the risk of endophthalmitis. In clinical trials, 2.0% of patients receiving a ranibizumab implant experienced at least one episode of endophthalmitis *(see Contraindications (4.1), Warnings and Precautions (5.1))*.

1 INDICATIONS AND USAGE

SUSVIMO (ranibizumab injection) is indicated for the treatment of patients with Neovascular (wet) Age-related Macular Degeneration (AMD) who have previously responded to at least two intravitreal injections of a Vascular Endothelial Growth Factor (VEGF) inhibitor medication.

4 CONTRAINDICATIONS

4.1 Ocular or Periocular Infections

SUSVIMO (ranibizumab injection) is contraindicated in patients with ocular or periocular infections.

4.2 Active Intraocular Inflammation

SUSVIMO (ranibizumab injection) is contraindicated in patients with active intraocular inflammation.

4.3 Hypersensitivity

SUSVIMO (ranibizumab injection) is contraindicated in patients with known hypersensitivity to ranibizumab products or any of the excipients in SUSVIMO (ranibizumab injection).

5 WARNINGS AND PRECAUTIONS

The SUSVIMO implant and/or implant-related procedures have been associated with endophthalmitis, rhegmatogenous retinal detachment, implant dislocation, septum dislodgement, vitreous hemorrhage, conjunctival erosion, conjunctival retraction, and conjunctival blebs. Patients should be instructed to report any signs or symptoms that could be associated with these events without delay. In some cases, these events can present asymptomatically. The implant and the tissue overlying the implant flange should be monitored routinely following the implant insertion, and refill-exchange procedures to permit early medical or surgical intervention as necessary. Special precautions need to be taken when handling SUSVIMO components *(see How Supplied/Storage and Handling (16.3))*.

5.1 Endophthalmitis

In the active comparator period of controlled clinical trials, the ranibizumab implant has been associated with a 3-fold higher rate of endophthalmitis than monthly intravitreal injections of ranibizumab (1.7% in the SUSVIMO arm vs 0.5% in the intravitreal arm). When including extension phases of clinical trials, 2.0% (11/555) of patients receiving the ranibizumab implant experienced an episode of endophthalmitis. Reports occurred between days 5 and 853, with a median of 173 days. Many, but not all, of the cases of endophthalmitis reported a preceding or concurrent conjunctival retraction or erosion event.

Endophthalmitis should be treated promptly in an effort to reduce the risk of vision loss and maximize recovery. The SUSVIMO (ranibizumab injection) dose (refill-exchange) should be delayed until resolution of endophthalmitis *(see Dosage and Administration (2.9) and Adverse Reactions (6.1))*.

Patients should not have an active or suspected ocular or periocular infection or severe systemic infection at the time of any SUSVIMO implant or refill procedure. Appropriate intraoperative handling followed by secure closure of the conjunctiva and Tenon's capsule, and early detection and surgical repair of conjunctival erosions or retractions may reduce the risk of endophthalmitis *(see Warnings and Precautions (5.5))*.

5.2 Rhegmatogenous Retinal Detachment

Rhegmatogenous retinal detachments have occurred in clinical trials of SUSVIMO and may result in vision loss. Rhegmatogenous retinal detachments should be promptly treated with an intervention (e.g., pneumatic retinopexy, vitrectomy, or laser photocoagulation). SUSVIMO (ranibizumab injection) dose (refill-exchange) should be delayed in the presence of a retinal detachment or retinal break *(see Dosage and Administration (2.9)*.

Careful evaluation of the retinal periphery is recommended to be performed, and any suspected areas of abnormal vitreo-retinal adhesion or retinal breaks should be treated before inserting the implant in the eye.

5.3 Implant Dislocation

In clinical trials, the device has dislocated/subluxated into the vitreous cavity or has extended outside the vitreous cavity into or beyond the subconjunctival space. Device dislocation requires urgent surgical intervention. Strict adherence to the scleral incision length and appropriate targeting of the pars plana during laser ablation may reduce the risk of implant dislocation.

5.4 Septum Dislodgement

In clinical trials, a type of implant damage where the septum has dislodged into the implant body has been reported. Perform a dilated slit lamp exam and/or dilated indirect ophthalmoscopy to inspect the implant in the vitreous cavity through the pupil prior to and after the refill-exchange procedure to identify if septum dislodgement has occurred. Discontinue treatment with SUSVIMO (ranibizumab injection) following septum dislodgement and consider implant removal should the benefit of the removal procedure outweigh the risk *(see Dosage and Administration (2.8))*.

Appropriate handling and insertion of the refill needle into the septum (avoid twisting and/or rotation) is required to minimize the risk of septum dislodgement *(see Dosage and Administration (2.7))*.

5.5 Vitreous Hemorrhage

Vitreous hemorrhages may result in temporary vision loss. Vitrectomy may be needed in the case of a non-clearing vitreous hemorrhage *(see Dosage and Administration (2.9)*.

In clinical trials of SUSVIMO including extension phases, vitreous hemorrhages were reported in 5.2% (23/443) of patients receiving SUSVIMO. The majority of these hemorrhages occurred within the first post-operative month following surgical implantation and the majority of vitreous hemorrhages resolved spontaneously. Patients on antithrombotic medication (e.g., oral anticoagulants, aspirin, nonsteroidal anti-inflammatory drugs) may be at increased risk of vitreous hemorrhage. Antithrombotic medications are recommended to be temporarily interrupted prior to the implant insertion procedure. The SUSVIMO (ranibizumab injection) dose (refill-exchange) should be delayed in the event of sight-threatening vitreous hemorrhage. The use of pars plana laser ablation and scleral cauterization should be performed to reduce the risk of vitreous hemorrhage.

5.6 Conjunctival Erosion or Retraction

A conjunctival erosion is a full thickness degradation or breakdown of the conjunctiva in the area of the implant flange. A conjunctival retraction is a recession or opening of the limbal and/or radial peritomy. Conjunctival erosions or retractions have been associated with an increased risk of endophthalmitis, especially if the implant becomes exposed. Surgical intervention (e.g., conjunctival/Tenon's capsule repair) is recommended to be performed in case of conjunctival erosion or retraction with or without exposure of the implant flange.

In clinical trials of SUSVIMO including extension phases, 3.6% (16/443) of patients receiving SUSVIMO reported conjunctival erosion and 1.6% (7/443) of patients receiving SUSVIMO reported conjunctival retraction in the study eye.

Appropriate intraoperative handling of conjunctiva and Tenon's capsule to preserve tissue integrity and secure closure of peritomy while ensuring placement of sutures away from implant edge may reduce the risk of conjunctival erosion or retraction. The implant and the tissue overlying the implant flange should be monitored routinely following the implant insertion.

5.7 Conjunctival Bleb

A conjunctival bleb is an encapsulated elevation of the conjunctiva above the implant flange, which may be secondary to subconjunctival thickening or fluid. Conjunctival blebs may require surgical management to avoid further complications, especially if the implant septum is no longer identifiable due to the conjunctival bleb.

In clinical trials of SUSVIMO including extension phases, 5.9% (26/443) of patients receiving SUSVIMO reported conjunctival bleb/conjunctival filtering bleb leak in the study eye. Strict adherence to the scleral incision length, appropriate intraoperative handling of conjunctiva and Tenon's capsule to preserve tissue integrity and secure closure of peritomy, and proper seating of the refill needle during refill-exchange procedures may reduce the risk of conjunctival bleb.

5.8 Postoperative Decrease in Visual Acuity

Visual acuity was decreased by 4 letters on average in the first postoperative month and 2 letters on average in the second postoperative month following initial implantation of SUSVIMO *(see Clinical studies (14))*.

5.9 Air Bubbles Causing Improper Filling of the Implant

Minimize air bubbles within the implant reservoir as they may cause slower drug release. During the initial fill procedure, if an air bubble is present, it must be no larger than 1/3 of the widest diameter of the implant. If excess air is observed after initial fill, **do not** use the implant. During the refill-exchange procedure, if excess air is present in the syringe and needle **do not** use the syringe and needle. If excess air bubbles are observed after the refill-exchange procedure, consider repeating the refill-exchange procedure.

5.10 Deflection of the Implant

Use caution when performing ophthalmic procedures that may cause deflection of the implant and subsequent injury. For example, B-scan ophthalmic ultrasound, scleral depression, or gonioscopy.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the label:

- Endophthalmitis *(see Warnings and Precautions (5.1))*
- Rhegmatogenous Retinal Detachment *(see Warnings and Precautions (5.2))*
- Implant Dislocation *(see Warnings and Precautions (5.3))*
- Vitreous Hemorrhage *(see Warnings and Precautions (5.4))*
- Conjunctival Erosion or Retraction *(see Warnings and Precautions (5.5))*
- Conjunctival Bleb *(see Warnings and Precautions (5.6))*
- Postoperative Decrease in Visual Acuity *(see Warnings and Precautions (5.7))*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in one clinical trial of a drug cannot be directly compared with rates in the clinical trials of the same or another drug and may not reflect the rates observed in practice.

The data below (Table 2) reflect exposure of 248 patients with nAMD in the Archway study following the SUSVIMO initial fill and implant insertion, refill, and implant removal (if necessary) procedures up to Week 40. In this patient population the most common (≥ 10%) adverse reactions up to Week 40 were conjunctival hemorrhage (72%), conjunctival hyperemia (26%), iritis (23%), and eye pain (10%).

Table 2 Adverse Reactions in nAMD patients occurring in ≥ 4% of patients in the SUSVIMO arm

	Week 40	
Adverse Reactions	**SUSVIMO n = 248**	**Intravitreal ranibizumab n = 167**
Conjunctival hemorrhage	72%	6%
Conjunctival hyperemia	26%	2%
Iritis[1]	23%	0.6%
Eye pain	10%	5%
Vitreous floaters	9%	2%
Conjunctival bleb/ filtering bleb leak[2]	9%	0
Foreign body sensation in eyes	7%	1%
Headache[3]	7%	2%
Hypotony of eye	6%	0
Vitreous detachment	6%	5%
Vitreous hemorrhage	5%	2%
Conjunctival edema	5%	0
Corneal disorder	4%	0
Corneal abrasion[4]	4%	0.6%
Corneal edema	4%	0

[1]Iritis includes: iritis, anterior chamber flare, and anterior chamber cell

[2]Conjunctival bleb/filtering bleb leak includes: conjunctival bleb, conjunctival filtering bleb leak, conjunctival cyst, subconjunctival cyst, and implant site cyst

[3]Headache includes: headache and procedural headache

[4]Corneal abrasion includes: corneal abrasion and vital dye staining cornea present.

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immune response in patients treated with ranibizumab including SUSVIMO. The detection of an immune response is highly dependent on the sensitivity, specificity, and drug tolerance level of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the study described below with the incidence of antibodies in other studies or to other products may be misleading.

In previously treated nAMD patients, anti-ranibizumab antibodies were detected in 2.1% (5 of 243) of patients prior to insertion of the SUSVIMO implant. After the SUSVIMO implant insertion and treatment, anti-ranibizumab antibodies developed in 12% (29 of 247) patients. No clinically meaningful differences in the pharmacokinetics, efficacy, or safety in patients with treatment-emergent anti-ranibizumab antibodies were observed.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate and well-controlled studies of SUSVIMO (ranibizumab injection) administration in pregnant women. Administration of ranibizumab to pregnant monkeys throughout the period of organogenesis resulted in a low incidence of skeletal abnormalities at intravitreal doses up to 41 times the human exposure (based on serum levels following the recommended clinical dose). No skeletal abnormalities were observed at serum trough levels similar to the human exposure after a single eye treatment at the recommended clinical dose *(see Animal Data)*.

Animal reproduction studies are not always predictive of human response, and it is not known whether ranibizumab can cause fetal harm when administered to a pregnant woman. Based on the anti-VEGF mechanism of action for ranibizumab *(see Clinical Pharmacology (12.1))*, treatment with SUSVIMO (ranibizumab injection) may pose a risk to human embryofetal development.

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

Data

Animal Data

An embryo-fetal developmental toxicity study was performed on pregnant cynomolgus monkeys. Pregnant animals received intravitreal injections of ranibizumab every 14 days starting on Day 20 of gestation, until Day 62 at doses of 0, 0.125, and 1 mg/eye. Skeletal abnormalities including incomplete and/or irregular ossification of bones in the skull, vertebral column, and hindlimbs and shortened supernumerary ribs were seen at a low incidence in fetuses from animals treated with 1 mg/eye of ranibizumab. The 1 mg/eye dose resulted in trough serum ranibizumab levels up to 41 times higher than observed human C_{max} levels of SUSVIMO (ranibizumab injection) after treatment of a single eye.

No skeletal abnormalities were seen at the lower dose of 0.125 mg/eye, a dose which resulted in trough exposures similar to single eye treatment with SUSVIMO (ranibizumab injection) in humans. No effect on the weight or structure of the placenta, maternal toxicity, or embryotoxicity was observed.

8.2 Lactation

Risk Summary

There are no data available on the presence of ranibizumab in human milk, the effects of ranibizumab on the breastfed infant or the effects of ranibizumab on milk production/excretion. 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 SUSVIMO is administered to a nursing woman.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for SUSVIMO (ranibizumab injection) and any potential adverse effects on the breastfed child from ranibizumab.

8.3 Females and Males of Reproductive Potential

Contraception

Females of reproductive potential should use effective contraception during treatment with SUSVIMO (ranibizumab injection) and for at least 12 months after the last dose of SUSVIMO (ranibizumab injection).

Infertility

No studies on the effects of ranibizumab on fertility have been conducted and it is not known whether ranibizumab can affect reproduction capacity. Based on the anti-VEGF mechanism of action for ranibizumab, treatment with SUSVIMO (ranibizumab injection) may pose a risk to reproductive capacity.

8.4 Pediatric Use

The safety and efficacy of SUSVIMO (ranibizumab injection) in pediatric patients have not been established.

8.5 Geriatric Use

In the Archway study, 90% (222 of 248) of the patients randomized to treatment with SUSVIMO were ≥ 65 years old and approximately 57% (141 of 248) were ≥ 75 years old. No notable difference in treatment effect or safety was seen with increasing age.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Advise patients on the following after the implant insertion procedure:

Positioning:

- Keep head above shoulder level for the rest of the day.
- Sleep with head on 3 or more pillows during the day and the night after surgery.

How to care for the treated eye after the procedure:

- Do not remove the eye shield until they are instructed to do so by their healthcare provider. At bedtime, continue to wear the eye shield for at least 7 nights following the implant surgery.
- Administer all post-operative eye medications as directed by their healthcare provider.
- Do not push on the eye, rub the eye, or touch the area of the eye where the implant is located (underneath the eyelid in the upper and outer part of the eye) for 30 days following the implant insertion.
- Do not participate in strenuous activities until 1-month after the implant insertion or after discussion with their healthcare provider.

Magnetic Resonance (MR) Conditional information:

- The SUSVIMO implant is MR conditional. Inform their healthcare provider that they have SUSVIMO implanted in their eye and show their healthcare provider the SUSVIMO implant card should they require Magnetic resonance imaging (MRI).

Advise patients on the following after the Refill-Exchange procedure:

- Refrain from pushing on the treated eye, rubbing the eye, or touching the eye in the area of the implant (located underneath the eyelid in the upper and outer part of your eye) for 7 days following the refill-exchange procedure.
- Administer eye drops as directed by their healthcare provider.

Advise patients on the following after the implant removal procedure (if it is deemed medically necessary):

- Keep your head above shoulder level for the rest of the day.
- Sleep with your head on 3 or more pillows if lying down during the day and the night after implant removal.
- Wear an eye shield for at least 7 nights following the implant removal.
- Do not participate in strenuous activities until 14 days following the implant removal.
- Administer all post-operative anti-inflammatory and antimicrobial drops, as directed by your healthcare provider.

Advise patients on the following throughout SUSVIMO treatment:

- Do not drive or use machinery until the eye shield can be removed and visual function has recovered sufficiently *(see Adverse Reactions (6.1))*.
- The SUSVIMO implant and/or implant related procedures have been associated with conjunctival reactions (bleb, erosion, retraction), vitreous hemorrhage, endophthalmitis, rhegmatogenous retinal detachment, the dislocation of the implant, septum dislodgement, and a temporary decrease in vision.
- While the implant is in the eye, avoid rubbing the eye or touching the area as much as possible. However, if necessary to do so, make sure hands are cleaned prior to touching the eye.
- Seek immediate care from an ophthalmologist if there are sudden changes in their vision (an increase in moving spots, the appearance of "spider webs", flashing lights, or a loss in vision), increasing eye pain, progressive vision loss, sensitivity to light, redness in the white of the eye, a sudden sensation that something is in their eye, or eye discharge or watering *(see Warnings and Precautions (5))*.

SUSVIMO™ [ranibizumab injection]
Manufactured by:
Genentech, Inc. A Member of the Roche Group
1 DNA Way, South San Francisco, CA 94080-4990
U.S. License No.: 1048

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SUSVIMO

The first and only continuous delivery treatment for nAMD[1]

Not to scale.

For more information, visit **SUSVIMO-HCP.com**

nAMD=neovascular (wet) age-related macular degeneration.

INDICATION

SUSVIMO (ranibizumab injection) is indicated for the treatment of patients with neovascular (wet) age-related macular degeneration (AMD) who have previously responded to at least 2 intravitreal injections of a vascular endothelial growth factor (VEGF) inhibitor medication.

IMPORTANT SAFETY INFORMATION

WARNING: ENDOPHTHALMITIS

The SUSVIMO implant has been associated with a 3-fold higher rate of endophthalmitis than monthly intravitreal injections of ranibizumab. In clinical trials, 2.0% of patients receiving an implant experienced at least 1 episode of endophthalmitis.

CONTRAINDICATIONS

- Ocular or periocular infections
- Active intraocular inflammation
- Hypersensitivity

WARNINGS AND PRECAUTIONS

- The SUSVIMO implant and/or implant-related procedures have been associated with endophthalmitis, rhegmatogenous retinal detachment, implant dislocation, septum dislodgement, vitreous hemorrhage, conjunctival retraction, conjunctival erosion, and conjunctival bleb. Patients should be instructed to report signs or symptoms that could be associated with these events without delay. Additional surgical and/or medical management may be required
- Vitreous hemorrhage: Temporarily discontinue antithrombotic medication prior to the implant insertion procedure to reduce the risk of vitreous hemorrhage. Vitrectomy may be needed
- Postoperative decrease in visual acuity: A decrease in visual acuity usually occurs over the first 2 postoperative months

ADVERSE REACTIONS

The most common adverse reactions were conjunctival hemorrhage (72%), conjunctival hyperemia (26%), iritis (23%), and eye pain (10%).

You may report side effects to the FDA at (800) FDA-1088 or www.fda.gov/medwatch. You may also report side effects to Genentech at (888) 835-2555.

Please see Brief Summary of full SUSVIMO Prescribing Information on adjacent page for additional Important Safety Information, including **BOXED WARNING**.

REFERENCE

1. SUSVIMO [package insert]. South San Francisco, CA: Genentech, Inc; 2022.

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