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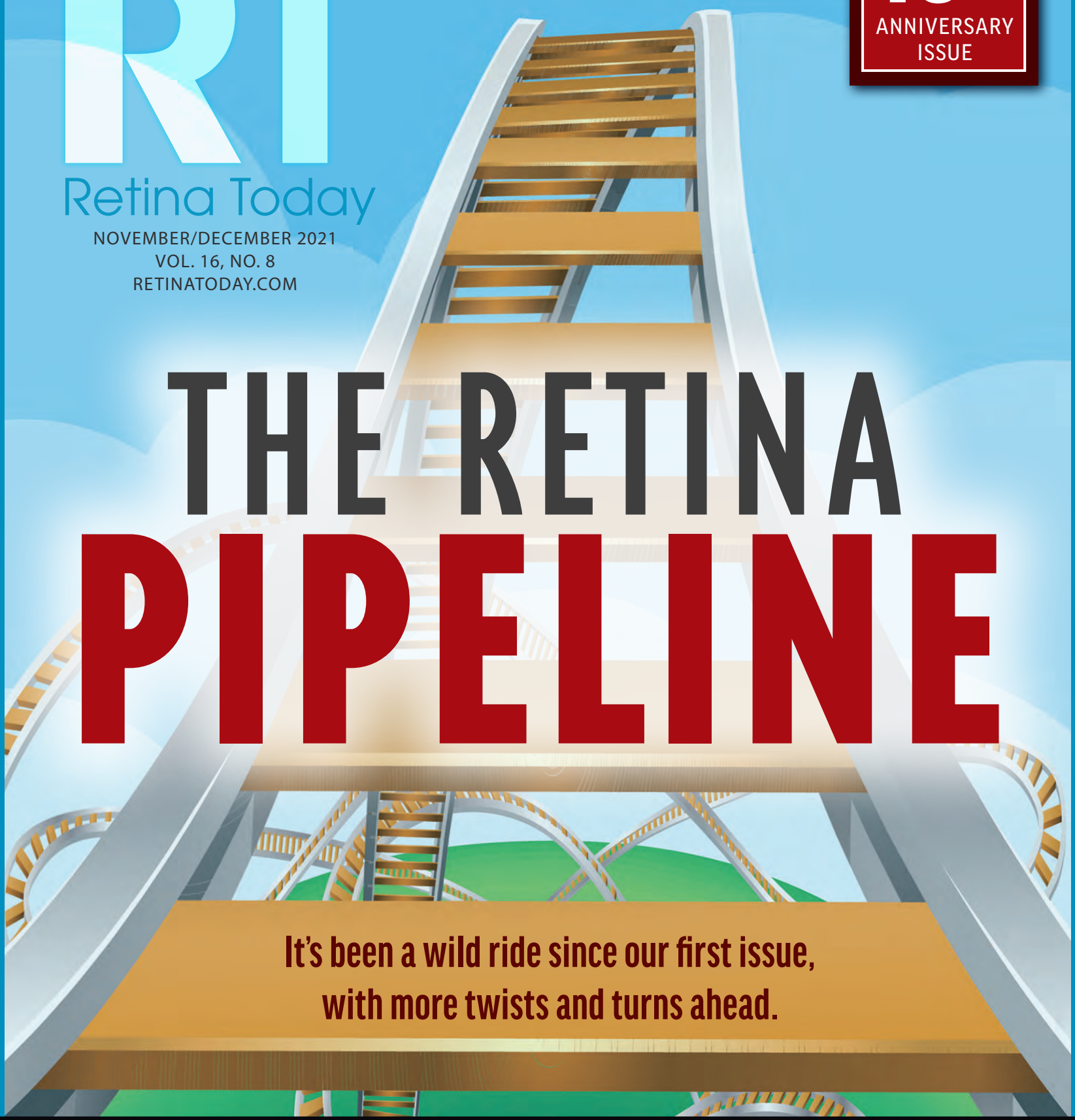
15TH ANNIVERSARY ISSUE



THE RETINA PIPELINE

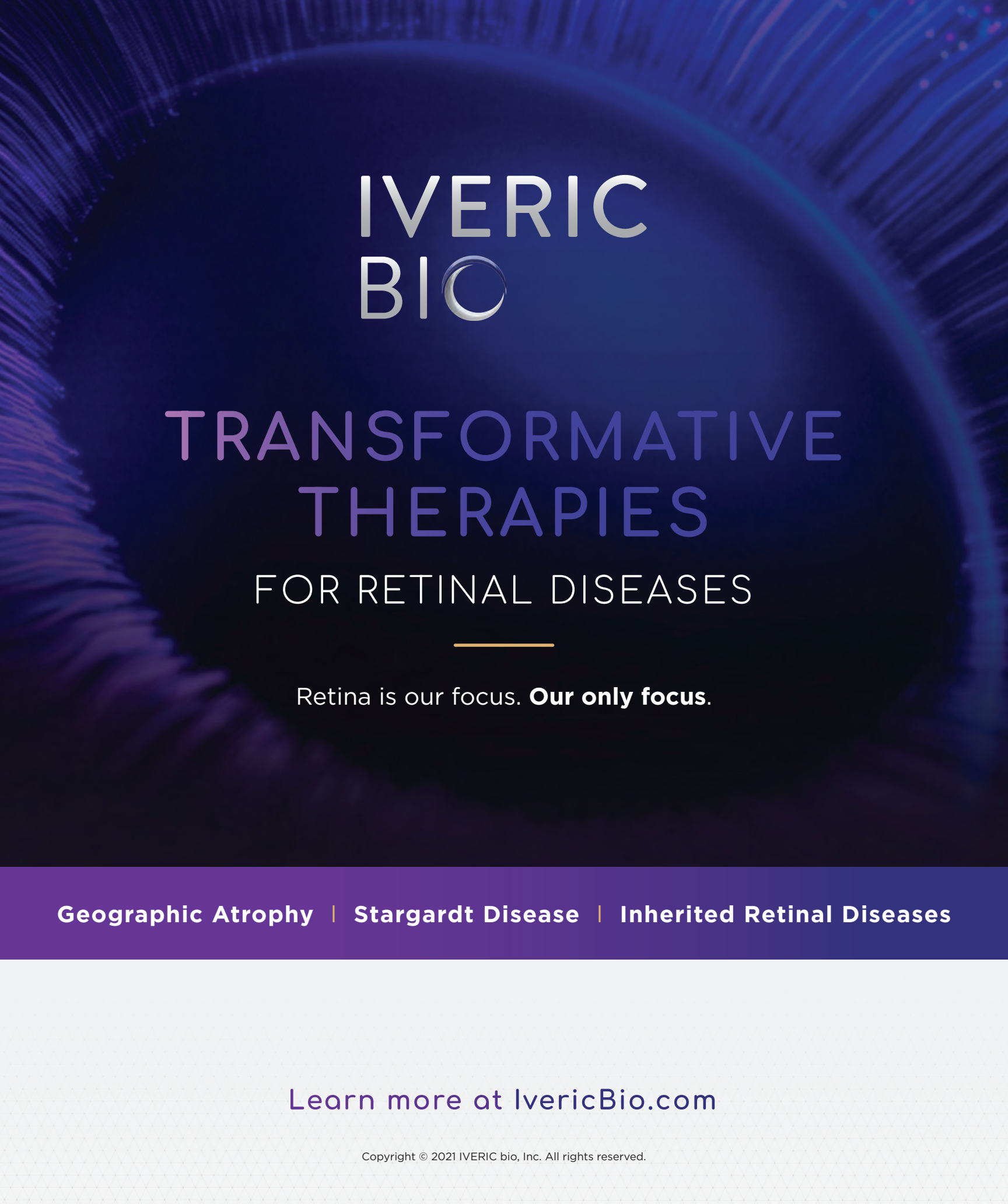
It's been a wild ride since our first issue, with more twists and turns ahead.

GA: TARGETING THE COMPLEMENT PATHWAY

EXPANDING YOUR TOOLBOX WITH BIOSIMILARS

SURGICAL INNOVATIONS TO TREAT MEDICAL DISEASES

eyetube



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DÉJÀ VU


When *Retina Today* launched 15 years ago, the anti-VEGF era was in its infancy, with the first intraocular agent, pegaptanib (Macugen, Bausch+Lomb), gaining approval just 2 years prior. In fact, we were reporting on the 2-year safety data for pegaptanib in our very first issue in March 2006, published mere months before ranibizumab (Lucentis, Genentech) was approved.[1] Everyone who was practicing at the time will never forget the excitement—and relief—we felt to finally have access to approved therapies that made a real difference for our patients with macular degeneration. Today, intravitreal injection of anti-VEGF agents encompasses a vast majority of our clinic hours, and this issue even includes a discussion of long-term outcomes in 130,247 eyes as far out as 5 years.

That first whirlwind of anti-VEGF approvals changed the face of retina care forever. Check out the infographic on page 28 to see what we mean. And now, it seems oddly fortuitous to be celebrating *Retina Today*'s 15th anniversary the same year the first extended-duration anti-VEGF option is approved. In our first year of publication, we rejoiced finding a treatment option that works; 15 years later, we are eager to welcome an approach that extends that efficacy up to 6 months. It's no wonder that the approval of the port delivery system (PDS) with ranibizumab (Susvimo, Genentech/Roche) gave us a little déjà vu. It's hopefully the first of many products that may help to reduce the treatment burden for our wet AMD patients.

But the PDS approval isn't the only event making us feel a little nostalgic. We are seeing promising phase 3 data for therapeutics to treat patients with geographic atrophy (GA) who currently have no treatment options. GA has remained an unmet need for so long, and the hope for an approved therapeutic to slow GA progression is tantalizing. Still, we have seen large prospective phase 3 studies that didn't meet their primary endpoints (think lampalizumab), reminding us to be cautious in our optimism.

Other therapies have made advances in drug delivery as well. In our first issue, we published an article detailing the pros and cons of off-label intravitreal triamcinolone use, in which Nancy M. Holekamp, MD, said she uses triamcinolone as a "salvage therapy when patients fail standard of care or if no standard of care is approved." Today, that treatment is FDA approved and uses a novel suprachoroidal delivery.[2]

This month's pipeline issue is the perfect space in which to explore the latest clinical trials—successful or otherwise—as well as celebrate the last 15 years that got us here. The plethora of trial data presented at The Retina Society, ASRS, and AAO is a testament to the drive that researchers, clinicians, and industry have to bring therapies to the patients who need them the most.

With so many groundbreaking developments rolling out and much more to come, we are more excited than ever to marry the old with the cutting-edge in this dual focus anniversary/pipeline issue. Within each of the featured pipeline articles, we added fun snippets of information from our first few issues to highlight just how far we have come regarding treatments for wet AMD, GA, biosimilars, diabetic eye disease, and surgical innovation.

When we look back fondly on where we started, we are astounded to see just how much has changed, for the better, in what feels like a very short amount of time. ■


ALLEN C. HO, MD
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ASSOCIATE MEDICAL EDITOR

1. Koury CB. Pegaptanib safety profile maintained through 2 years. *Retina Today*. 2006;1(1).
2. Suarez L. Considerations for intravitreal triamcinolone use. *Retina Today*. 2006;1(1).

***Retina Today*'s inaugural issue focused on macular diseases and treatments; because most of the latter were still under investigation, it felt much like a pipeline issue. Scan the QR code to check it out.**

0.18 mg
YUTIQ®
(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

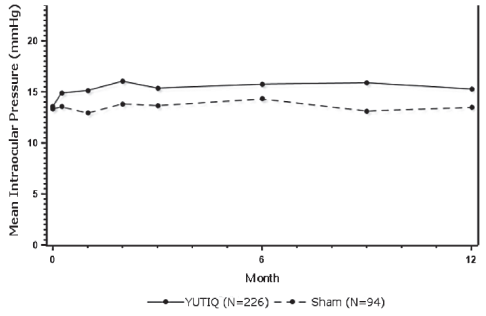
Ocular		
ADVERSE REACTIONS	**YUTIQ (N=226 Eyes) n (%)**	**Sham Injection (N=94 Eyes) n (%)**
Vitreous Hemorrhage	4 (2%)	0
Iridocyclitis	3 (1%)	7 (7%)
Eye Inflammation	3 (1%)	2 (2%)
Choroiditis	3 (1%)	1 (1%)
Eye Irritation	3 (1%)	1 (1%)
Visual Field Defect	3 (1%)	0
Lacrimation Increased	3 (1%)	0
Non-ocular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

Manufactured by:
EyePoint Pharmaceuticals US, Inc., 480 Pleasant Street, Watertown, MA 02472 USA
Patented.

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DRY AMD THERAPIES SHOW PROMISE IN PHASE 1/2A TRIALS

Two cell therapies for dry AMD, both of which are designed to replace damaged retinal pigment epithelium (RPE) cells, recently reported positive results from phase 1/2a clinical trials.

Regenerative Patch Technologies released 1-year follow-up data from its phase 1/2a trial of a novel subretinal implant consisting of polarized human embryonic stem cell-derived RPE cells on an ultrathin parylene substrate.[1] In the study, 16 patients received the investigational implant, and inclusion criteria included eyes with vision worse than or equal to 20/200 (cohort 1) and 20/80 to 20/400 (cohort 2). Safety was assessed at 1 year, and, overall, the implant was well tolerated with no new or unexpected adverse events; four participants experienced serious ocular adverse events, many of which may be minimized in future trials by taking steps to prevent leakage from the retinotomy site.[1]

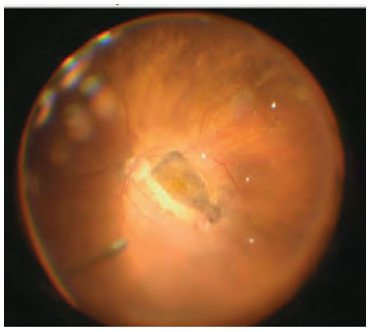

Figure. During AAO 2021, Dr. Humayun showed RPE cells on an ultrathin substrate surgically implanted over the area of geographic atrophy.

The results demonstrated preliminary improvements in visual acuity in patients treated with the RPE cell implant. During AAO 2021, Mark S. Humayun, MD, PhD, presented on the findings, noting that 27% of study patients experienced visual improvement of 7 to 15 letters, while 80% of the untreated eyes lost 8 to 21 letters (Figure).[2] "We have a technology, very early stage, that we think could help to improve visual acuity in geographic atrophy, but we have to wait and see if that plays out in subsequent studies," he concluded in his lecture.[2]

A second treatment in development is OpRegen (Lineage Cell Therapeutics), which consists of human embryonic stem-cell derived RPE cells transplanted subretinally in patients with geographic atrophy. Interim results of the phase 1/2a trial demonstrated a promising safety profile as well as preliminary improvements in visual acuity and structural restoration of the retina, according to an AAO 2021 presentation by Michael S. Ip, MD.[3]

The study included 24 patients with bilateral, advanced, dry AMD who were divided into four cohorts; three cohorts enrolled only patients with BVCA worse than 20/200 and the fourth enrolled patients with BCVA between 20/65 and 20/250 and small mean areas of geographic atrophy. The transplant therapy was well tolerated, with no new or unexpected ocular or systemic adverse events. No serious adverse events were observed.[3]

Analyses of OCT and other imaging results suggest structural benefit, with certain areas thought to be atrophic showing evidence of retinal restoration. Patients also tended to experience improvement in visual acuity in the treated eye compared with the fellow eye; in cohort 4, these improvements were statistically significant at months 9 (P = .0280), 12 (P = .0709), and 15 (P = .0273). "Earlier intervention and perhaps a more central placement of these transplanted RPE cells may be beneficial, and we plan to evaluate that in a clinical trial in the future," Dr. Ip concluded in his presentation.

1. Kashani AH, Lebkowski JS, Rahhal FM, et al. One-year follow-up in a phase 1/2a clinical trial of an allogeneic RPE cell bioengineered implant for advanced dry age-related macular degeneration. *Transl Vis Sci Technol.* 2021;10(10):13.
2. Humayun MS. The Charles L Schepens MD Lecture: advanced retinal implants. Presented at AAO 2021; November 12, 2021; New Orleans, LA.
3. Ip MS. OpRegen trial: phase I/IIa dose escalation study of human embryonic stem cell–derived retinal pigment epithelium cells transplanted subretinally in patients with advanced AMD. Presented a: AAO 2021; November 12, 2021; New Orleans, LA.

WATCH IT NOW

Promising Findings with Transplanted RPE Cells for Patients with GA

FIRST WIRELESS VISUAL PROSTHETIC BRAIN IMPLANT RECEIVES TRIAL FUNDING

The Intracortical Visual Prosthesis (ICVP) is an implant system that connects directly to the brain's visual cortex, bypassing the retina and optic nerve. The project recently received $2.5 million in funding from the National Institutes of Health. The funds were awarded to researchers at the Illinois Institute of Technology to complete the first year of a 3-year clinical trial to test whether individuals who receive the implant system experience any visual improvements.[1]

The ICVP is composed of a group of miniature wireless microelectrode arrays (Figure). It is designed for patients who lack an intact retina or optic nerve but possess a healthy visual cortex.

Researchers from eight institutions have spent 20 years developing the ICVP in collaboration with surgeons who have helped them refine the surgical technique to implant the device. The prosthesis can be implanted for an extended period, potentially a lifetime, which could allow researchers to evaluate whether individuals with the implant can, over time, visualize images in real-time through visual perception.[1]

The ICVP clinical trial is an FDA-approved, first-in-human study enrolled with five volunteers. The study team includes researchers from Illinois Institute of Technology, Rush University Medical Center, the Chicago Lighthouse, Johns Hopkins University, University of Texas (Dallas), Microprobes for Life Science, Sigenics, and University of Chicago.

The ICVP, which can contain up to 640 electrodes, will be implanted in the occipital lobe of one side of the patient's brain. The extracorporeal transmitter can communicate with any one of the electrodes to tell it how to send electrical signals to the brain. Using images, captured with a glasses-mounted camera, that are translated into stimulation commands, the ICVP system will communicate image information directly to the brain.

"While this is not a restoration of biological vision, and at this point in the clinical trial, specific benefits of the system remain unknown, the electrical stimulation will produce visual percepts that will be used as the building blocks of artificial vision," said Philip R. Troyk, PhD, the study's lead researcher and the executive director of the Pritzker Institute of Biomedical Science and Engineering at the Illinois Institute of Technology, in an email to *Retina Today*. "Earlier studies have shown that even a low level of artificial vision can

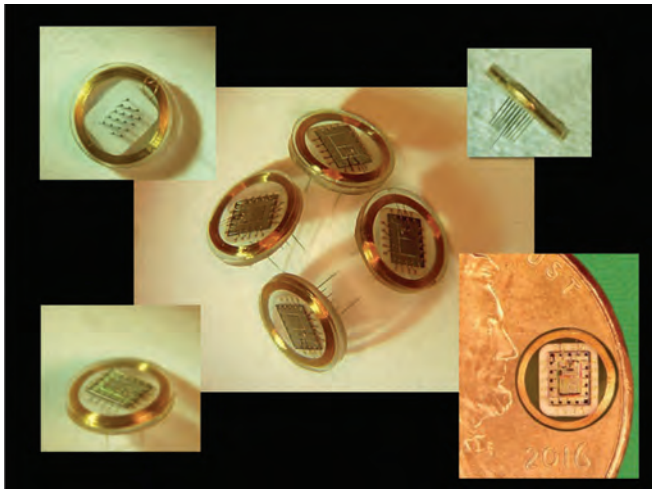

Image courtesy of Illinois Institute of Technology.

Figure. Miniature electical stimulation modules that include up to 640 electrodes comprise the ICVP implant system.

OTHER VISUAL IMPLANTS TO WATCH

Results from a 6-month study detail the experience of one patient who received a brain implant that connects directly to the visual cortex.[1] The intracortical microelectrode array consists of 96 electrodes, about 4 mm by 4 mm in size, and was placed in the brain of a 57-year-old woman with total blindness due to toxic optic neuropathy.

Researchers found that visually deprived neurons were responsive to stimuli, and they were able to obtain high-quality recordings. The patient was able to discern some letters and object boundaries, and simultaneous stimulation via multiple electrodes were associated with a significant reduction in thresholds ($P < .001$). Although the device will need to be tested in more patients and for longer periods of time, the study results suggest preliminary safety and efficacy, the authors concluded in their paper.[2]

The Implantable Miniature Telescope (IMT; Samsara Vision), an FDA-approved monocular implant that works to restore central vision, is indicated for implantation in the eyes of patients 65 years and older with scarring associated with late-stage AMD. The device is now on its second generation with the first patients in Europe successfully implanted with the smaller-incision new-generation IMT. The 3.6 mm telescope device is surgically placed in the capsular bag following removal of the eye's natural lens. The device uses novel biconvex and biconcave convergent and divergent microlenses coupled with air lenses to magnify images onto the healthy retina surrounding the degenerated macula up to 2.2 or 2.7 times their normal size, depending on the model. The new design includes foldable haptic loops that allow the surgeon to use a smaller incision, leading to faster recovery times, according to a company press release.[3]

After the outpatient surgery, patients attend occupational therapy sessions to practice performing tasks with their improved vision. Following these successful cases, the company is planning a worldwide launch of the product.[3]

1. Intracortical visual prosthesis project (ICVP). The Chicago Lighthouse. Accessed November 18, 2021. chicagolighthouse.org/icvp
2. Fernández E, Alfaro A, Soto-Sánchez C, et al. Visual percepts evoked with an intracortical 96-channel microelectrode array inserted in human occipital cortex. Preprint. Published online October 19, 2021. *J Clin Invest*.
3. Samsara Vision reports that patients blinded by macular degeneration benefit from milestone in implant technology [press release]. May 25, 2021. Accessed November 18, 2021. www.samsaravision.com/press-releases/detail/61/samsara-vision-reports-that-patients-blinded-by-macular

provide useful visual perception and can be an improvement to quality of life."

The language of the brain is still unknown, particularly for artificial vision. "The brain is a powerful image processor, and learning how to effectively communicate through the ICVP technological interface will be an important outcome of the study," stated Dr. Troyk.

The ICVP study is actively recruiting participants. For more information about the study, please contact the researchers at ICVP@iit.edu.

GENE THERAPY FOR WET AMD SHOWS LONG-TERM SAFETY AND EFFICACY

Data from the phase 1 OPTIC trial to evaluate a single intravitreal injection of ADVM-022 (Adverum Biotechnologies) gene therapy demonstrate a promising safety and efficacy profile, according to a press release from the company. The novel gene therapy has the potential to reduce treatment burden for wet AMD patients who currently require frequent anti-VEGF injections.

OPTIC is a multicenter, open-label, dose-ranging clinical trial to assess safety and tolerability of a single injection of ADVM-022. The 30 participants were divided into four cohorts; cohorts 1 and 4 received the $6x10^{11}$ vg/eye dose of ADVM-022, while cohorts 2 and 3 received the $2x10^{11}$ vg/eye dose.

Data revealed that all ocular adverse events related to ADVM-022 were mild (81%) to moderate (19%) across the four cohorts, according to the press release. Treatment with the low dose resulted in > 80% reduction in anti-VEGF injection frequency annually, and 50% of participants required no supplemental anti-VEGF injections at 1.7 years median follow-up. Aflibercept levels remained robust after 2 years, and visual acuity improvements were durable.

"We are excited to see that ADVM-022 has the potential to extend the treatment benefit from weeks to years," Adverum President and CEO Laurent Fischer, MD, stated in the press release. Plans for a phase 2 trial of the lower dose of ADVM-022 are currently underway.

CURACLE AND THÉA ENTER AGREEMENT FOR ORALLY ADMINISTERED TREATMENT FOR DME AND WET AMD

Korean biopharmaceutical company Curacle has entered into an exclusive license and collaboration agreement with Théa Open Innovation, the sister company of Théa, for the development and commercialization of Curacle's CU06-RE, which could become the first orally administered treatment for diabetic macular edema and wet AMD. CU06-RE is a small molecule VEGF blocker developed with Curacle's Solvadys platform technology and can be applied to patients whose symptoms have worsened due to resistance to anti-VEGF injections.

Under the terms of the agreement, Curacle will receive an up-front payment of $6 million and will be responsible for the phase 1 and 2 clinical studies with Théa Open Innovation providing both financial and infrastructure support. Curacle will also retain the marketing rights in all Asian countries under the agreement, while Théa will have the marketing rights in all other countries.

RECENT FDA APPROVALS EXPAND TREATMENT OPTIONS FOR WET AMD AND MACULAR EDEMA

October saw the FDA approval of two new products, the anticipated port delivery system (PDS) with ranibizumab for patients with wet AMD and an injectable steroid to treat macular edema associated with uveitis.

RANIBIZUMAB IMPLANT

Fifteen years after the initial approval of ranibizumab (Lucentis, Genentech), the FDA has approved the PDS (Susvimo, Genentech) for patients with wet AMD who have previously responded to at least two anti-VEGF injections.

The implant is surgically implanted into the eye and continuously delivers a concentrated form of ranibizumab, requiring a refill every 6 months. Approval is based on results from the phase 3 Archway trial that showed that patients who received the implant experienced and maintained visual acuity gains equivalent to monthly ranibizumab injections.

The PDS will be available in the coming months in the United States. "Susvimo represents a major advancement in the treatment of retinal disease and is an important new option for patients with wet AMD," said Carl Regillo, MD, Chief of Retina Service at Wills Eye Hospital in Philadelphia and an Archway study investigator, in a company press release.

INJECTABLE STEROID

The triamcinolone acetonide injectable suspension (Xipere, Bausch + Lomb/Clearside Biomedical) gained FDA approval for the treatment of macular edema associated with uveitis. This injectable suspension is the first approved therapy to deliver the drug into the suprachoroidal space.

The therapy uses the proprietary SCS Microinjector (Clearside Biomedical) to access the back of the eye to provide targeted drug delivery, leading to higher rates of absorption than typical intravitreal injection, according to a company press release. Approval was based on phase 3 data from the PEACHTREE trial demonstrating safety and efficacy, with statistically significant improvement in BVCA ($P < .01$) compared with a control arm. ■

THE RETINA PIPELINE

Cover image credit: ©iStockphoto.com

DEPARTMENTS

THE PRE-LESION–WHERE COMPLEMENT OVERACTIVATION IS CAUSING THE NEXT WAVE OF DESTRUCTION IN GEOGRAPHIC ATROPHY[1,2]

This is where you'll find C3, the linchpin of complement overactivation in the growth of GA lesions

C3 is where all three complement pathways converge, driving multiple damaging downstream effects—inflammation, opsonization, and formation of the membrane attack complex. All of this can lead to permanent retinal cell death in the pre-lesion, which is where your patients have the most to save.[2-9]

Scan the code to explore pre-lesion.com

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Apellis

WATCH FOR RETINAL FINDINGS WITH SYSTEMIC PAZOPANIB

Delayed wound healing after retinal surgery may be a side effect associated with this chemotherapy.

BY RITA VIEIRA, MD; JOÃO COELHO, MD; AND JOÃO NUNO MELO BEIRÃO, MD, PHD

We report the case of a patient receiving pazopanib for metastatic renal cell carcinoma (RCC) who experienced rhegmatogenous retinal detachment (RRD) and retinal tears. The main purpose of this report is to provide an example of the possible association between treatment with pazopanib (Votrient, Novartis) and retinal findings, which in this case may be associated with delayed healing after retinal laser retinopexy.

THE CASE

A 69-year-old man with a history of hypertension and metastatic RCC presented with myodesopsias and decreased best-corrected distance visual acuity (CDVA; 20/63) in the left eye 4 months after starting treatment with pazopanib. He had been diagnosed with RCC stage T3aN0M0 in 2015 and underwent radical right nephrectomy of his right kidney. One year later, a routine CT scan revealed liver and bilateral lung metastasis, and 50 mg sunitinib (Sutent, Pfizer) daily was initiated. Early hematological toxicity (mild leukopenia and thrombocytopenia) forced a brief suspension of sunitinib, which was reintroduced after normalization.

The patient was in remission for 30 months while receiving sunitinib, but recurrent perianal mucositis motivated the switch to nivolumab (Opdivo, Bristol-Myers Squibb). In June 2020, the patient went to the hospital with an iatrogenic pneumonitis related to nivolumab, successfully treated with high doses of steroids. A daily dose of 600 mg pazopanib was then initiated in August 2020, which was increased to 800 mg daily 2 months later.

Upon presentation to our clinic 2 months after initiating the increased dosage, a superior macula-sparing RRD with a retinal tear at the 1:00 clock position in the left eye was evidenced on fundoscopy. The patient underwent uncomplicated pars plana vitrectomy (PPV) with retinal tear cryoablation and 0.8 mL SF_6 gas. Two weeks after surgery, the retina was flat with a vestigial gas bubble and a pale white cryotherapy scar in the superior temporal quadrant.

The day after the 2-week follow-up, the patient went to the hospital with complaints of decreased visual acuity in the right eye, bilateral photopsia, and myodesopsias. A broad peripheric macula-sparing RRD—from the 6:00 to 10:00 clock position and from the 2:00 to 5:00 clock position—with mild hemovitreous and multiple small peripheric breaks was observed in the right eye; the left eye presented with a macula-sparing retinal redetachment in the inferior and temporal sectors. Laser retinopexy was performed on the temporal quadrant in each eye to stop the progression and avoid macular involvement.

The patient consulted with an oncology specialist, who recommended suspending pazopanib. The patient underwent bilateral PPV 5 days after the emergency retinopexy, at which time the right eye detachment had progressed from the laser barricade temporally to involve the macula. A 360° cryoablation and endolaser retinopexy in the inferior and temporal sectors were performed in the right and left eye, respectively, followed by air-fluid exchange and injection of 0.8 mL SF_6 gas in each eye.

The day after this procedure, the patient's retinas were flat, with cryoablation scars in the periphery of the right eye and inferior laser scars in the left eye with a pale white appearance. Intraocular gas fill was approximately 80% in each eye, and the patient was instructed to adhere strictly to the positioning care.

One week later, both retinas remained flat, with a gas fill of 30% to 40%. Five weeks after bilateral PPV, the patient was recovering visual acuity and the retinas remained flat without vestigial gas (Figure). In the left eye, the inferior laser scars started to show dark pigmentation inferiorly but

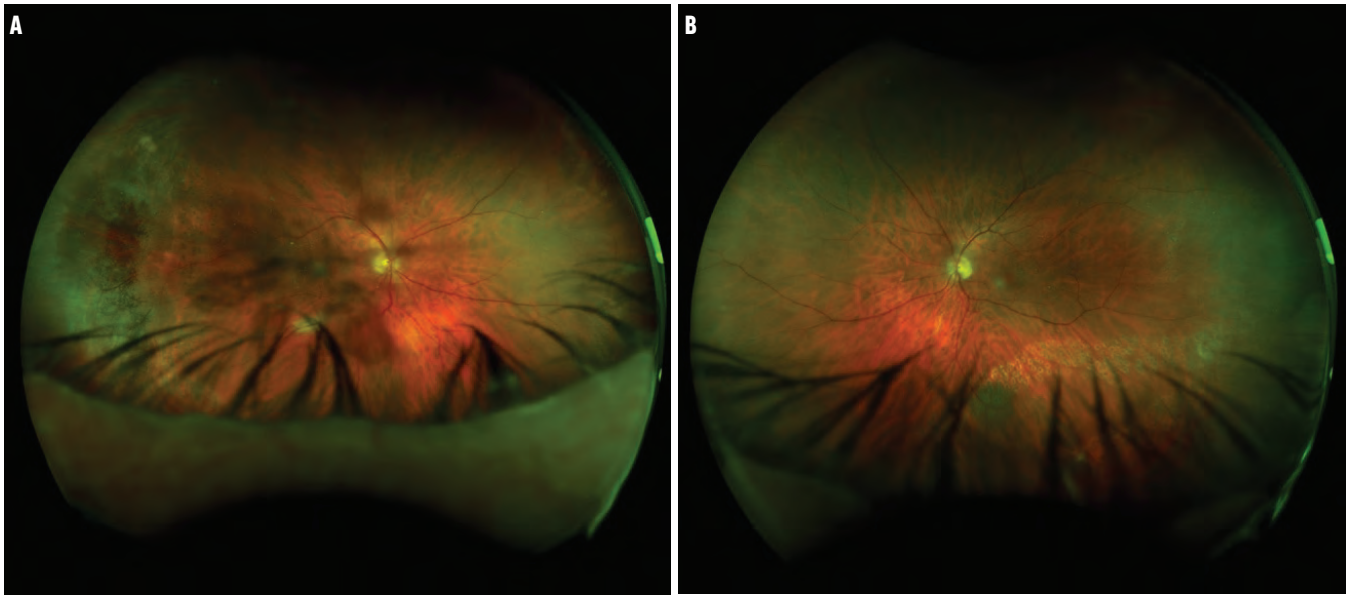

Figure. Six weeks after bilateral PPV of the right (A) and left (B) eyes, the left eye shows pale white laser scars temporally.

maintained a pale white color in the temporal sector. In the right eye, the cryoablation scars remained pale white.

Pazopanib was reintroduced 6 weeks after the second surgery, without any known complication. The final CDVA was 20/100 OD and 20/50 OS. A bilateral nuclear sclerosis was exacerbated after surgery.

PAZOPANIB AND RRD

Pazopanib, an anti-VEFG drug that consists of an oral multitargeted tyrosine kinase inhibitor, is primarily used to treat advanced cancers. It also inhibits the platelet derived growth factor receptor, stem cell factor receptor, and fibroblast growth factor receptor. Inhibition of these pathways may interrupt angiogenesis, cell proliferation, cell migration, and vascular permeability, all of which slows tumor growth. Pazopanib has been shown to be effective for the treatment of advanced or metastatic RCC and is associated with fewer systemic side effects than other anti-VEGF drugs.[1]

Fraunfelder et al reported a possible link between pazopanib and retinal detachments and tears.[2] Impaired wound healing has also been postulated as a side effect, and a previous report hypothesized that pazopanib therapy may delay retinal scar formation after retinopexy.[3] It is generally recommended that treatment with pazopanib be interrupted at least 1 week before any scheduled major surgery.[4]

Lifton et al also reported a possible effect of pazopanib on retarding the retinal scarring process after laser photocoagulation.[3] Similar to our case, the patient presented with a retinal detachment, and laser scars remained white 2 months after the first intervention, which may indicate abnormal retinal healing. Nonetheless, the authors admit that the pigmentary changes in the retina after photocoagulation may be impaired in patients receiving pazopanib, since the drug appears to affect melanin production.

CONCLUSION

Although this report does not prove a direct link between pazopanib and retinal detachment, it does support the hypothesis that pazopanib may slow wound healing, particularly in the eye, and contribute to various retinal complications after ocular surgery. ■

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ANTERIOR SIGNS OF A POSTERIOR PROBLEM

Nevus of Ota, which affects the ophthalmic and maxillary trigeminal nerve, causes hyperpigmentation of the eye.

BY KEATON TABER, BS; MICHAEL WEAVER, DO; CHRIS JACQUINOT, OD; AND HEERAL R. SHAH, MD

THE CASE

A 64-year-old female was referred to our clinic by her optometrist for a choroidal nevus of the right eye. She complained of blurred vision in each eye for several years but had no history of retinal pathology.

Her medical history was limited to hypothyroidism and gall bladder cancer. Ocular family history was significant for cataracts in both parents and a brother. Ocular medical history was significant for choroidal and conjunctival nevi in the right eye and nuclear cataracts in each eye.

Uncorrected VA was 20/25 OD and 20/30 OS, and IOP was 14 mm Hg OD and 8 mm Hg OS. External examination of the right eye revealed diffuse hyperpigmentation superior to her upper brow and lateral to her orbit. The left external examination was normal. Slit lamp examination of the right eye was significant for multiple pigmented nevi inferiorly on the conjunctiva (Figure 1). Anterior segment examination of the left eye was normal. Dilated fundus examination of the right eye was significant for a mildly cupped optic nerve with a cup-to-disc ratio of 0.6 with temporal rim thinning. There was a moderately elevated pigmented choroidal nevus in the superior periphery of the right eye that had traces of overlying subretinal fluid (Figures 2-4). Dilated examination of the left eye revealed a healthy nerve with a cup-to-disc ratio of 0.2 and normal macula, vessels, and periphery.

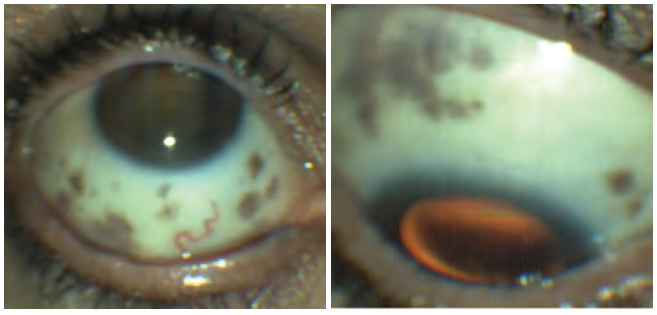

Figure 1. Anterior segment photography reveals conjunctival and scleral hyperpigmentation.

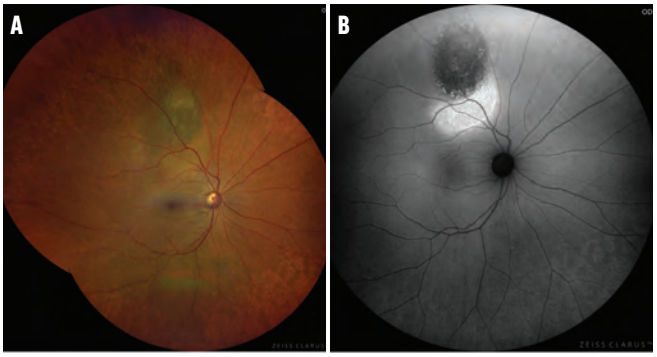

Figure 2. Fundus photography of the right eye shows a thickened pigmented choroidal nevus superior to the macula (A). Autofluorescence shows hyperautofluorescence inferior to the lesion (B).

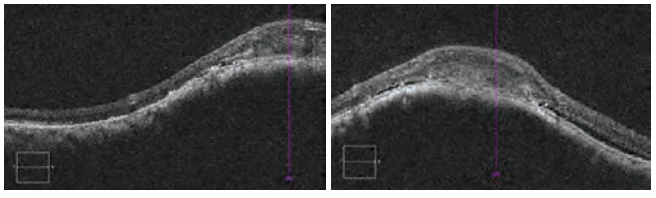

Figure 3. OCT of the right eye shows choroidal elevation with subretinal fluid.

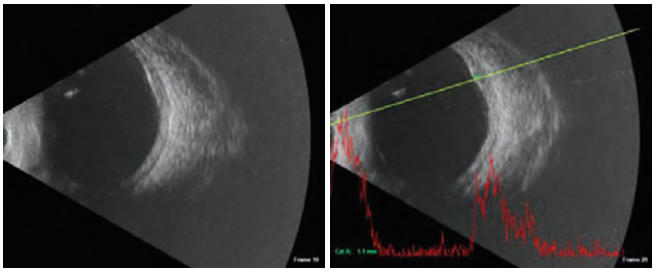

Figure 4. B-scan reveals focal choroidal elevation with a low internal reflectivity.

Based on the clinical findings, diagnoses of nevus of Ota with a suspicious choroidal nevus and open-angle glaucoma in the right eye were made. The patient was scheduled for a glaucoma evaluation, including a visual field examination, and close periodic examinations of the choroidal nevus.

DISCUSSION

Nevus of Ota (oculodermal melanocytosis) is a melanocytic lesion that affects the first and second branches of the trigeminal nerve, as well as the sclera, ocular muscles, retrobulbar fat, periosteum, and buccal mucosa.[1] These lesions are thought to be caused by arrested migration of dermal melanocytes from neural crest origin.[2] In the two-thirds of patients presenting with ocular involvement, the lesions are present from birth. Other regions are not generally affected until the teenage years.[1] Generally, nevus of Ota is asymptomatic, though there are rare cases of associated sensory loss.[3]

This rare condition is more commonly seen in Asian populations with a prevalence of 0.2% to 1.0% and a strong female predominance, representing 80% of cases.[1,4]

Diagnosis of nevus of Ota is primarily clinical.[3] For suspected cases, a complete ophthalmic examination should be performed, including gonioscopy to evaluate hyperpigmentation of the trabecular meshwork. A dilated peripheral retinal examination is important to rule out choroidal masses or melanomas. An oral examination should also be considered to assess for palate lesions.[3]

Vishnevskia-Dai et al recently proposed a new classification system for the ocular involvement of nevus of Ota. The updated system uses both anatomic involvement and the number of quadrants affected (Table).[5] A designation of "+" is added to any level of anatomic involvement of class 2 or greater. For example, lesions affecting the choroid in supero- and inferotemporal quadrants as well as the sclera would be denoted as class 3B+.[5]

Treatment of nevus of Ota is generally focused on alleviating the symptoms. This condition is usually benign, though some patients may desire cosmetic removal of the spots, for which several approaches are available.[6] Nevus of Ota is associated with the development of pigmentary glaucoma in the affected eye, requiring treatment in up to 10% of patients.[7] Additionally, as is common with melanocytic conditions, malignant transformation has been noted in up to 1 in 400 patients, more commonly in White individuals.[3] Yearly follow up is recommended for asymptomatic patients to rule out development of glaucoma and malignant melanoma.[3]

CONCLUSION

Nevus of Ota presents as a benign accumulation of melanocytes along the first and second branches of the trigeminal nerve and can be seen in up to 1% of the population, with predominance in women and Asian populations. It can be unilateral or bilateral. Treatment is symptom-based and usually only cosmetic. Pigmentary glaucoma is seen in up to 10% of cases and malignant transformation in up to 0.25%, more commonly in White individuals. The patient described here exhibited both glaucomatous nerve changes and possible early malignant transformation of a choroidal nevus. ■

TABLE. VISHNEVSKIA-DAI CLASSIFICATION OF OCULAR NEVUS OF OTA[5]

Anatomic Involvement	Quadrant Involvement
1 - Surface only-involvement of the conjunctiva and/or sclera	**A** - One quadrant
2 - Iris	**B** - Two quadrants
3 - Choroid	**C** - Three quadrants
4 - Iris and choroid	**D** - All quadrants

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ESTABLISHING THE PEDIATRIC RETINA SOCIETY


Top lectures at the 2021 Advances in Pediatric Retina Course included the long-anticipated creation of a pediatric retina organization.

BY SHWETHA MANGALESH, MBBS, AND NITA VALIKODATH, MD, MS

The third Advances in Pediatric Retina (APR) Course was packed with lectures and panels focused on cutting-edge diagnostic tools, management techniques, and research for pediatric retinal diseases.

This year's virtual platform allowed participants from all over the world to connect and exchange expertise on various treatment strategies and surgical approaches. It also gave the program chairs—Cynthia Toth, MD; Lejla Vajzovic, MD; and Mary Elizabeth Hartnett, MD—the global platform they needed to establish a very special and much-needed organization: the Pediatric Retina Society.

Below is a summary of several key lectures, and the first look at the benefits the new society will afford its members.

> A Pediatric Retina Society would also provide a more formal interdisciplinary collaboration between retinal specialists and pediatric ophthalmologists, beyond the ROP collaborations that now exist.
>
> *- Gil Binenbaum, MD, MSCE, Chief of the Division of Ophthalmology, Children's Hospital of Philadelphia*

> Thanks everyone for an excellent meeting. I really enjoyed it and, as an adult vitreoretinal surgeon, I learned so much.
>
> *- Anwar Zaman, Consultant Vitreoretinal Surgeon, Nottingham University Hospitals, UK*

ROP CLASSIFICATION

One of the highlights of the meeting was a panel discussion on the updated Classification for Retinopathy of Prematurity (ICROP3). The panelists included experts involved in the update itself: Dr. Hartnett; Michael F. Chiang, MD; Anna Ells, MD; David Wallace, MD, MPH; and Antonio Capone, MD. Dr. Chiang, who spearheaded the committee of 34 experts, addressed the need for an updated classification and elaborated on the key changes, including the addition of ophthalmic imaging and anti-VEGF therapy.

Dr. Hartnett discussed the committee's addition of regression and reactivation, which she noted differs in clinical presentation and time course for patients treated with anti-VEGF agents compared with those treated with laser photocoagulation.

The panel reiterated the importance of standardizing ROP terminology to provide consistent research endpoints. Hopefully, ICROP3 will be a useful framework for defining these endpoints, the panelists agreed.

KEYNOTE: CHALLENGES IN TREATMENT

This year's keynote speaker was Hiroko Terasaki, MD, a world-renowned physician-scientist with expertise in adult and pediatric retinal diseases. Dr. Terasaki addressed the challenges in the treatment of severe ROP, first noting that the eyes are small, the retinal detachments are complex at the time of surgery, and the success rate of a second surgery is low. However, if you understand the process of progression (from stage 4a to stage 5, for example), you can "untie the entwined thread," she quipped.

She punctuated her talk with incredible videos of complicated ROP surgeries, including open-sky vitrectomy and lensectomy in eyes with stage 5 ROP. In patients with stage 5 ROP, surgeons must focus on opening the funnel and then opening the trough, she advised, narrating several surgical videos to drive home the point.

Dr. Terasaki touched on the benefits of having access to anti-VEGF agents, which allows surgeons to operate on severe ROP sooner, she said. Research shows that the amount of VEGF in the aqueous humor increases as the stage

of ROP increases, and a preoperative injection of bevacizumab (Avastin, Genentech) significantly reduces the amount of VEGF, aiding in the surgery. And never forget about buckling, she added, showing the audience several cases in which a scleral buckle saved the patient's retina.

During the panel discussion that followed, Dr. Terasaki reminded the audience that managing ROP is no easy task, and it's a long-term treatment process.

At the end of the session, Dr. Terasaki was honored by the course directors for her many contributions and mentoring to the pediatric retina community.

> THANK YOU to all who made this wonderful virtual APR possible! Outstanding talks and videos from all over the world; we have learned a lot these 2 days for the benefit for our patients. I am looking forward for more meetings like this! Congratulations and kind regards from Buenos Aires, Argentina.
>
> *- Sofia Vidal, Vitreoretinal Surgeon, Garrahan Hospital, Buenos Aires, Argentina*

PEDIATRIC RESEARCH

The session on cutting-edge research in pediatric retina covered anti-VEGF treatment of ROP, hypoxia-inducible factor stabilization to prevent ROP and proliferative vitreoretinopathy, and regenerative medicine for familial exudative vitreoretinopathy. In addition, discussions of recent studies were interspersed throughout the entire event. Eric Nudleman, MD, PhD, delivered an exciting talk on intravitreal V1233, a novel anti-VEGF agent that may prove safe in ROP.

Anand Vinekar, MD, discussed the possible creation of biomarker kits for ROP using tear film angiogenic factors. He and his team looked at 36 preterm infants and found that infants with ROP had lower levels of VEGF and higher levels of angiogenin than infants without ROP. In addition, the angiogenin levels negatively correlated with both birth weight and gestational age in infants with ROP. Further analysis showed that angiogenin/birth weight, angiogenin/gestational age, and angiogenin/VEGF ratios were useful for differentiating study participants with and without ROP—leading Dr. Vinekar to suggest that these ratios could serve as potential screening biomarkers for ROP.[1]

GENE THERAPY

Gene therapy for pediatric inherited retinal diseases is a hot topic, and the meeting coverage did not disappoint. Robert Sisk, MD, offered practical considerations and pearls for surgical techniques of delivering subretinal gene therapy, including how to select an ideal target area and bleb formation. Aaron Nagiel, MD, PhD, addressed the postoperative complication of progressive perifoveal chorioretinal atrophy and its relationship to the bleb and/or vector. Cagri Besirli, MD, PhD, discussed outcomes of voretigene neparvovec-rzyl (Luxturna, Spark Therapeutics) subretinal gene therapy for pediatric patients with the biallelic *RPE65* mutation. The panel that followed, which also included Antonio Capone Jr, MD, shared strategies for managing various other postoperative complications such as inflammation and elevated IOP.

CALL FOR A PEDIATRIC RETINA SOCIETY

The seed for the formation a pediatric retina society was planted at the first APR meeting in 2017. This year, Drs. Toth, Vajzovic, and Hartnett reiterated the need for this society, sharing several of the benefits such a society would provide the wider retina community:

- A platform for sharing rare and challenging cases to facilitate discussions about clinical approaches and management.
- The creation of a repository of specialists for patient referral.
- A space for early-career pediatric retina surgeons to find global mentoring, especially when navigating the logistical problems of a surgical setup.

> YES! You have created this incredible meeting. The start of the Pediatric Retina Society!
>
> *- Alice Lyon, MD, Director, Retina Service; Professor of Ophthalmology, Northwestern University, Chicago*

Course participants wholeheartedly supported the society's creation by using the chat function; many were already thinking of additional ways the society could help the retina community. For example, Dominico Lepore, MD, mentioned that it would be an ideal way to organize a big data collection system for future research studies. Thus marked the establishment of the Pediatric Retina Society.

We are excited to see what the future holds for the pediatric retina community and are looking forward to participating in these ongoing efforts. ■

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AMD PIPELINE UPDATES: A DIFFERENT WAY OF THINKING ABOUT THE COMPLEMENT CASCADE

A new layout of the complement cascade highlights the major changes to this year's two-sided poster.

BY PETER K. KAISER, MD, AND MARIELLE MAHAN, MD

The retina community should be proud that it continues to educate itself rather than rest on the educations we received in our training. Yes, it comes naturally to us—we're a scientifically curious group by nature, and there is no shortage of vitreoretinal mysteries waiting to be unlocked—but it also requires time and effort. With this year's iteration of the annual age-related macular degeneration (AMD) pipeline poster, we hope to make that education a bit easier.

It became clear that a deepened understanding of the complement cascade will be foundational for our practice if a therapy for geographic atrophy is approved by regulatory bodies, so we thought it was best to create a more specific schematic for readers this year (Figure).

Figure. Drs. Kaiser (left) and Marielle Mahan (right) meet with *Retina Today* at the famous Café du Monde in New Orleans to sketch the pipeline poster.

The limitations of a 2-dimentional illustration of the complement cascade should be noted; we addressed them the best we could. For example, the alternative pathway reactions occur on the surface of a cell, not in the extracelluar space around it. Still, we think this year's depiction of the complement cascade will provide an excellent reference point for readers who need a refresher on a biologic cascade many of us haven't considered at length since our medical training.

The next generation of ophthalmologists will be instrumental to continuing the tradition of continued education. To that end, Marielle Mahan, MD, joined the team responsible for creating the poster this year. As an ophthalmology resident with a talent for artistic depictions, Dr. Mahan led the charge in redesigning the complement cascade schematic. Her future in ophthalmology is bright, and we're happy to have her included on the team this year. ■

Remember that the drugs listed in this poster are not exhaustive. If there is a drug that you think we should include in next year's poster, email us at cdeming@bmctoday.com.

PETER K. KAISER, MD

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MARIELLE MAHAN, MD

- Ophthalmology Resident, MedStar Georgetown University Hospital/Washington Hospital Center, Washington, D.C.

EXPERTS WEIGH IN ON PHARMACOLOGIC THERAPY FOR RETINAL DISEASE

Aspen Retinal Detachment Society panelists discussed various management strategies for DME and RVO.

BY THE STAFF OF *RETINA TODAY*

After a year hunkered down at home due to the COVID-19 pandemic, it was a true pleasure to see friends and colleagues in person at the 49th annual Aspen Retinal Detachment Society (ARDS) meeting in Snowmass, Colorado. Even with our masks on, it was easy to see just how excited everyone was to step away from their computers to share cutting-edge clinical techniques and tools among peers.

A key component of every ARDS meeting is our panel discussions, during which experts share their clinical insights, ask questions, and field comments from the audience. In this issue, we summarize the panel on pharmacologic therapy of non-AMD retinal diseases. We examined a case of diabetic macular edema (DME) submitted by Dennis P. Han, MD, and a patient who presented to Timothy W. Olsen, MD, with central retinal vein occlusion (CRVO). We were joined by Allen C. Ho, MD, FACS, and Ryan M. Rich, MD. Together, we worked through some of the toughest clinical questions, including what imaging is beneficial for each presentation, what clinical signs dictate the course of treatment, and how to pivot when the patient isn't responding to the chosen therapy.

Registration is already open for ARDS 2022—our 50th anniversary meeting—set for March 5-9. Head to https://aspenretina.com for more information, and get ready to hit the slopes and the lecture hall…together.

- Timothy G. Murray, MD, MBA

The field of retina is constantly evolving with advances in diagnostics and therapeutics, and it's important to consider how each new tool and therapy will fit into current management strategies. Several questions worth asking include: How do we move from one therapy to another? When do we combine therapies? What is the role of imaging? What is the burden of treatment on patients?

At this year's ARDS annual meeting, a panel of retina specialists—Dennis P. Han, MD; Allen C. Ho, MD; Timothy W. Olsen, MD; and Ryan M. Rich, MD—addressed some of these questions while evaluating patient cases to consider how pharmacologic therapies might factor into management.

THE CASES

Diabetic Macular Edema

Panel moderator, Timothy G. Murray, MD, MBA, opened the discussion with Dr. Han's case of a 54-year-old patient with type 2 diabetes, who presented with decreased visual acuity. The patient's medical history included previous treatment with panretinal photocoagulation (PRP) and a focal grid. Panelists were asked to weigh in on the best possible treatment approaches.

Dr. Han noted that the patient likely has severe DME in both eyes. He stated he would order an OCT, check for neovascularization, and prescribe anti-VEGF therapy—an approach that prompted a discussion about when to order fluorescein angiography for patients with diabetes. In cases where intraretinal fluid persists despite treatment or inflammation is suspected, fluorescein can be helpful.

For patients with systemic risk factors such as heart attack or stroke, Dr. Ho said he considers monotherapy with steroids, although anti-VEFG injection is preferred. With these patients, Dr. Ho educates them on the theoretical concern for a blood clot causing an occlusion with anti-VEGF therapy, which dictates the use of a steroid as a firstline approach in lieu of anti-VEGF.

The panelists also discussed the benefits of imaging; OCT is "the single best educational tool that I have ever had, and patients really engage with that," Dr. Murray said. "I thought I was doing it for me, but I'm really doing it for them." Dr. Rich agreed, noting that using widefield angiography to

(Continued on page 24)

THE DIABETIC EYE DISEASE PIPELINE IN 2021

The future remains bright with many clinical trials reporting promising data.

BY XUEJING CHEN, MD, MS; ARSHAD M. KHANANI, MD, MA; AND CAROLINE R. BAUMAL, MD

Continued advancement in the treatment of diabetic eye disease is critical as the global burden of diabetes increases. Intravitreal injections of ranibizumab (Lucentis, Genentech), aflibercept (Eylea, Regeneron), and bevacizumab (Avastin, Genentech) have a long history of efficacy and safety for the treatment of diabetic macular edema (DME), with increasing use for diabetic retinopathy (DR). Still, unmet needs remain for more durable agents and improved efficacy. To manage the shortcomings of current anti-VEGF therapies, new agents and novel delivery systems are under investigation.

ANTI-VEGF ADVANCES

Faricimab (Genentech/Roche) is an investigational bispecific antibody designed as an intravitreal injection to neutralize both the angiopoietin-2 (Ang-2) and VEGF-A pathways.[1] Under pathologic conditions, Ang-2 is upregulated and blocks angiopoietin-1, a vascular stability factor, from binding to the Tie-2 receptor. This competitive inhibition results in endothelial cell destabilization, pericyte destruction, upregulation of inflammatory cytokines, and sensitization of the vasculature to the effects of VEGF-A.[1]

YOSEMITE and RHINE are two identical, fully enrolled, pivotal phase 3 trials evaluating 6 mg faricimab for the treatment of DME.[2-4] A total of 1,891 treatment-naïve patients were randomly assigned to one of three treatment arms: every 8 weeks after six monthly loading doses; a personalized treatment interval (PTI) regimen after four monthly loading doses; or every 8 weeks after five monthly loading doses.

The trials met their primary endpoints at 1 year with both faricimab arms offering noninferior/equivalent visual gains compared with aflibercept with at least a 10-letter gain in each treatment arm.[2-4]

As for secondary endpoints, more than 70% of faricimab PTI patients were in the 12- or 16-week treatment interval group at the end of the first year.[1]

Faricimab was well tolerated without any unexpected safety

15TH ANNIVERSARY ISSUE

HOW IT STARTED

The first issue of *Retina Today* included an article detailing the latest pharmacologic treatments for diabetic macular edema (DME), with the understanding that laser photocoagulation was the standard.[1] Most of today's therapies, including steroid injections and implants, were still under investigation.[1] Anti-VEGF therapy with pegaptanib (Macugen, Bausch+Lomb), already FDA approved for wet AMD, was in phase 2 trials for DME with promising data; phase 3 was recruiting.[2]

After Philip Rosenfeld, MD, PhD; Andrew Moshfeghi, MD, MBA; and Carmen Puliafito, MD, first published on the use of intravitreal bevacizumab (Avastin, Genentech) in wet AMD in 2005, several retina specialists began exploring the benefits of its off-label use for DME.[3] By March 2006, Dante J. Pieramici, MD; Robert L. Avery, MD; and others were offering patients with advanced disease a single intravitreal injection of 1.25 mg bevacizumab; they noted that, in some cases, the treatment resulted in rapidly reduced DME and increased vision.[4]

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signals or cases of occlusive retinal vasculitis. The 2-year results are expected by early 2022, and the phase 3 extension study RHONE-X will follow patients for an additional 2 years.[5]

The FDA accepted faricimab's biologics license application in July 2021, and the EMA accepted faricimab's marketing authorization application.

Brolucizumab (Beovu, Novartis) is a humanized single-chain fragment that binds to VEGF-A, administered by intravitreal injection.[6] Compared with other VEGF-A inhibitors, brolucizumab is smaller with a molecular weight of 26 kDa, allowing for a higher molar concentration per injection and possibly more anti-VEGF effect than current treatments.[6]

The phase 3 KITE and KESTREL trials evaluated 6 mg or 3 mg brolucizumab, respectively, for patients with center-involving DME. Patients in the treatment arms received injections every 6 weeks for five loading doses followed by maintenance injections every 12 weeks for 1 year, with an option to adjust to every 8 weeks. The comparator arm received aflibercept every 8 weeks after five monthly loading doses.[7,8]

Both trials achieved their primary endpoints showing noninferiority to aflibercept at 1 year with a comparable 9 to 10 letters of improvement; patients in KITE recieved a lower number of total injections at longer intervals for brolucizumab-treated eyes.[9,10]

KINGFISHER, a separate DME trial that enrolled 517 participants randomly assigned to 6 mg brolucizumab or aflibercept every 4 weeks, also met its primary endpoint of noninferiority to aflibercept at 1 year.[9]

In KITE, 2.2% of participants receiving brolucizumab experienced intraocular inflammation (IOI) compared with 1.7% of patients receiving aflibercept, and no events of retinal vasculitis were seen in either arm. Retinal vascular occlusions occurred at a rate of 0.6% in both groups and were not associated with inflammation or vasculitis.[9] In KINGFISHER, IOI was seen in 4% of brolucizumab-treated eyes and 2.9% of aflibercept eyes, and retinal vasculitis was seen in 0.9% of brolucizumab eyes and 0.6% of aflibercept eyes. Retinal vascular occlusions were reported in 0.3% of brolucizumab eyes and 0.6% of aflibercept eyes and were not associated with inflammation or vasculitis in either group.[9]

OPT-302 (Opthea Limited), a 'trap' agent that binds to and neutralizes VEGF-C/-D, is being explored as an adjuvant intravitreal injection for patients undergoing standard anti-VEGF therapies. A multicenter phase 1b/2a trial evaluated OPT-302 in combination with aflibercept for refractory DME.[11] The phase 1b was a nine-patient dose escalation study where OPT-302 was given with aflibercept, and phase 2a randomly assigned 144 participants 2:1 to aflibercept with 2 mg OPT-302 or aflibercept monotherapy.[9] Of patients treated with combination therapy, 53% achieved the primary endpoint of ≥ 5 letter gain at week 12 compared with baseline, which was greater than the predefined success measure of 38%.[11] In a subgroup of patients with a prior history of aflibercept treatment, the mean change in BCVA at week 12 was +6.6 letters after switching to the combination therapy and +3.4 letters for those continuing on monotherapy.[11]

MANY NOVEL TREATMENTS UNDER INVESTIGATION HAVE THE POTENTIAL TO IMPROVE DURABILITY AND/OR EFFICACY OF CURRENT THERAPY.

KSI-301 (Kodiak Sciences) is an intravitreal anti-VEGF biologic built on a proprietary antibody biopolymer conjugate platform.[6] This feature, combined with its large molecular weight, may allow for a longer intraocular half-life.[12] It is designed to have a duration of approximately 6 months. A phase 1a single-dose escalation study of nine patients with severe previously treated DME showed rapid improvement in vision and anatomy as early as 1 week after injection without any drug-related adverse events.[13] This was maintained 12 weeks after injection across all dose levels.[13]

The phase 1b trial was an open-label exploratory study that evaluated treatment-naïve patients with wet AMD, retinal vein occlusion, or DME over 72 weeks.[13,14] Patients received three monthly loading doses of either 2.5 mg or 5 mg KSI-301 followed by subsequent doses per retreatment criteria.[14] At 24 weeks, there was a mean gain of 5.9 letters and a 58 µm reduction in central subfield thickness.[13,14]

GLEAM and GLIMMER, pivotal phase 3 trials enrolling 450 participants with treatment-naïve DME, are comparing KSI-301 with aflibercept. The primary endpoint will be visual acuity change from baseline at 1 year with 2-year follow-up.[15]

The port delivery system (PDS) with ranibizumab (Susvimo, Genentech/Roche), approved by the FDA for the treatment of wet AMD, remains under investigation for DME.[16] The fully enrolled phase 3 PAGODA trial of 545 DME patients is comparing the PDS (with refill exchanges at 6-month intervals) with monthly 0.5 mg ranibizumab. The primary endpoint is the visual acuity change from baseline averaged over weeks 60 and 64.[17]

The phase 3 PAVILION trial of moderately severe or severe nonproliferative diabetic retinopathy without DME is evaluating the percentage of participants with ≥ 2-step letter improvement at 1 year.[18] The 160 patients will be randomly assigned to either two monthly intravitreal injections of ranibizumab followed by the PDS with fixed refills every 36 weeks or observation with as-needed monthly injections

of 0.5 mg ranibizumab until crossing over to the PDS arm.[18]

High-dose 8 mg aflibercept (Regeneron) is being investigated as an alternative to the standard 2 mg aflibercept dose for DME. PHOTON is a fully enrolled (660 patients) phase 3 noninferiority trial evaluating the efficacy and safety of 8 mg aflibercept at intervals of 12 or 16 weeks compared with 2 mg aflibercept dosed every 8 weeks for DME.[19]

GENE THERAPY UPDATES

ADVM-022 (Adverum) uses an AAV.7m8 vector carrying the coding sequence for aflibercept and is administrated via intravitreal injection.[20] Adverum unmasked all patients in the phase 2 INFINITY trial after an unexpected serious adverse reaction of hypotony was noted in a participant who received a single high dose of the study drug.[21] After further review, the company announced that it will not pursue DME as an indication for future ADVM-022 trials.[22]

RGX-314 (Regenxbio) is an AAV8 vector carrying an anti-VEGF monoclonal antibody fragment. The phase 2 ALTITUDE trial is looking at patients with DR without DME who are treated with a single dose of RGX-314, delivered suprachoroidally.[23] Positive 3-month interim data from cohort 1, treated with a single injection at a dose level of $2.5x10^{11}$ genomic copies per eye, show that treatment is well tolerated and 33% of patients had a ≥ 2-step improvement from baseline on the ETDRS-DRSS compared with 0% of patients in the control arm.[24]

STEROID DEVELOPMENTS

OCS-01 (1.5% ophthalmic suspension, Oculis), a topical formulation of dexamethasone, uses the company's proprietary soluble nanoparticle technology. The phase 2 clinical trial met its primary endpoint at week 12, showing a mean central macular thickness of -53.6 µm in the treatment group compared with -16.8 µm in the control arm.[25] In addition, the mean change in BCVA at week 12 was higher in the OCS-01 group (+2.62 letters) compared with the control arm (+1.04 letters). The study found no significant differences in tolerability between the two groups, but did note that IOP increases were more common in the treatment arm, consistent with the known effects of steroids.[25] Oculis announced the beginning of the phase 3 trial for DME at AAO 2021.

AR-1105 (Aerie) is a bioerodible intravitreal implant (manufactured using PRINT technology) that releases dexamethasone. The phase 2 trial evaluated two formulations of AR-1105 in 49 patients with macular edema associated with retinal vein occlusion. Topline results at 6 months demonstrated increased BCVA and reduced macular edema, with one formulation reaching peak efficacy earlier than the other; however, the slower-acting formulation demonstrated a longer overall duration—up to 6 months. Both formulations of AR-1105 were well tolerated with no unexpected safety findings. The company is preparing for phase 3 studies in DME.[26]

NOVEL MOLECULAR TARGETS

THR-149 (Oxurion) is a plasma kallikrein inhibitor given in the form of an intravitreal injection. In a phase 1 safety trial, 12 patients had an average improvement of 6.4 letters at 90 days after one injection.[27] No dose-limiting toxicity or drug-related adverse events were seen.[27] The KALAHARI phase 2 trial is currently enrolling 122 patients and will randomly assign them to three monthly injections of THR-149 or aflibercept. The primary outcome measure will be mean change in vision from baseline at 3 months.[28]

UBX1325 (Unity Biotechnology) is a Bcl-xL inhibitor currently under investigation in a phase 1 study of patients with DME or AMD for whom anti-VEGF therapy was not considered beneficial.[29] The 24-week data released in November demonstrated that 50% of patients receiving UBX1325 had a ≥ 10 letter gain and 62.5% experienced a ≥ 5 letter gain. Additionally, a majority of the patients did not meet rescue criteria after a single UBX1325 injection through week 24.

A phase 2a study is currently enrolling 62 patients with DME who will be randomly assigned to a single intravitreal injection of UBX1325 or sham therapy.[30] The primary outcome measures are ocular and systemic safety and tolerability over 24 weeks.[30]

IN SUMMARY

Many novel treatments under investigation have the potential to improve durability and/or efficacy of current therapy for DME and DR. The recently encountered safety hurdles remind us to tread cautiously, as new complications may accompany novel therapies. However, the future remains promising in our quest to improve the therapeutic landscape for patients with DME and DR. ■

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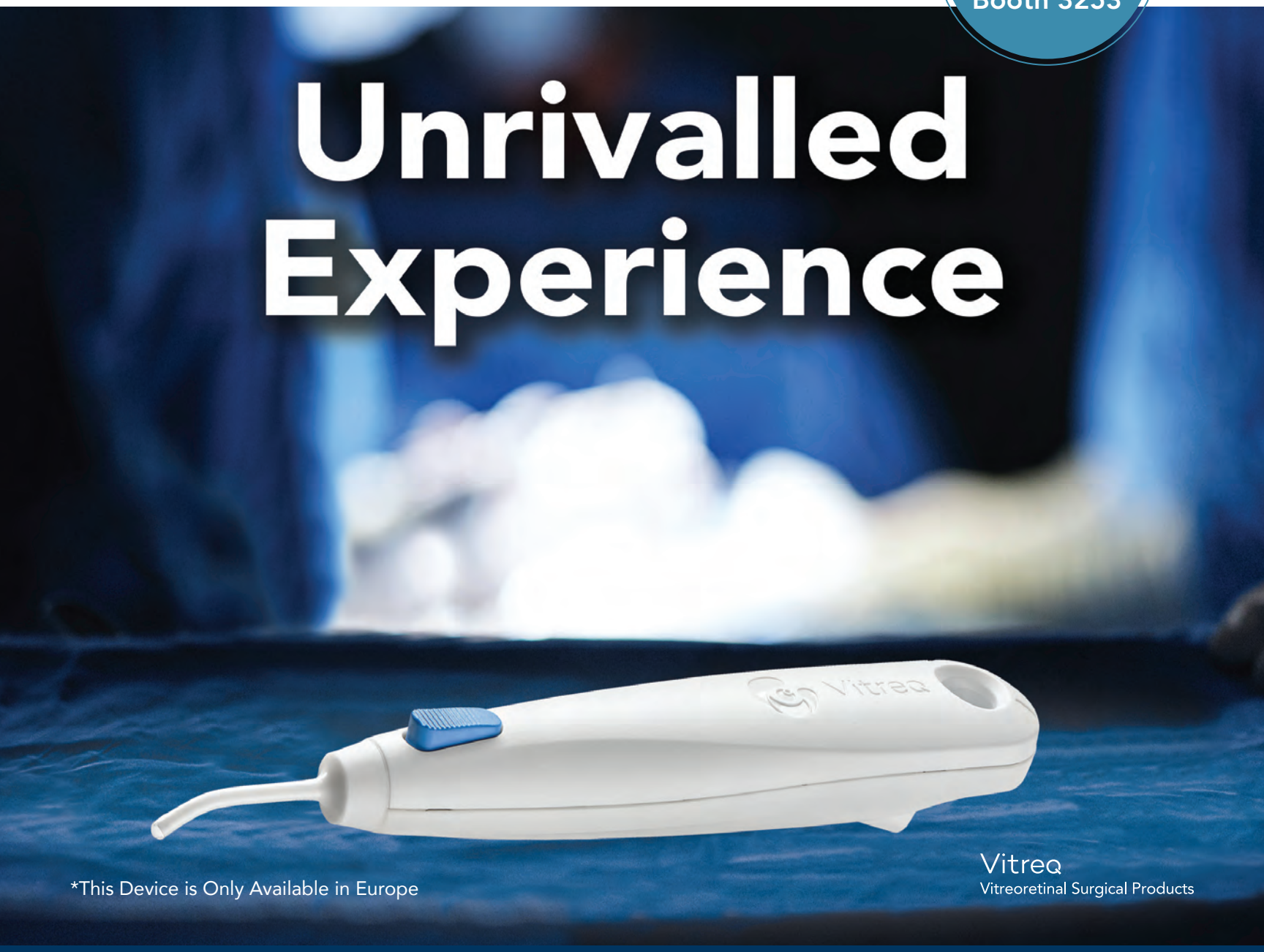

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ARDS

(Continued from page 19)
show patients the regression of vessels after PRP helps them understand the benefit of the treatment.

Finishing up, the panelists discussed when it would be appropriate to perform surgery along with anti-VEGF therapy. If a taut hyloid is present, surgery might be useful to enable an anti-VEGF response, Dr. Han said. Maria Berrocal, MD, joined the conversation from the audience, adding her belief that operating early, rather than reserving surgery as a last resort, may be beneficial in patients with severe disease progression or excess intraretinal fluid.

Retinal Vein Occlusion

Dr. Murray then introduced the next case, initially seen by Dr. Olsen. A 64-year-old man with decreased visual acuity for the past 2 weeks (20/20 OD and 20/200 OS) and a history of glaucoma presented with a CRVO. Dr. Olsen said the pupil examination was normal, which ruled out ischemia. He skips the ERG in CRVO patients in favor of OCT and, in this patient, chose to initiate anti-VEFG therapy.

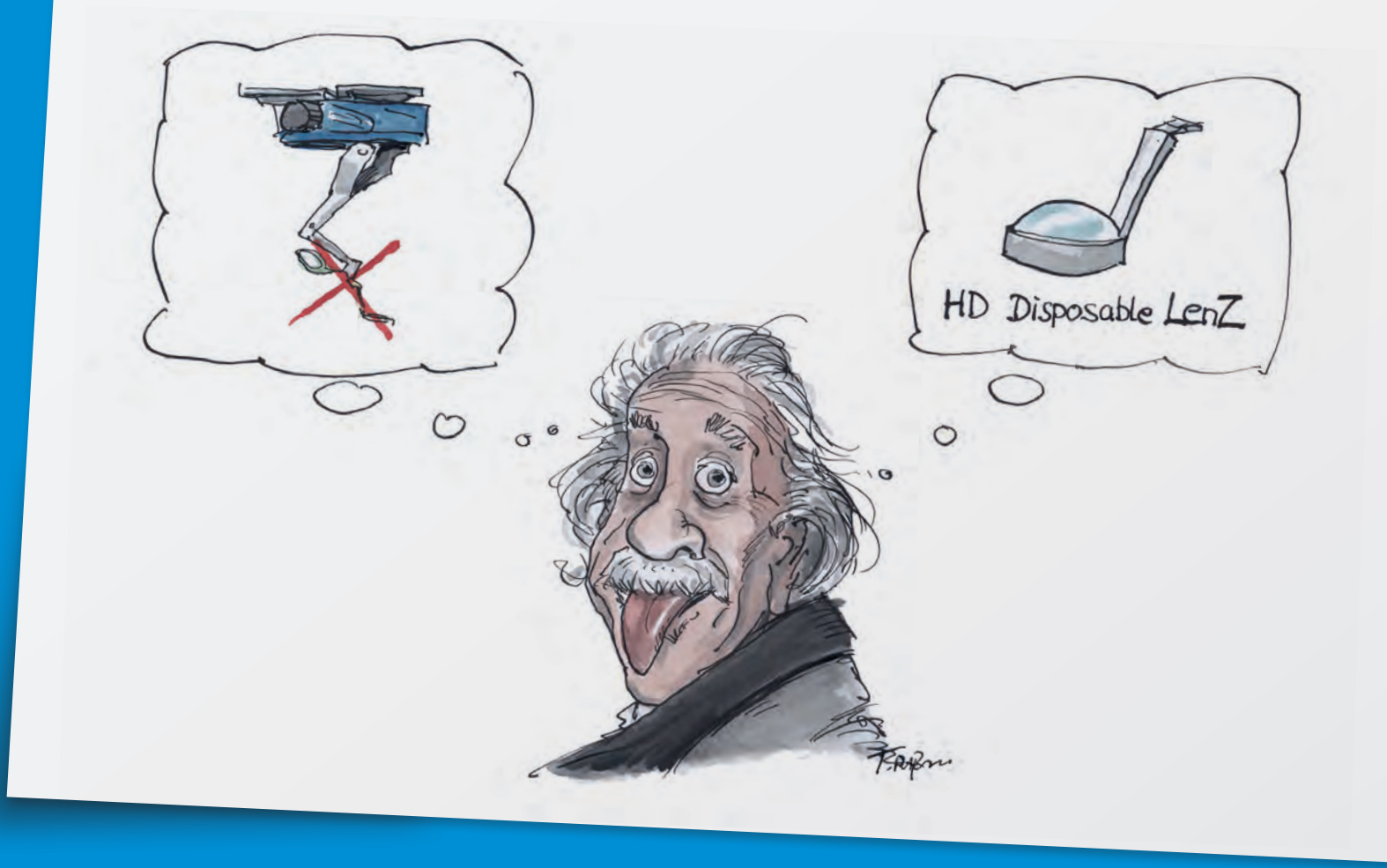
Which anti-VEGF agent to start with, however, is another question altogether. Dr. Murray suggested most clinicians start with bevacizumab (Avastin, Genentech), although the panelists agreed that insurance companies dictate the drug choice most of the time. A lively discussion ensued, punctuated by Dr. Han's pointed commentary: "The problem is that there's a dearth of evidence-based information that supports using something other than bevacizumab for the first few injections," he said.

The panelists also discussed the best approach for patients whose visual acuity does not improve after their first anti-VEGF injection. Before moving to a different drug or deciding that the patient is nonresponsive to anti-VEGF therapy, it is often worthwhile to give injections more frequently (every 2 or 3 weeks) to determine an effective treatment interval. Another option is to add topical carbonic anhydrase inhibitors, such as dorzolamide, to reduce fluid in the retina, Dr. Murray said.

When a patient does have a positive response, the next question is if/when to extend treatment. Most panelists agreed that their first move is to extend out to 6 weeks. Dr. Murray noted that extending no more than 2 weeks at a time can help ensure the patient is consistently seeing a clinical benefit. For many of Dr. Murray's CRVO patients, 16 weeks is the maximum treatment interval, but in some cases 6 months is possible, depending on the presence of ischemia. Even if you can extend anti-VEGF injections to every 6 months, you can't really stop injecting these patients, according to Dr. Murray, because if you do, they are at risk for developing neovascular glaucoma.

FINAL THOUGHTS

Advances in pharmacology are changing the retina landscape, and retina specialists must work hard not only to keep up with new products and technologies, but also to personalize therapy to their patients' needs. ■



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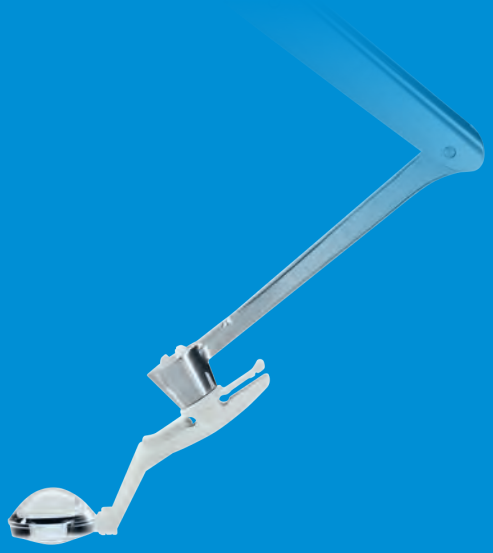

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ADVANCES IN WET AMD RESEARCH

Several drug candidates are showing promise, with plenty more in the works.

BY ABTIN SHAHLAEE, MD; ALLEN CHIANG, MD; AND ALLEN C. HO, MD

Although intravitreal anti-VEGF injections are an effective therapy for wet AMD, the associated treatment burden is significant, pushing researchers to search for novel approaches. Numerous therapeutics and drug delivery systems are in the research pipeline, offering hope for a reduced treatment burden and improved outcomes in the future.

RECENT UPDATES

IBI302

In April, Innovent Biologics announced that the first patient was successfully dosed in a phase 2 clinical trial of IBI302, a first-in-class ophthalmic recombinant human anti-VEGF and anticomplement bispecific fusion protein.[1] The phase 1 open-label, multicenter, dose-escalation clinical trial enrolled a total of 31 patients and evaluated the safety and tolerability of a single intravitreal injection (IVT) of IBI302 in patients with wet AMD.[2] The data showed good safety and tolerability, with no serious adverse events or dose-limiting toxicity reported. At week 12, the mean change in BCVA was 4.83, 8.00, and 9.17 letters for the 2-mg IBI302, 4-mg IBI302, and aflibercept groups, respectively, compared with baseline. The treatment groups had reduced central subfield thickness similar to that of the aflibercept group.[2]

RGX-314

In November, Regenxbio reported 2-year data from all cohorts of its RGX-314 phase 1/2a trial for the treatment of wet AMD and cohort 3 of its long-term follow-up study.[3,4] The therapy was generally well tolerated, and patients in cohorts 3, 4, and 5 experienced improved vision over 2 years and a significant reduction in the need for supplemental anti-VEGF injections. For more on the subretinal delivery of RGX-314 for the treatment of AMD, see *Surgical Innovations to Treat Medical Retinal Diseases* on page 34.

15TH ANNIVERSARY ISSUE

HOW IT STARTED

When *Retina Today*'s first issue was published in March 2006, the first anti-VEGF drug, pegaptanib (Macugen, Bausch+Lomb), had only recently been approved by the FDA.[1] At the time, ranibizumab (Lucentis, Genentech) was still undergoing priority review and was approved in June of that year.[2]

Also under investigation was VEGF-trap, better known as aflibercept (Eylea, Regeneron), which was enrolling phase 1 and 2 clinical trials during *Retina Today*'s founding year.[1] Aflibercept wasn't approved to treat wet AMD until November 2011.

Since then, it has taken 10 years for another anti-VEGF therapy to make it out of the pipeline. This year, two new treatment options gained FDA approval: the ranibizumab biosimilar ranibizumab-nuna (Byooviz, Samsung Bioepis/Biogen) and the port delivery system (Susvimo, Genentech/Roche), which is the first sustained-release ocular implant that delivers a concentrated formulation of ranibizumab.[3,4]

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AAVIATE is a phase 2 randomized, active-controlled, dose-escalation trial investigating the efficacy, safety, and tolerability of RGX-314 delivered with the in-office SCS suprachoroidal microinjector (Clearside Biomedical).[5] The trial is investigating three dose levels: $2.5x10^{11}$ genomic copies per eye (GC/eye; cohort 1), $5x10^{11}$ GC/eye (cohorts 2 and 3), and $1x10^{12}$ GC/eye (cohorts 4 and 5).

At 6 months, central retinal thickness was stable or improved in cohorts 1 and 2 compared with monthly 0.5 mg ranibizumab, with little to no difference in BCVA between the groups. Treatment with RGX-314 led to a more than 70% reduction in treatment burden at 6 months. The drug has been well tolerated with intraocular inflammation in 26.7% of patients in cohort 1 and 20.0% of patients in cohort 2 at 6 months.[5]

In September, Regenxbio and AbbVie announced a strategic partnership for the development and commercialization of RGX-314.[6]

ADVM-022

ADVM-022 (Adverum Biotechnologies) uses a propriety vector capsid, AAV.7m8, carrying a codon-optimized aflibercept coding sequence under the control of a proprietary expression cassette administered as a one-time IVT. Long-term data from the phase 1 OPTIC trial (n = 30) of ADVM-022 for wet AMD have demonstrated durability and maintained efficacy following a single, in-office IVT injection. Safety and efficacy data showed that 60% of patients were injection-free beyond 1 year, and patients had an 85% reduction in annualized injection frequency following a single low dose (n = 15).[7]

In July, a comparison of the data from the INFINITY clinical trial in patients with diabetic macular edema (DME) and OPTIC showed marked differences in the safety profile between the two patient populations and between the low ($2x10^{11}$ vg/eye) versus high ($6x10^{11}$ vg/eye) doses. Adverum no longer plans future development for DME after a dose-limiting toxicity was observed at the high dose in patients with DME. The company will continue to evaluate ADVM-022 at low doses ($2x10^{11}$ vg/eye and lower) and with alternative prophylactic regimens in a phase 2 clinical trial for wet AMD.[8]

Faricimab

In January, Genentech/Roche announced positive top-line results from two identically designed global phase 3 studies, TENAYA and LUCERNE, evaluating its investigational bispecific antibody, faricimab, in wet AMD. Faricimab targets angiopoietin-2 and VEGF-A. Both studies met their primary endpoint and showed that patients receiving faricimab injections at fixed intervals of up to every 16 weeks achieved visual outcomes that were noninferior to those receiving aflibercept (Eylea, Regeneron) injections every 8 weeks. Nearly half (45%) of patients in both studies were treated with faricimab every 16 weeks during the first year, and it was generally well tolerated with no new or unexpected safety signals. Both trials will continue out to 2 years to evaluate efficacy, durability, and safety, and the AVONELLE-X extension study will generate 4-year long-term data.[9]

In August, the FDA accepted the company's biologics license application, under priority review, for faricimab.

KSI-301

The phase 2b/3 DAZZLE study is a global, multicenter, randomized study designed to assess the durability, efficacy, and safety of KSI-301 (Kodiak Sciences), an investigational anti-VEGF therapy built on the company's antibody biopolymer conjugate. Patients with treatment-naïve wet AMD are randomly assigned to receive either KSI-301 on an individualized dosing regimen (every 3 to 5 months) or to receive aflibercept every 8 weeks, each after 3 monthly loading doses. The 1-year data showed that 66% of wet AMD patients in the treatment arm achieved a 6-month or longer treatment-free interval at 1 year. An average of two retreatments were given over the 10 months following three loading doses. Moreover, 78% of treated patients were on a 4-month or longer interval at 1 year. More than half (54%) of wet AMD patients required only one retreatment. A mean 5.7 letter improvement, to 69.7 ETDRS letters (~20/40 Snellen), was observed.[10]

GB-102

In September, Graybug Vision reported a full-data analysis from the 18-month ALTISSIMO trial, a masked, controlled phase 2b study consisting of two doses—1 mg and 2 mg—of GB-102 and a single control arm of patients on 2 mg aflibercept for the treatment of wet AMD. GB-102 is a proprietary formulation of sunitinib malate injected intravitreally twice a year. The primary endpoint included median time to first supportive therapy with an anti-VEGF agent. Secondary endpoints consisted of safety and pharmacodynamics, measured as the mean change in BCVA and central subfield thickness.[11]

The trial consisted of two phases, the first being a 12-month treatment phase where patients were dosed at day 1 and month 6, while the control arm received every-other-month aflibercept. The second phase included 6 months of observation to determine the effect duration.[11]

The 18-month data showed that 58% of patients participated in the extended study, and 11 participated in the 1 mg GB-102 arm, 55% of whom achieved treatment duration for 12 months or longer and maintained visual acuity and central subfield thickness. The injection burden was reduced by 73% on an annualized basis for 1 mg GB-102 patients who took part in the extended study. GB-102 was well tolerated and sustained a favorable safety profile during the extended phase. No drug-related adverse events or vision-threatening inflammation was reported.[11]

EYP-1901

In November, EyePoint Pharmaceuticals announced positive interim safety data from its phase 1 clinical trial of EYP-1901, a sustained delivery anti-VEGF treatment targeting wet AMD. EYP-1901 combines a bioerodible formulation of the Durasert (EyePoint Pharmaceuticals) sustained-release technology with vorolanib, a tyrosine kinase inhibitor (TKI).[12]

The ongoing phase 1 DAVIO open-label, dose-escalation trial has enrolled 17 wet AMD patients across three dose cohorts. All patients were previously treated with anti-VEGF therapies. At least 6 months after dosing, no serious adverse events were reported, and there have been no reported adverse events related to significant intraocular inflammation, BCVA reduction, or IOP elevation. At 4 and 6 months, 76% and 53% of patients did not require rescue following a single dose of EYP-1901, respectively. Patients experienced a 79% reduction in treatment burden at 6 months, and a median time to rescue of 6 months.[12]

TRIALS TO WATCH

OPT-302 (Opthea Limited) is a soluble form of the human VEGF receptor-3, expressed as an Fc-fusion protein designed to inhibit VEGF-C and VEGF-D. Opthea is currently recruiting approximately 990 treatment-naïve patients each into the phase 3 SHORE and COAST trials to assess the efficacy and safety of intravitreal 2.0 mg OPT-302 in combination with ranibizumab or aflibercept compared with ranibizumab or aflibercept monotherapy, respectively.[13]

Cohort 2 of OASIS, the phase 1/2a clinical trial of **CLS-AX (Clearside Biomedical)** in patients with wet AMD, completed dosing. CLS-AX is a proprietary suspension of axitinib for suprachoroidal injection. Axitinib is a TKI approved to treat renal cell cancer that achieves pan-VEGF blockade, directly inhibiting VEGF receptors 1, 2, and 3 with high potency and specificity.

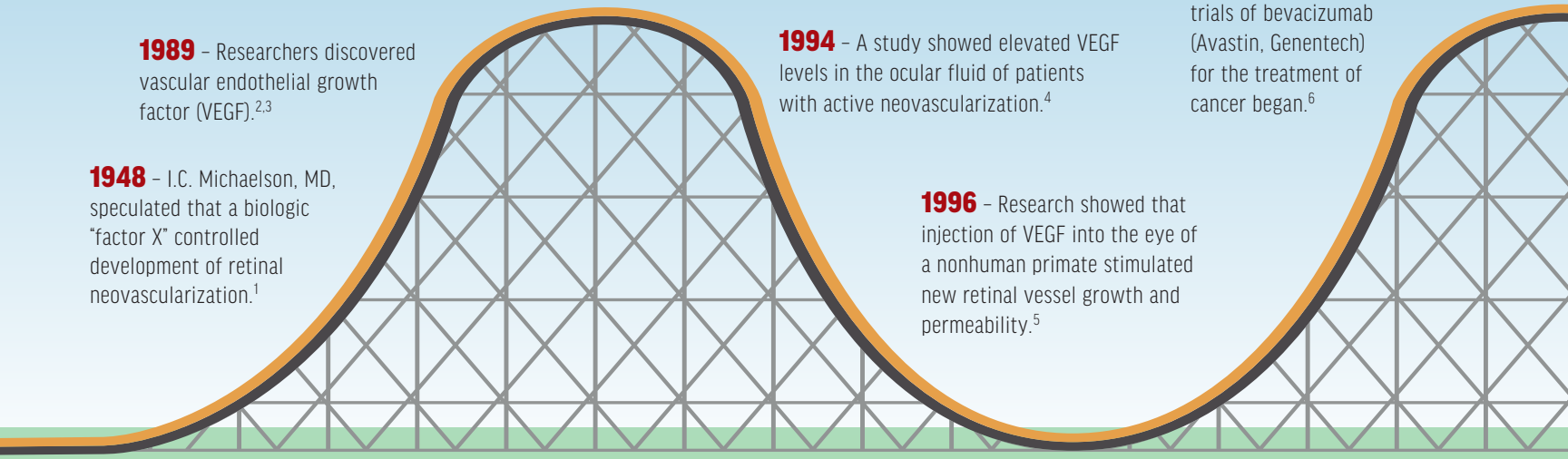
OASIS is an open-label, dose-escalation trial in wet AMD patients to assess the safety and tolerability of a single dose of CLS-AX. All patients in cohort 2 received aflibercept at their first visit and a single dose of CLS-AX at their second visit 1 month later. The primary endpoint for the trial will assess the safety and tolerability of CLS-AX at 3 months.[14]

OTX-TKI (Ocular Therapeutix) is a bioresorbable hydrogel implant incorporating axitinib being evaluated for wet AMD and other retinal diseases. Interim data from the phase 1 clinical trial assessing the safety and biological activity of the implant showed no serious ocular adverse events or IOP elevations. At month 2, some subjects in the 400 µg and 600 µg treatment arms experienced reduced central subfield thickness and durability up to 12 months; one patient experienced treatment effect for 17 months. To date, OTX-TKI has been generally well tolerated and showed preliminary biological signals of durability.[15]

CONCLUSION

Ultimately, the success of one or more of these investigational therapies is likely to generate a paradigm shift in the

THE ANTI-VEGF JOURNEY



management of wet AMD, particularly if substantially better durability is achieved. With an increasingly robust research pipeline, the future is bright for our fight against blindness from this condition. ■

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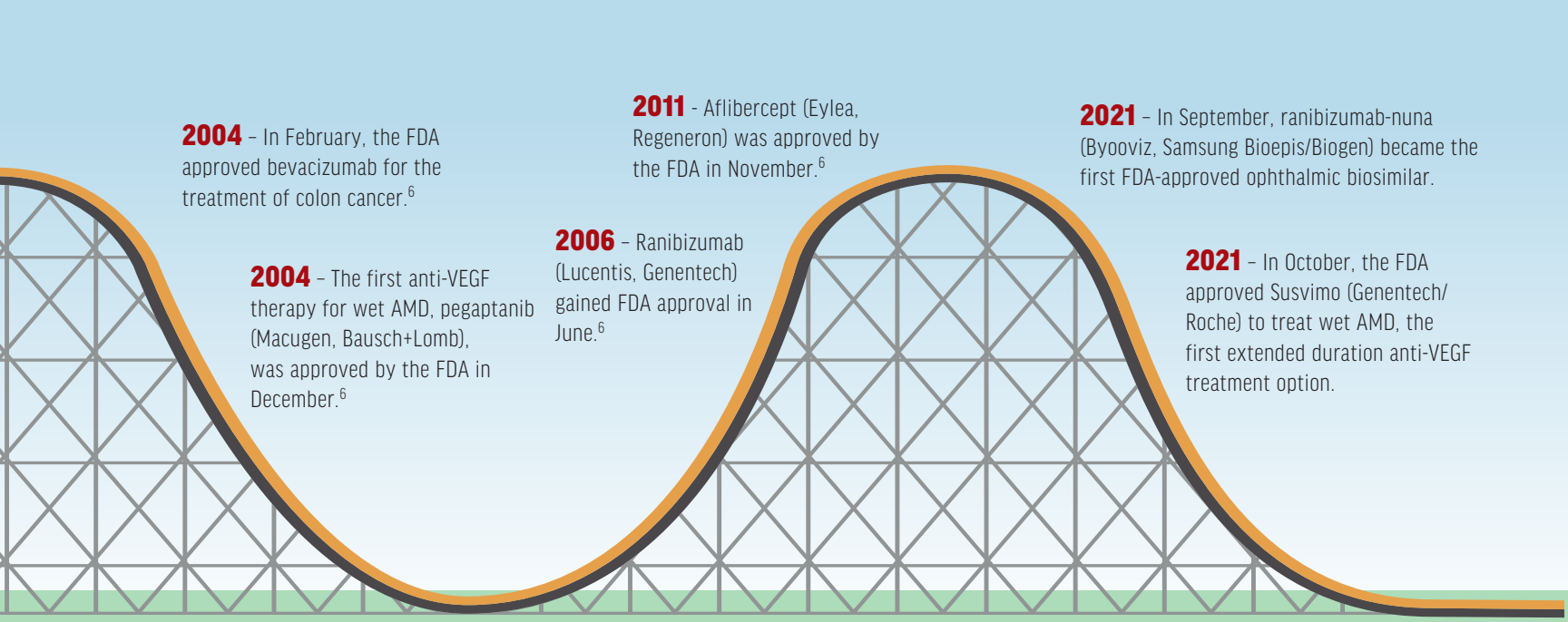

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GEOGRAPHIC ATROPHY: TARGETING THE COMPLEMENT PATHWAY

This form of AMD is creating a lot of buzz with novel therapeutics under investigation.

BY YINGNA LIU, MD, AND JEFFREY S. HEIER, MD

To date, no treatments are approved to reverse, prevent, or reduce the rate of geographic atrophy (GA) progression—an area of urgent unmet medical need as the population ages. A leading contributor to the pathogenesis of GA is complement system–mediated inflammation and retinal cell degeneration.[1] Genome-wide association studies identified polymorphisms in a number of complement proteins among patients with AMD.[2] In addition, patients with GA had alterations in complement cascade components both systemically and within the eye.[1,3] Active research is underway to find a treatment for GA, and most studies focus on the complement cascade.

This article discusses several therapies on the horizon and the latest research findings (Table).

C3 INHIBITION

Pegcetacoplan (Apellis Pharmaceuticals) is a pegylated inhibitor of complement C3. In the phase 2 FILLY study, 15-mg monthly and every-other-month intravitreal injections were found to reduce the growth rate of GA lesions by 29% ($P = .008$) and 20% ($P = .067$), respectively, compared with sham therapy at 12 months.[4]

The results of the confirmatory phase 3 OAKS study of 637 patients demonstrated that monthly injections of 15 mg/0.1 mL pegcetacoplan led to a 22% ($P = .0003$) reduction in GA lesion growth compared with sham therapy at 12 months; every-other-month treatment resulted in a 16% ($P = .0052$) reduction.[5]

The results of the second confirmatory phase 3 study, DERBY (621 patients), did not meet the primary endpoint.

In the combined analyses of the phase 3 trials, pegcetacoplan demonstrated a greater effect on eyes with extrafoveal lesions at baseline; GA lesion growth decreased by 26% ($P < .0001$) and 23% ($P = .0002$) with monthly and every-other-month injections, respectively.[5]

Pegcetacoplan was well tolerated in both phase 3 trials.[6] Combined results reported three cases of confirmed

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HOW IT STARTED

In *Retina Today*'s first issue in 2006, the Age-Related Eye Disease Study II (AREDS II) wasn't even recruiting patients yet—that didn't happen until October of that year.[1] Still, some studies were focused on geographic atrophy, also known as *atrophic macular degeneration* back then.

An implant containing encapsulated human NTC-201 cells releasing ciliary neurotrophic factor was in a phase 2 trial for participants with vision loss due atrophic macular degeneration.[1]

Another study involving patients with GA and/or choroidal neovascularization with drusen was evaluating whether certain genetic polymorphisms predisposed individuals to develop AMD.[1]

A September 2006 article shared information on complement factor H and noted that the complement factor H gene *Y402H* polymorphism appeared to account for a substantial proportion of AMD.[2]

Complement factors 3 and 5 hit the scene in 2008, with preliminary research showing a new association between complement system variations and AMD—setting the stage for where we are today with promising therapeutics targeting C3 and C5.[3]

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or suspected infectious endophthalmitis (0.047% risk per injection), 13 cases of intraocular inflammation (0.21% risk per injection), and no retinal vasculitis or vascular occlusion. Pooled phase 3 data also provided further evidence that pegcetacoplan was associated with a dose-dependent increased incidence of new-onset wet AMD with rates of 6.0% in the monthly cohort, 4.1% in the every-other-month cohort, and 2.4% in the sham group.[6]

Based on these findings, the company plans to submit a New Drug Application for pegcetacoplan for GA. Both studies will continue masked injections for a total of 24 months.

NGM621 (NGM Biopharmaceuticals) is a humanized IgG1 antibody that inhibits the enzymatic cleavage of complement C3. Unlike the other complement-targeting therapeutics for GA, NGM621 is not pegylated.[7]

In phase 1, the study agent was well tolerated with no drug-related adverse events.[7]

Currently, the phase 2 CATALINA trial is ongoing with approximately 320 patients enrolled.[8] The study is designed to randomly assign patients to receive intravitreal injections of 15 mg versus sham therapy (2:1 ratio), every 4 or 8 weeks, for a total of 52 weeks. The primary efficacy endpoint is the rate of change in GA lesion area measured by fundus autofluorescence (FAF) over the course of 52 weeks.

C5 INHIBITION

Avacincaptad pegol (Zimura, Iveric Bio), a pegylated RNA aptamer, inhibits the enzymatic cleavage of C5, thus inhibiting the downstream complement cascade and C5-mediated activities, such as those hypothesized to lead to retinal cell degeneration in GA.

The results of the pivotal phase 2/3 trial of 286 patients showed that monthly intravitreal injections of 2 mg or 4 mg avacincaptad pegol led to a reduction in the mean rate of GA growth by 27.4% (P = .0072) and 27.8% (P = .0051), respectively, over 12 months.[9] Treatment effect, measured by FAF, was observed as early as month 6 and was maintained at month 12. It was well tolerated with no drug-related adverse events and no cases of endophthalmitis. However, there was an increased risk of choroidal neovascularization or wet AMD in treated eyes, with rates of 9.0% in the 2-mg cohort and 9.6% in the 4-mg cohort compared with 3.5% in the fellow eyes and 2.7% in the sham group.[9]

A second phase 3 trial, GATHER2, completed enrollment of 448 patients.[10] Patients were randomly assigned in a 1:1 ratio to receive monthly intravitreal injections of 2 mg avacincaptad pegol or sham therapy, with a primary efficacy endpoint of the mean rate of change in GA area over 12 months.

C1Q INHIBITION

ANX007 (Annexon Biosciences) is the antigen-binding fragment of a humanized recombinant monoclonal antibody. ANX007 binds to the globular heads of C1q and blocks the downstream activation of the classical complement cascade.

Data from two phase 1 studies involving patients with primary open-angle glaucoma showed promising safety and efficacy.[11,12] The phase 2 ARCHER study is investigating the efficacy of intravitreal injections of ANX007 for patients with GA. The study is enrolling approximately 240 individuals randomly assigned to monthly or every-other-month intravitreal injections of 5 mg ANX007 or sham therapy over 12 months, followed by an off-treatment period of 6 months. The primary efficacy endpoint is the change in GA lesion area.[13]

GENE THERAPY

HMR59 (Hemera Biosciences) consists of a recombinant adeno-associated viral (AAV2) vector containing the *sCD59* gene. CD59 is a glycosylphosphatidylinositol-anchored membrane inhibitor of the membrane attack complex. It prevents the recruitment of complement C9.[14] Membrane attack complex is the terminal step of an activated complement cascade.

A completed phase 1 study of HMR59 investigated the dose-escalating safety and tolerability of a single intravitreal injection for GA with a total of 17 patients.[15] No systemic or severe adverse events were associated with HMR59 injections. Mild ocular inflammation occurred in three patients' treated eyes, including two eyes that developed vitreous inflammation that resolved after 6 weeks of observation and one eye that developed anterior chamber and vitreous inflammation that resolved with topical corticosteroids. None of the 17 patients converted to wet AMD during the 18-month follow-up period.

TABLE. NOVEL THERAPIES FOR GA THAT TARGET THE COMPLEMENT PATHWAY

Study Drug (Company)	Complement Target	Delivery Method	Current Trial Phase	Most Recent Trial(s)	Study Status
Pegcetacoplan (Apellis)	C3	IVI	3	OAKS, DERBY	Active, not recruiting
Avacincaptad pegol/ Zimura (Iveric Bio)	C5	IVI	3	GATHER2	Active, not recruiting
NGM621 (NGM)	C3	IVI	2	CATALINA	Active, not recruiting
ANX007 (Annexon)	C1q	IVI	2	ARCHER	Recruiting
HMR59 (Hemera)	C9	IVI	1	HMR-1001	Completed
GT005 (Gyroscope Therapeutics)	Complement factor I	Subretinal	1/2 and 2	FOCUS, EXPLORE, HORIZON	Recruiting

Abbreviations: GA, geographic atrophy; IVI, intravitreal injection.

GT005 (Gyroscope Therapeutics) is a recombinant AAV2 vector that contains a nucleotide sequence encoding complement factor I (CFI). The therapy, delivered via subretinal injection, is designed to enable cellular transduction and induce secretion of CFI. While low serum CFI levels have been associated with a much higher risk of AMD,[4] an increase in intraocular CFI level could dampen an overactivated alternative complement pathway and potentially reduce AMD progression.[16]

FOCUS is a phase 1/2 study evaluating the safety and tolerability of subretinal delivery of GT005 gene therapy in patients with GA. Dose escalation cohorts 1 to 3 have completed dosing via transvitreal delivery, and cohort 4, a dose expansion cohort, is still enrolling.[17] Cohorts 5 to 7 receive gene therapy via the Orbit Subretinal Delivery System (Gyroscope Therapeutics).[18]

Interim results from cohorts 1 to 4 showed that GT005 subretinal delivery was well tolerated.[18,19] There was an average increase of 146% in CFI levels compared with baseline. The first patient treated had a sustained CFI increase at 84 weeks. In addition, reductions in downstream complement biomarkers were detected, with an average decrease of 42% in C3 breakdown proteins and a 41% decrease in Ba levels compared with weeks 24 and 56.

Two phase 2 studies, EXPLORE and HORIZON, are actively enrolling patients.[20,21] Both studies are evaluating the safety and efficacy of two doses of GT005 administered as a single subretinal injection, with GA lesion growth measured by FAF at 48 weeks as the primary efficacy endpoint.

HTRA1 INHIBITION

An outlier to the complement pathway inhibitors, FHTR2163 (Genentech) is an antigen-binding fragment of a humanized monoclonal antibody against the high-temperature requirement A1 protein. A single nucleotide polymorphism associated with elevated expression levels of the high-temperature requirement A1 protein was estimated to confer a risk of 49.3%.[1]

FHTR2163 was well tolerated in phase 1, with no dose-limiting toxicities, ocular serious adverse events, or drug-related systemic adverse events reported.[2] The phase 2 GALLEGO study is ongoing. It is evaluating the efficacy of intravitreal injections of 20 mg FHTR2163 every 4 or 8 weeks over the course of 76 weeks.[3] The primary efficacy endpoint is the growth of GA lesion area measured on fundus autofluorescence imaging from baseline to 72 weeks.

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NEXT STEPS

These data are encouraging, and we are certainly getting closer to finding an effective treatment for GA, but we aren't there yet. We will continue to follow these trials closely to assess each therapy's safety and efficacy. ■

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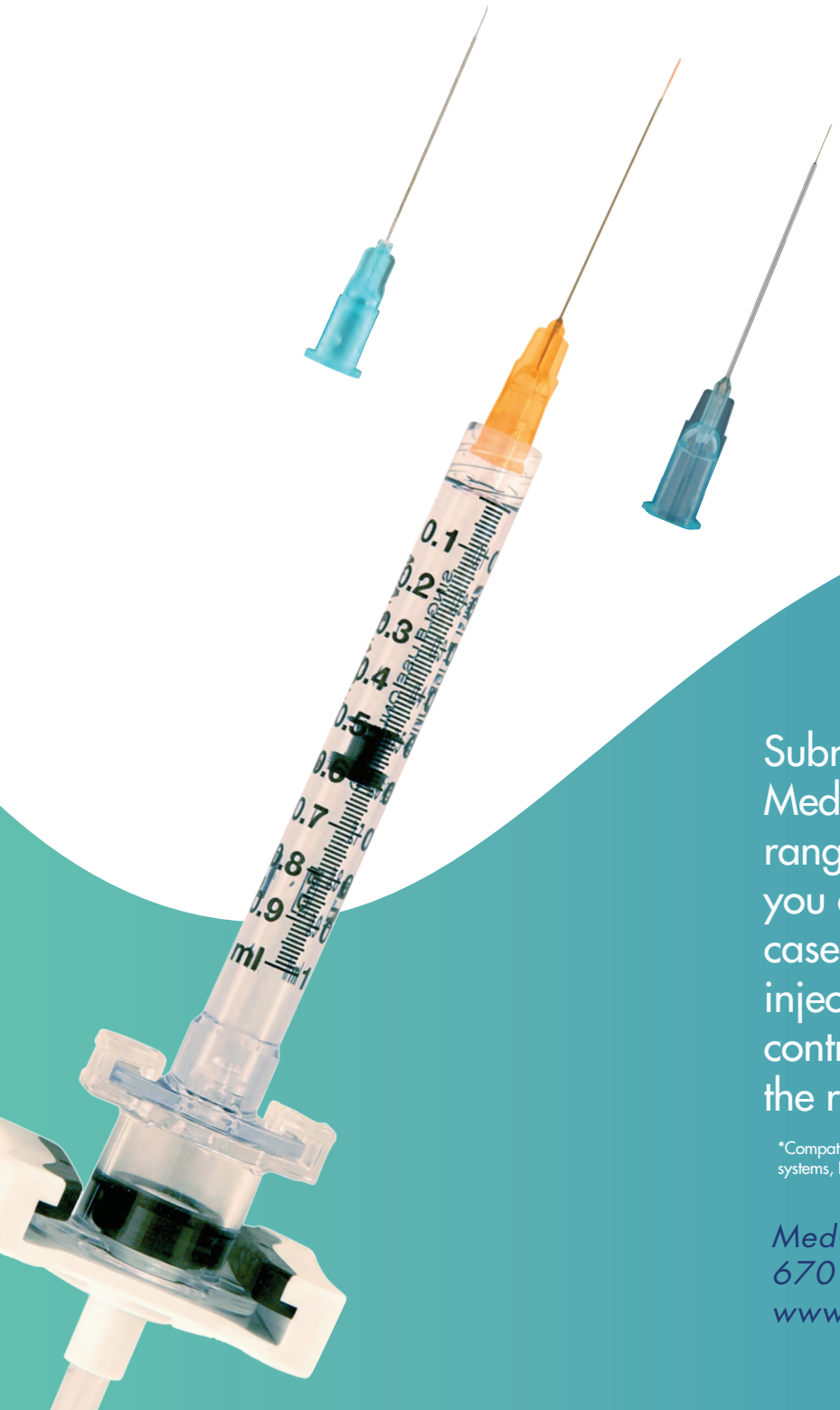

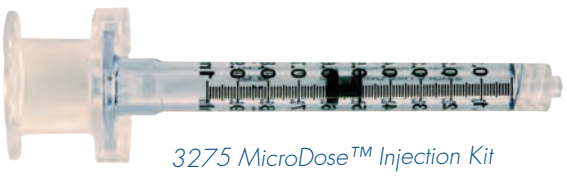

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SURGICAL INNOVATIONS TO TREAT MEDICAL RETINAL DISEASES

Several advances working their way through clinical trials have the potential to change our approach to patient care.

BY JORDAN D. DEANER, MD, AND LEJLA VAJZOVIC, MD, FASRS

The primary treatment approach for retinal diseases, particularly for wet AMD, has oscillated between medical management (in-office laser treatment, injections, and systemic therapies) and surgical management (subretinal choroidal neovascular membrane removal, macular translocation, and surgical transplantation of the retinal pigment epithelium [RPE]). The introduction of anti-VEGF therapy effectively sidelined the surgical management of wet AMD.[1] The widely adopted off-label use of intravitreal bevacizumab (Avastin, Genentech) drove the treatment of wet AMD further into the medical realm.[2]

A similar treatment trend is occurring with diabetic retinopathy (DR), with a shift from primary surgical correction of proliferative DR complications, such as vitreous hemorrhage and tractional retinal detachments, toward prevention of these complications altogether using anti-VEGF therapies.

PANORAMA is a phase 3 clinical trial assessing patients with moderately severe to severe nonproliferative DR without center-involving diabetic macular edema treated with loading doses of aflibercept (Eylea, Regeneron) followed by fixed-interval injections or sham injections. At years 1 and 2, fewer patients in the aflibercept arms developed a vision-threatening complication due to proliferative DR, including vitreous hemorrhage and tractional retinal detachments, either of which would require surgical intervention.[3,4]

Potential in-office intravitreal anti-VEGF therapies now in phase 2 and 3 trials include faricimab (Genentech/Roche), conbercept (Chengdu Kanghong Biotech), OPT-302 (Opthea), KSI-301 (Kodiak), and GB-102 (Graybug Vision).[5-20] Many of these promise increased durability or sustained release for the treatment of neovascular AMD and DR.

(*See pages 20 and 26 for more on these therapies.*)

WET AMD SURGICAL INNOVATIONS

The medical retina pipeline is robust, but so is the surgical pipeline—and it's already proving fruitful. In October, the FDA approved the port delivery system with ranibizumab (Susvimo, Genentech/Roche), expanding our clinical armamentarium for wet AMD. Several other innovations on the horizon have the potential to revolutionize the treatment of retinal disease, and many of them harness the power of gene

15TH ANNIVERSARY ISSUE

HOW IT STARTED

Retina surgery has changed dramatically since *Retina Today*'s first issue. Surgeons in 2006 were still hotly debating the utility of 25-gauge surgery, with some concluding that the time saved by the sutureless technique was lost because of the longer surgery time.[1,2]

Autologous transplantation of retinal pigment epithelium remained a go-to treatment option for many patients with AMD, and meeting lecturers were still trying to figure out when it was appropriate to forego anti-VEGF therapy in favor of the tried-and-true subretinal surgical removal of neovascular membranes.[3,4]

Oh, and that implantable miniature telescope (SING IMT, Samsara) that's now in its second generation?[5] The FDA's Ophthalmic Devices Advisory Panel suggested it was "not approvable" in July 2006.[6]

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therapy to provide continuous dosing of medications.

RGX-314 (Regenxbio) is a novel adeno-associated virus serotype 8 vector used to deliver a gene encoding for an anti-VEGF antigen-binding fragment. It is designed to produce continuous anti-VEGF therapy to treat wet AMD and DR.[21-23] Subretinal delivery of this therapy requires a pars plana vitrectomy (PPV) followed by creation of a subretinal bleb using a 41-gauge needle (Figure).[21,24]

The phase 1/2a clinical trial of patients with wet AMD is complete with 2-year data from all five dose cohorts. Patients in cohorts 3, 4, and 5 showed improved vision and a significant reduction in the need for supplemental anti-VEGF injections. Anti-VEGF protein levels were dose-dependent and durable for at least 2 years.[21,24] All six patients in cohort 3 enrolled in the long-term follow-up study, and treatment effect was demonstrated over 3 years with a mean BCVA improvement of +12 letters from baseline. Cohort 3 showed a 66.7% decrease in the rate of annual anti-VEGF injections compared with the 12 months prior to RGX-314 therapy. Cohorts 4 and 5 showed a 58.3% and 81.2% reduction of anti-VEGF injections, respectively, at 1.5 years. Both cohorts experienced stable vision and decreased retinal thickness.[24]

Notably, no immunologic reactions, drug-related ocular inflammation, or postsurgical inflammation was seen beyond what is anticipated after routine PPV.[21] However, retinal pigmentary changes in 69% of patients necessitated a change in the surgical technique to help prevent macular changes.[21,25]

The phase 2b/3 ATMOSPHERE trial is now recruiting and will randomly assign 300 pseudophakic patients with wet AMD to receive subretinal RGX-314 or monthly intravitreal ranibizumab. The primary endpoint is the change in visual acuity compared with monthly ranibizumab at week 54.[26]

Oscillating back to medical management, the phase 2 AAVIATE and ALTITUTE trials are assessing in-office suprachoroidal injection of RGX-314.[22,23]

GEOGRAPHIC ATROPHY SURGICAL INNOVATIONS

Geographic atrophy (GA) is a disease for which an efficacious surgical intervention might have the greatest impact. Future surgical therapies for GA will rely on early detection followed either by gene therapy to slow the progression of GA or cellular therapy to replace damaged RPE cells.

In the HORIZON and EXPLORE phase 2 clinical trials, **GT005 (Gyroscope Therapeutics)** is surgically injected into the subretinal space via a pars plana approach.[27,28] GT005 is an adeno-associated virus vector designed to deliver a gene encoding for complement factor I.[27-29] The FOCUS phase 1/2 is a safety and dose-finding study where GT005 is delivered subretinally using either a transvitreal approach (cohorts 1–4) or the Orbit Subretinal Delivery Device System (Gyroscope Therapeutics) where GT005 is delivered via suprachoroidal cannulation (cohorts 5–7).[29] Interim data showed that GT005 was well tolerated at all doses and treatment resulted in sustained increases in

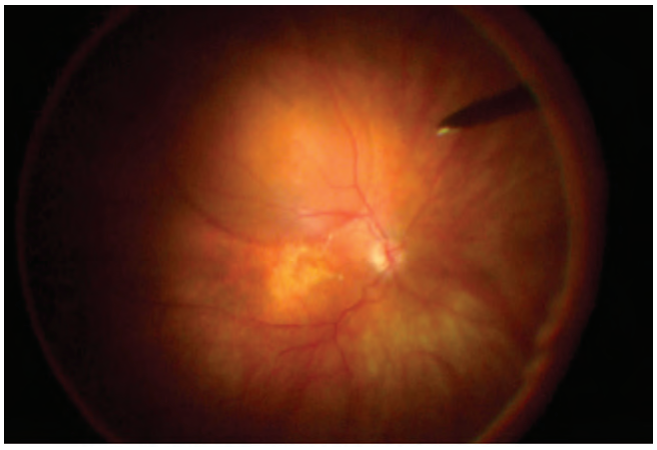

Image courtesy of Jeffrey S. Heier, MD

Figure. A subretinal bleb of RGX-314.

OUT OF THE PIPELINE AND INTO PRACTICE

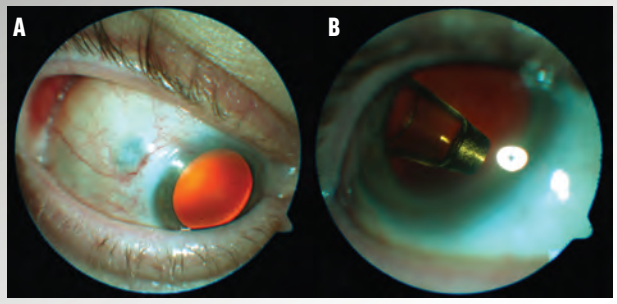

Figure. These images of the PDS demonstrate excellent postoperative closure of the overlying conjunctiva (A) and good intraocular positioning in the vitreous chamber (B).

The port delivery system (PDS) with ranibizumab (Susvimo, Genentech/Roche) gained FDA approval in October.[1] The permanent, refillable intraocular implant is filled with the concentrated formulation in the OR and then surgically implanted through a pars plana incision (Figure). Subsequent refill-exchange procedures are performed in the office.

The approval comes on the heels of positive data from the phase 3 ARCHWAY study, in which patients with wet AMD in the PDS treatment arm achieved and maintained vision gains equivalent to those who recieved monthly ranibizumab injections at weeks 36 and 40 of treatment. Notably, 98.4% of patients in the PDS arm did not require supplemental treatment out to the first refill-exchange at 24 weeks.[2]

PAGODA and PAVILION are phase 3 randomized trials evaluating the PDS with ranibizumab in the treatment of diabetic retinopathy.[3,4]

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vitreous complement factor I levels in the majority of patients.[30] There have been no clinically significant GT005-related ocular inflammatory events.[30]

A phase 1/2a clinical trial at the National Eye Institute is evaluating the feasibility of **subretinal transplantation of induced pluripotent stem cell–derived RPE**.[31] Induced pluripotent stem cells are generated from a GA patient's somatic cells, differentiated into RPE cells, and grown on a monolayer of biodegradable polylactic-co-glycolic acid scaffold. The cells are then transplanted into the subretinal space of the same patient with the goal of rescuing the overlying neurosensory retina from further degradation.[31-33] A PPV is required, and the transplant is placed through a planned retinotomy, requiring a gas tamponade.[31]

OpRegen (Lineage Cell Therapeutics) uses human embryonic stem cell–derived RPE cells that are transplanted subretinally in patients with GA. The phase 1/2a trial includes four cohorts, the first three of which are complete. Data show that the treatment was well tolerated with no unexpected adverse events and no inflammatory events. At 15 months, treated eyes had a statistically significant improvement in BCVA compared with the fellow eyes. Early OCT imaging suggests the possible resolution of incomplete RPE and outer retinal atrophy after treatment.[34]

FINAL THOUGHTS

Inevitably, the primary treatment of retinal diseases will continue to oscillate between medical and surgical interventions as new approaches emerge. We have an arsenal of therapeutics, many of which are surgical, on the horizon that may provide a longer duration of therapy and perhaps even permanent solutions to these challenging diseases. ■

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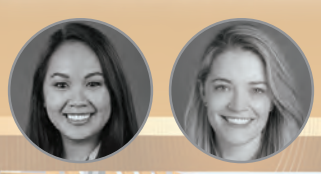
EXPANDING YOUR TOOLBOX WITH BIOSIMILARS



New options are under investigation—and some are already headed to the retina clinic.

BY HONG-UYEN HUA, MD, AND ALEKSANDRA RACHITSKAYA, MD

Biologics—large, complex molecules produced by various biotechnologies and living cell processes—are mainstays of pharmacologic therapy. Biosimilars are biological products that, as the name suggests, are structurally highly similar to their corresponding FDA-approved reference products; there are no clinically meaningful differences in safety and efficacy compared with their references.[1] Bevacizumab (Avastin, Genentech), ranibizumab (Lucentis, Genentech), aflibercept (Eylea, Regeneron), and brolucizumab (Beovu, Novartis) serve as FDA-approved anti-VEGF biologic reference products, although bevacizumab is approved for nonretinal indications.[1]

Because biosimilars are not exact formulaic copies of biologic reference products, there is concern about immunogenicity.[2] It is important to note that biosimilars are not generic drugs, though both may offer more affordable treatment options for patients.

Generic drugs are derived from simpler organic pharmacologic chemical reactions. They have the exact same active ingredient and chemical formulation as branded drugs and are bioequivalent (eg, acetaminophen vs Tylenol [Johnson & Johnson]). Biosimilars are more complex, involving reverse-engineered biologic systems and living cell lines; they may also have minor differences in inactive products compared with the biologic reference product (Figure).

APPROVAL AND ECONOMICS

The cost and time to develop drugs vary significantly depending on the type.[2-4] A biologic reference drug takes 10 to 15 years to develop, costing $1.2 to $2.5 billion. Biosimilars take 8 to 10 years and $100 to $200 million to develop, and generics take 3 to 5 years and $1.0 to $5.0 million to develop.

Once similar pharmacokinetics and pharmacodynamics are established, biosimilars require fewer clinical trials than biologic reference drugs.[3] After biosimilarity has been established for a product, it may be approved for all the same indications as the reference drug through extrapolation.[3] In theory, these savings pass to the patient, and it is estimated that biosimilars may save more than $100 billion by 2024.[4]

INDIA'S BIOSIMILAR EXPERIENCE

India's experience with Razumab (biosimilar ranibizumab, Intas Pharmaceuticals) provides important insight into the ophthalmic biosimilar experience.

15TH ANNIVERSARY ISSUE

HOW IT STARTED

Biosimilars weren't even part of the conversation when *Retina Today* first launched. In fact, the reference drug ranibizumab (Lucentis, Genentech) was still under FDA review when we published our first issue in March 2006.[1]

It wasn't until April 2015 that *Retina Today* even used the word *biosimilar*. We reported on the first FDA approval of any biosimilar, filgrastim-sndz (Zarxio, Sandoz) to treat patients with leukemia.[2]

Anti-VEGF biosimilars debuted in the magazine in 2017.[3] The phase 3 trial for FYB201 (Formycon and Bioeq) was still enrolling patients, and the now approved ranibizumab-nuna (Byooviz, Samsung Bioepis/Biogen) wasn't even in the picture yet.

1. Singh RP, Kaiser PK. Targeting VEGF in AMD. *Retina Today*. 2006;1(1).
2. Medical Update. *Retina Today*. 2015;10(3):19.
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Compounding pharmacies are rare in India; furthermore, insurance companies do not always reimburse for anti-VEGF therapy. Thus arose an unmet need for affordable anti-VEGF agents, and researchers in India quickly found themselves on the frontier of biosimilar development. In 2015, the Drug Controller General of India approved Razumab. The RE-ENACT Razumab study was a 12-week retrospective, non-comparative, multicenter study of pooled patients with wet AMD, diabetic macular edema, and retinal vein occlusion. The data showed overall improvements in BCVA and central macular thickness.[5]

Razumab became the world's first biosimilar for ranibizumab, and it was rapidly adopted in India. A survey by Sheth et al showed that use of Razumab by vitreoretinal specialists in India grew from 41% in 2018 to 56% in 2020.[6] Since then, several biosimilars of bevacizumab have been approved in India, such as Zybev (Zydus Cadila) and Bevatas (Intas Pharmaceuticals), although retina specialists in India have been slower to adopt these.[6]

Razumab's rapid adoption in India has not been without controversy. Clusters of sterile endophthalmitis were reported in patients treated with early batches of the drug in 2015 as well as in 2017 and 2019; these reports may have contributed to adoption hesitancy.[6,7]

BIOSIMILARS IN THE UNITED STATES

Ranibizumab-nuna (Byooviz, Samsung Bioepis/Biogen) is the United States' first FDA-approved ophthalmic biosimilar. Woo et al conducted a phase 3 randomized controlled trial with wet AMD patients that showed equivalent BCVA, central subfield thickness improvements, and low immunogenicity in the biosimilar group compared with the ranibizumab group.[8] These results suggest that ranibizumab-nuna is a viable and safe alternative biosimilar treatment for the biologic reference drug ranibizumab.

However, the cost of the drug remains to be seen, as neither Samsung nor Biogen has commented on its potential pricing strategy. Notably, ranibizumab-nuna will not be brought to the US market until June 2022, due to a licensing agreement with Genentech.[9]

The buzz surrounding biosimilars continues to build in the United States, propelled in part by two bills signed into law on April 23, 2021: The Ensuring Innovation Act and the Advancing Education on Biosimilars Act.[10] The goal of these two bills is to educate health care professionals about biosimilars and promote generic and biosimilar competition.

Numerous ophthalmic biosimilars are in the pipeline and are discussed in this article (Table).

Ranibizumab

Another biosimilar on the horizon for this reference agent is FYB201 (Formycon and Bioeq). The phase 3 COLUMBUS-AMD trial met its primary endpoint and showed no significant difference in BCVA improvement or adverse events between FYB201 and ranibizumab for the treatment of wet AMD.[11] Formycon and Bioeq announced submission of a biologics license application (BLA) for FYB201 on August 5, 2021. If it's approved, Coherus BioSciences will exclusively distribute FYB201 in the United States, starting as early as 2022.[12]

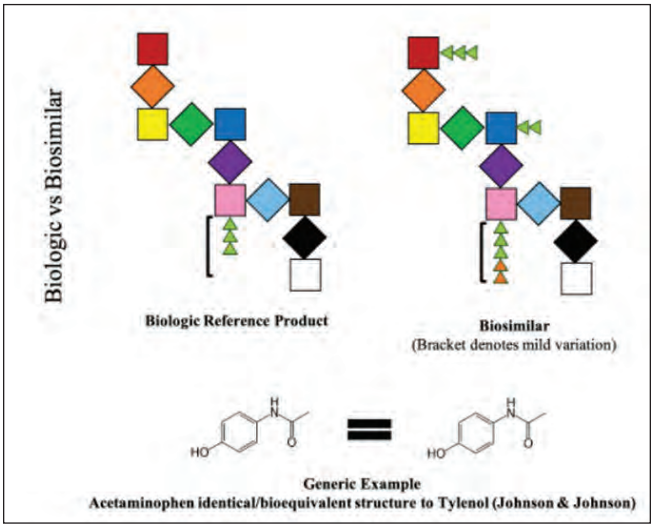

Figure. Biosimilars are reverse-engineered and may have minor differences compared with the biologic reference product.

The ranibizumab biosimilar Xlucane (Stada Arzneimittel and Xbrane Biopharma) recently met the primary endpoint of equivalent improvement in BCVA after 8 weeks of treatment of wet AMD in the multicenter phase 3 XPLORE trial; adverse events and immunogenicity were similar between the two treatment groups.[13] Xbrane plans to submit a BLA in the second half of 2021, according to the company.[13]

PF582 (Pfenex) is another ranibizumab biosimilar under investigation, although development has been on hiatus.[14]

Aflibercept

Formycon and Bioeq are sponsoring the phase 3 MAGELLAN-AMD trial for aflibercept biosimilar FYB203 and are expecting to introduce the product to the US market in 2024.[15] MYL1710 (Momenta Pharmaceuticals and Mylan) is being studied in a phase 3 randomized controlled trial for diabetic macular edema treatment.

Other potential aflibercept biosimilars under investigation include ALT-L9 (Alteogen), ABP 938 (Amgen), SB15 (Samsung Bioepis/Biogen), CT-P42 (Celltrion), SOK583A1 (Sandoz), and SCD411 (Sam Chun Dang Pharm).[16-21]

Bevacizumab

Given the cost-effectiveness, safety, availability, and popularity of off-label bevacizumab, the demand for a biosimilar in the United States may be limited. Nevertheless, at least

TABLE. OPHTHALMIC ANTI-VEGF BIOSIMILARS IN THE PIPELINE

Biosimilar	Reference Biologic	Clinical Trial Phase	Developer(s)
FYB201	Ranibizumab	Phase 3 complete BLA submitted	Formycon and Bioeq
Xlucane	Ranibizumab	Phase 3 complete	Stada Arzneimittel and Xbrane Biopharma
PF582	Ranibizumab	Phase 1/2	Pfenex
FYB203	Aflibercept	Phase 3	Formycon and Bioeq
MYL1710	Aflibercept	Phase 3	Momenta Pharmaceuticals and Mylan
ABP 938	Aflibercept	Phase 3	Amgen
SCD411	Aflibercept	Phase 3	Sam Chun Dang
CT-P42	Aflibercept	Phase 3	Celltrion
SOK583A1	Aflibercept	Phase 3	Sandoz
ALT-L9	Aflibercept	Phase 1	Alteogen
Bevacizumab-vikg (ONS-5010/Lytenava)	Bevacizumab	Phase 3	Outlook Therapeutics

Abbreviations: BLA, biologics license application.

one is in the works. Bevacizumab-vikg (Lytenava/ONS-5010, Outlook Therapeutics) is an ophthalmic preparation of bevacizumab designed to address the potential complications of off-label use of repackaged bevacizumab. Bevacizumab-vikg showed a favorable safety profile similar to that of bevacizumab in the NORSE THREE phase 3 trial, and the company plans to file a BLA in the first quarter of 2022.[22]

Importantly, the AAO recently denounced the push by insurance companies for the off-label use of nonophthalmic bevacizumab biosimilars bevacizumab-bvzr (Zirabev, Pfizer) and bevacizumab-awwb (Mvasi, Amgen).[23] These biosimilars, approved for intravenous therapy for oncologic indications, have never been tested in the eye.

FUTURE DIRECTIONS

The anti-VEGF biosimilar pipeline is booming, and many promising cost-effective alternatives are working their way through trials. Immunogenicity remains a concern, although current data from phase 3 clinical trials showed similar safety profiles to biologic reference drugs. It is critical that ophthalmic and retina providers educate themselves on the differences between biologics, biosimilars, and generics.

Given the favorable safety profile and widespread availability of current biologic reference anti-VEGF agents in the United States, the future adoption of biosimilars remains to be seen. Retina specialists will have to consider many factors, including immunogenic and overall safety profile, availability, cost, and effectiveness. ■

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LONG-TERM OUTCOMES OF ANTI-VEGF THERAPY


Data out to 5 years provide new insights into efficacy and burden of treatment in AMD and other conditions.

BY THOMAS A. CIULLA, MD, MBA, AND REHAN M. HUSSAIN, MD

Wet AMD, diabetic macular edema (DME), and retinal vein occlusion–related macular edema (RVO-ME) are leading causes of legal blindness in the industrialized world. In randomized clinical trials (RCTs), anti-VEGF agents have yielded meaningful improvements in vision for patients with these conditions. However, outcomes studies have demonstrated that patients in real-world situations receive fewer anti-VEGF injections and experience less visual improvement after 1 year than do those receiving protocol-based anti-VEGF therapy in large RCTs, with underperformance by approximately 8 to 9 letters for branch RVO-ME (BRVO-ME), 6 to 9 letters for central RVO-ME (CRVO-ME), 5 to 8 letters for DME, and 4 to 8 letters for wet AMD.[1-15]

There is a dearth of large long-term clinical outcomes studies of anti-VEGF therapy for these disorders. In wet AMD, small extension studies of RCTs have shown that visual acuity declines over time with a gain from baseline of only 2 letters by year 4,[16] loss of 3 letters by 5.5 years,[17] and loss of 8.6 letters by 7.3 years.[18] In these studies, injection frequency declined meaningfully after cessation of the initial clinical trial protocol–mandated treatments. Similarly, in a DME extension study, mean VA improved from baseline by 7.4 letters at 5 years, but it had decreased by 4.7 letters between 2 and 5 years.[19]

REAL-WORLD STUDY

We recently assessed clinical outcomes in 130,247 eyes out to 5 years for DME and wet AMD and 3 years for RVO-ME using a large database of electronic health records (EHRs) from a demographically and geographically diverse panel of retina specialists in the United States.

Mining EHR data has many limitations, including its retrospective nature, the use of aggregated data, and lack of standardization of visual acuity assessments. Still, the data can yield important longitudinal insights to better understand patient outcomes in clinical practice.

Treatment-naïve wet AMD, DME, CRVO-ME, and BRVO-ME patients who underwent anti-VEGF injections between 2014 and 2019 were included in this study. To understand how treatment intensity and initial visual acuity influenced outcomes, results were also stratified by number of anti-VEGF injections and by baseline visual acuity.

With respect to baseline features, two-thirds of wet AMD patients were women, whereas sex distribution was more equal for RVO-ME and DME patients (Table 1). DME patients were the youngest on average (mean age of 60). Mean age for RVO-ME and wet AMD patients was in the

TABLE 1. BASELINE FEATURES

	Wet AMD	DME	BRVO-ME	CRVO-ME
Number of Eyes				
1 year	67,666	40,832	12,451	9,298
3 years	21,305	7,728	3,027	2,264
5 years	5,208	1,192		
Female				
1 year	64%	46%	56%	51%
3 years	65%	48%	56%	51%
5 years	66%	50%		
Mean Age (years)				
1 year	79.9	60.6	71.9	72.5
3 years	79.2	60.3	71.6	72.2
5 years	78.2	60.0		
Mean Baseline VA (letters)				
1 year	54.3	60.1	56.2	43.2
3 years	56.7	62.8	57.8	46.7
5 years	57.4	62.7		

TABLE 2. TOP-LINE RESULTS

	Wet AMD	DME	BRVO-ME	CRVO-ME
Number of Eyes				
1 year	67,666	40,832	12,451	9,298
3 years	21,305	7,728	3,027	2,264
5 years	5,208	1,192		
Mean Number of Injections				
1 year	7.6	6.2	7.1	7.3
3 years	19.5	15.4	18.2	18.8
5 years	32.0	26.0		
Mean Change in VA (letters)				
1 year	+3.1	+4.7	+9.5	+8.3
3 years	-0.2	+3.3	+7.7	+6.0
5 years	-2.2	+3.1		

early 70s and late 70s, respectively. The mean baseline visual acuity was lowest for CRVO-ME and highest for DME.

OUTCOMES

DME patients received the fewest injections on average and wet AMD patients received the most during each period studied (Table 2). Despite receiving the most injections, wet AMD patients gained the fewest letters at each point, whereas BRVO-ME patients gained the most. Across all disorders, 3- and 5-year data showed worse outcomes compared with 1-year outcomes. This study's 1-year outcomes are consistent with those from earlier smaller studies that used the same database, revealing underperformance compared with RCTs (Figure). Across all disorders, the greatest number of injections occurred in year 1, which may partially account for the declining visual acuity results over time.

Cross-trial comparisons are limited by differences in eligibility criteria, therapeutic regimens, and endpoint evaluations, including nonstandardized visual acuity assessments in real-world studies. Nevertheless, the results presented here are similar to those of other long-term real-world studies with smaller sample sizes. The LUMINOUS study was a 5-year global, multicenter, open-label observational study evaluating real-world ranibizumab use in wet AMD.[20] Recent data from the Belgian cohort of 229 wet AMD patients showed that injection frequency declined over time irrespective of prior treatment status, with treatment-naïve eyes receiving a mean of 4.2 ± 2.9 yearly injections and those with prior ranibizumab treatment receiving 3.6 ± 2.7. Regression analysis confirmed visual acuity increases for treatment-naïve eyes of 3.9 letters (P = .002) in year 1, followed by a slight decrease of 1.8 letters per year.[20]

Another retrospective study of 95 eyes reported 8-year real-world outcomes in eyes with wet AMD receiving as-needed ranibizumab treatment.[21] A mean of 31.6 injections were given over the 8-year period, with a median of six injections in the first year and three injections in the eighth year. Baseline median VA was 61 ETDRS letters, increasing to 70 letters after initial loading doses but decreasing to 55 letters by year 8 (mean VA change from baseline -9.1 letters). Stable or improved vision was maintained in 47% of eyes at year 8.[21]

A 12-year retrospective study of 7,802 wet AMD patients reported that patients were more likely to experience positive visual outcomes (70 letters) within 2 years of beginning treatment, maintaining this vision for 1.1 years before deteriorating to poor vision (35 letters) within 8.7 years.[22]

The visual outcomes for DME and RVO patients were less favorable in our study compared with other smaller long-term studies. With respect to DRCR Retina Network's Protocol T, approximately two-thirds of DME patients had 5-year follow-up data and had been managed at clinician discretion (simulating real-world treatment patterns) during the 3 years after Protocol T completion. Between years 2 and 5, 68% of eyes had at least one anti-VEGF injection (a median of four injections). Mean VA improved by 7.4 letters from baseline (compared with +3.1 letters in our study) but had decreased by 4.7 letters between year 2 and 5.[19]

Compared with our study, 8-year vision outcomes for anti-VEGF treatment in RVO were favorable in a retrospective multicenter study of 94 eyes.[23] Despite being followed for 5 years longer than our study, BRVO-ME eyes gained 14.3 letters and CRVO-ME eyes gained 14.4 letters from baseline (compared with +7.7 and +6.0 in our study, respectively), while receiving a mean of four injections in year 8.[23]

UNDERTREATMENT

A common explanation for poor visual outcomes in real-world studies is undertreatment. For all disease states in our study, final visual acuity generally increased with greater treatment intensity. Of note, wet AMD patients who were treated with ≤ 43 injections over 5 years lost visual acuity on average, and the greatest losses were seen in those that received ≤ 21 injections. BRVO-ME and CRVO-ME patients at 3 years and DME patients at 5 years generally did not lose vision in any of the subgroups of treatment intensity.

One reason for fewer injections in the real world than in RCTs is the adoption of variable-frequency anti-VEGF therapy regimens that aim to decrease treatment burden for patients. The 2015 American Society of Retina Specialists Preferences and Trends survey of over 2,700 retina specialists in 60 countries found that more than 90% of responding retina specialists used OCT-guided variable-frequency anti-VEGF treatment protocols for patients with wet AMD.

Multiple prospective RCTs have demonstrated that variable-frequency anti-VEGF therapy for wet AMD results in a less favorable visual outcome compared with fixed, frequent anti-VEGF injections.[24-28] In CATT, for example, patients assigned to monthly treatment experienced a

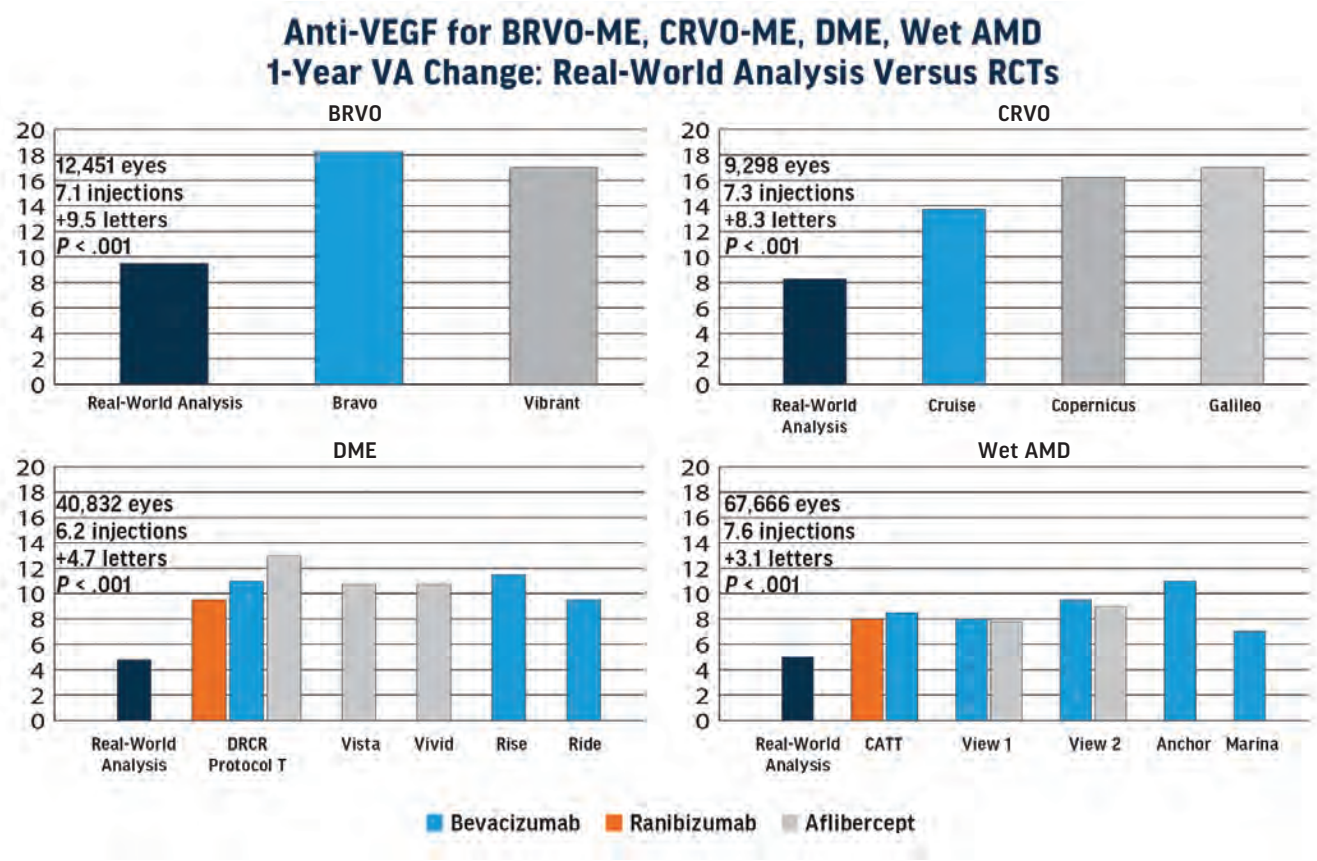


Figure. Mean 1-year visual acuity change: real-world outcomes versus randomized clinical trials.

statistically significant greater benefit in visual acuity gain compared with those receiving as-needed therapy (difference, 2.4 letters at 2 years; $P = .046$).[24]

Two studies have shown favorable outcomes for a treat-and-extend (TAE) regimen: the LUCAS study, which compared ranibizumab and bevacizumab for wet AMD,[29] and the small, prospective, controlled TREX-AMD study, which compared TAE versus monthly dosing of ranibizumab.[30] The mean number of treatments in the first year was 10.1 in the TREX study and 8.0 for ranibizumab and 8.9 for bevacizumab in the LUCAS study. Like the fixed, frequent regimens, the treatment intensity in these TAE studies also exceeded that of the current study, further supporting that relative undertreatment takes place in the real world.

BASELINE VISION AND OUTCOMES

When eyes were stratified by baseline visual acuity, the mean number of injections was similar across all groups; however, there was a consistent trend of diminishing improvement with better baseline visual acuity for all disease states at the end of year 3. Eyes with a mean baseline visual acuity of 20/40 or better had worsening vision for all conditions at the end of year 3, with losses of 6.4, 3.5, 2.9, and 8.0 letters in eyes with wet AMD, DME, BRVO-ME, and CRVO-ME, respectively.

Conversely, eyes with mean baseline visual acuity worse than 20/200 had the most impressive improvement, with gains of 16.3, 32.8, 36.9, and 23.0 letters for wet AMD, DME, BRVO-ME, and CRVO-ME, respectively. Generally, wet AMD eyes had worse outcomes compared with the other disease states, with visual acuity gains obtained only in eyes with baseline VA of 20/70 or worse.

BRVO-ME eyes had the best visual acuity outcomes across all groups, gaining up to 36 letters if baseline VA was 20/200 or worse, and losing only 3 letters if baseline VA was 20/40 or better. DME and CRVO-ME eyes followed a similar trend, although DME eyes had better outcomes than CRVO-ME eyes by approximately 5 letters across all subgroups.

THE FUTURE

Given the limited outcomes of anti-VEGF therapy for AMD in the real world, as highlighted by the studies discussed here, along with the burden of repeated intravitreal injections to sustain efficacy, long-acting therapies are under development. In addition, therapies that address pathways beyond the VEGF axis are being studied. These sustained-delivery treatments, new classes of therapies, and even combinations of therapies may meaningfully enhance outcomes for patients with wet AMD, DME, and RVO—leading causes of legal blindness. These

(Continued on page 47)

THE NEW OCULUS CBC LENS


An intuitive, free-floating lens that can improve surgical outcomes.

BY JEFFREY D. BENNER, MD, AND STEVEN COHEN, MD, FACS

Since the invention of closed vitrectomy surgery in 1971 by Robert Machemer, MD, techniques that optimize visualization of the posterior pole during surgery have evolved. Initially, surgeons used the Machemer handheld irrigating lenses. These lenses require a skilled assistant to provide excellent visualization of the macula. Later, the sutured Landers lens systems enabled visualization of the posterior pole through lenses that sat in a ring sutured to the eye. In the 21st century, several sutureless contact lenses have become available. These sutureless lenses do not require an assistant, nor do they necessitate suturing a ring to the eye. However, these lenses suffer from two significant drawbacks: 1) They are not firmly attached to the eye and may shift during surgery; and 2) they extend beyond the cornea limbus and may wick blood and air between the lens and the cornea, which degrades surgical visualization.

Enter the OCULUS CBC Lens, the newest addition to the OCULUS Surgical family of intuitive lenses that are designed to make surgery easier for vitreoretinal surgeons. In 2016, we collaborated to create a better contact lens, one that would solve the problems of stability and obstructed view. After developing many prototypes with 3D printing and obtaining several patents, we teamed up with OCULUS Surgical, Inc., to produce a new type of sutureless surgical contact lens. We wanted a lens that would stay centered on the cornea and provide a clear and stable view of the macula. Today, we are excited to introduce the CBC Lens (Figure 1).

A NEW FAMILY OF INTUITIVE SURGICAL LENSES

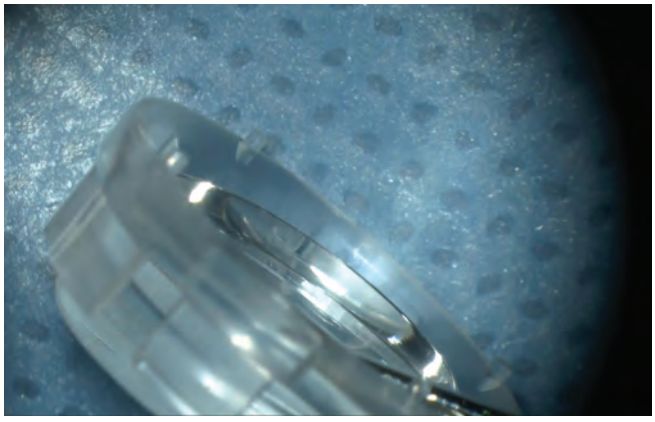
The CBC Lens is part of a new family of intuitive surgical contact lenses produced by OCULUS Surgical, Inc. The CBC Lens contains proprietary technology that is an improvement over the previous generation of disposable contact lenses. In our hands, the CBC Lens is intuitive, resists sliding, and remains stable because of its unique design.

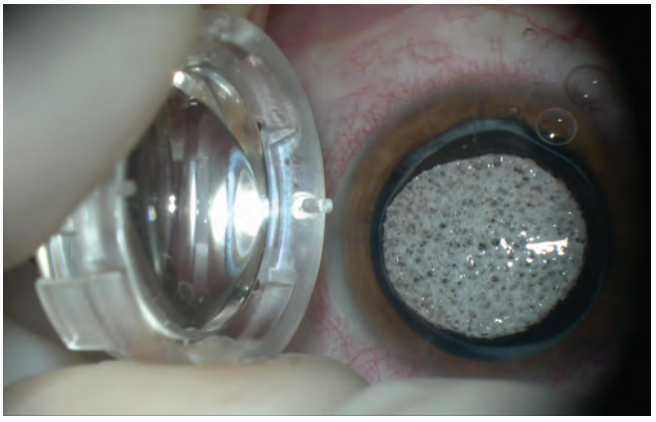
Most sutureless surgical contact lenses float on the viscous tear film and rely on lateral extensions to re-center the lens by pushing against the cannulas and eyelid speculum.

Figure 1. The CBC macular contact lens by OCULUS Surgical, Inc., is part of a family of new, intuitive surgical lenses.

These lenses frequently slide, causing the surgeon to lose his or her view during the most critical part of the surgery. The CBC Lens adopts the familiar two-piece design, but it is the first surgical contact lens to be stabilized by micronized studs, or *microstuds*, that increase the coefficient of friction, thereby minimizing the sliding of the lens during macular surgery. These four microstuds—blunt pieces of polymethyl methacrylate molded to the outer ring—penetrate the viscous tear film to make direct contact with the cornea (Figures 2 and 3). This stabilizing system makes the CBC Lens a "set-it-and-forget-it "contact lens.

To prevent the aspiration of air, blood, and debris beneath the CBC Lens, we used a proprietary two-piece design that ensures that the free-floating central optical lens always remains in contact with the tear film. Additionally, the CBC Lens has a smaller profile than other surgical lenses (10 mm vs 13 mm) that helps it to remain centered. Because the outer diameter of the lens' ring does not extend to the conjunctiva, it does not impact the vitrectomy cannulas or eyelid speculum.





Images courtesy of Steven Cohen, MD, FACS.

Figures 2 and 3. Four molded microstuds of polymethyl methacrylate enable the CBC macular contact lens to contact the cornea directly and prevent it from shifting during surgery. The lens grips the edge of the cornea, whereas all other surgical contact lenses grip the limbus. This corneal fixation keeps the CBC lens in place and prevents the wicking of air, blood, and other debris from the eye's surface.

In our hands, these two design features—the anti-slip microstuds and the smaller, free-floating contact lens—enable the CBC Lens to achieve our goals of stability and visibility within the surgical field.

TECHNIQUE: EASY ON, EASY OFF

Using the CBC Lens for high resolution macular surgery has been easy and fast in our experience. Prior to draping the eye, we verify that the patient's eye is level. A wide-lid speculum is helpful to avoid the lid hindering the performance of the contact lens. After applying a viscoelastic agent to the cornea, we place the lens on the cornea. We use a Weck-Cel sponge (Beaver-Visitec International) to push the lens down onto the center of the cornea, causing the four microstuds to engage with the cornea. In our experience, the lens remains stable and centered, even when we manipulate the globe during the procedure.

Removing the CBC Lens at the conclusion of surgery is also simple: We gently lift it off the cornea with our fingers. The lens leaves no visible marks or indentations on the cornea. In our patients, the lens is comfortable and well tolerated.

PERFORMANCE

The CBC Lens has the same refractive index of an ocular instruments lens and a field of view of 36°. Its polymethyl methacrylate material provides surgeons with a clear, high-resolution view of the macula. Dr. Benner reports that, "The CBC Lens has been transformative for my macular pucker and hole surgeries. The stability and high optical quality of this lens in my hands has knocked 5 to 10 minutes off of each case because the procedure is no longer interrupted by the need to reposition or clean the contact lens." Our colleagues who have tried the lens appreciate its stability and the clarity of the view.

I, Dr. Cohen, feel that the CBC Lens increases the safety of macular procedures. If a contact lens destabilizes at a critical point during surgery—say, for subretinal surgery or macular pucker surgery—having to exit the eye to clean and reposition a contact lens and then re-enter the surgical space may increase the procedure's duration and also the potential for unwanted variables. The opportunity to reduce any extra steps during surgery is, to me, one of this lens' greatest advantages. I am now using this lens for all of my macular surgeries.

CONCLUSION

The CBC Lens became available for use in the United States on October 1, 2021, at a price point similar to other surgical contact lenses. We anticipate that this lens' surgical advantages—what we personally consider to be its greater stability and excellent view—will make it a welcome tool in any surgery, but especially those for macular holes or diabetic retinopathy where visibility is often difficult. ■

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THE CASE OF AN IRIS MELANOMA MASQUERADER



A careful examination is necessary to properly diagnose iridocorneal endothelial syndrome with iris nevus.

BY MALLORY E. BOWERS, PHD; AHMED SHEIKH, MD; AND CAROL L. SHIELDS, MD

During a routine eye examination, a 61-year-old White woman was discovered to have two pigmented iris lesions with corectopia and ectropion in her right eye, suspicious for uveal melanoma. She denied any history of ocular trauma and was unaware of the mass but recognized the progressively distorted pupil. She was referred to ocular oncology for evaluation.

On our examination, BCVA was 20/70 OD and 20/80 OS, with an IOP of 18 mm Hg OD and 19 mm Hg OS. The left eye was unremarkable; the anterior segment showed a round pupil with no iris pigmentary abnormality. The anterior segment examination of the right eye showed a nonsuspicious nevus in the inferior iris without seeding that measured 2.0 mm in diameter (Figure 1A). There was ectropion and corectopia with two-point traction pulling the iris inferomedially away from the nevus and toward a second pigmented region that represented iridocorneal touch. There was no tumor or corneal endotheliopathy. The dilated fundus examination was unremarkable.

Imaging with anterior segment OCT (AS-OCT) confirmed broad-based peripheral anterior synechiae (PAS) inferomedially with no evidence of solid melanoma (Figures 1B and 1C). These features were consistent with iridocorneal endothelial (ICE) syndrome and coincident iris nevus, simulating melanoma. Observation and specular microscopy to assess corneal endothelial cell count were recommended.

DISCUSSION

ICE syndrome is a rare ophthalmic disorder that can mimic iris melanoma due to shared clinical features of corectopia, ectropion uveae, and a gray-brown iris lesion.[1-4] In the case presented here, the features were most consistent with ICE syndrome with corectopia showing two-point traction. AS-OCT imaging confirmed iridoendothelial adhesion with iris elevation and no solid mass. Most iris nevi or melanoma with corectopia tend to show only one-point traction directed toward the lesion without iris atrophy or endothelial adhesion.[5]

Other considerations for iris nevus or melanoma were absent, including feeder or intrinsic vessels; tumor seeding on the iris stroma or anterior chamber angle; and hyphema.[5] The coincidental finding of an unrelated iris nevus in this eye with ICE syndrome created a diagnostic challenge.

In the Literature

In 2011, Shields et al reviewed 71 consecutive cases of individuals with ICE syndrome misconstrued as possible iris nevus or melanoma referred for ocular oncology consultation.[2] The study provided a comparative analysis of eyes with ICE syndrome versus those with iris melanoma (n = 169) and found that the following findings were suggestive of ICE syndrome: corneal guttatae (46% vs 0%), corneal edema (10% vs 0%), iris atrophy (58% vs 0%), PAS (80% vs 0%), and polycoria (1% vs 0%). Features more suggestive of iris melanoma versus ICE syndrome included episcleral sentinel vessels (25% vs 8%), extrascleral extension of the tumor (6% vs 0%), iris mass or nodule (72% vs 7%), iris tumor seeds (56% vs 0%), solid mass in angle (46% vs 0%), and angle seeding (57% vs 0%). Some overlapping features for ICE syndrome and iris melanoma included mean age at presentation (51 vs 48 years), female sex (76% vs 50%), corectopia (75% vs 62%), ectropion iridis (34% vs 44%), and IOP greater than 22 mm Hg (8% vs 30%) or greater than 30 mm Hg (4% vs 17%).

The mechanism of glaucoma in ICE patients is uniformly angle-closure.[2,6] In patients with iris melanoma and glaucoma, the glaucoma is typically secondary to tumor infiltration of the anterior chamber angle.[2] Shields et al also highlighted corneal guttatae, corneal edema, multidirectional corectopia, iris atrophy, PAS, and elevated IOP from angle-closure as the major differentiating features of ICE syndrome from circumscribed or diffuse iris melanoma.[2]

Lakosha et al similarly found that essential iris atrophy, a clinical subtype of ICE syndrome, can mimic iris neoplasms and that longitudinal ultrasound biomicroscopy was useful in establishing a diagnosis by demonstrating progressive iris thinning and contraction of PAS.[4]

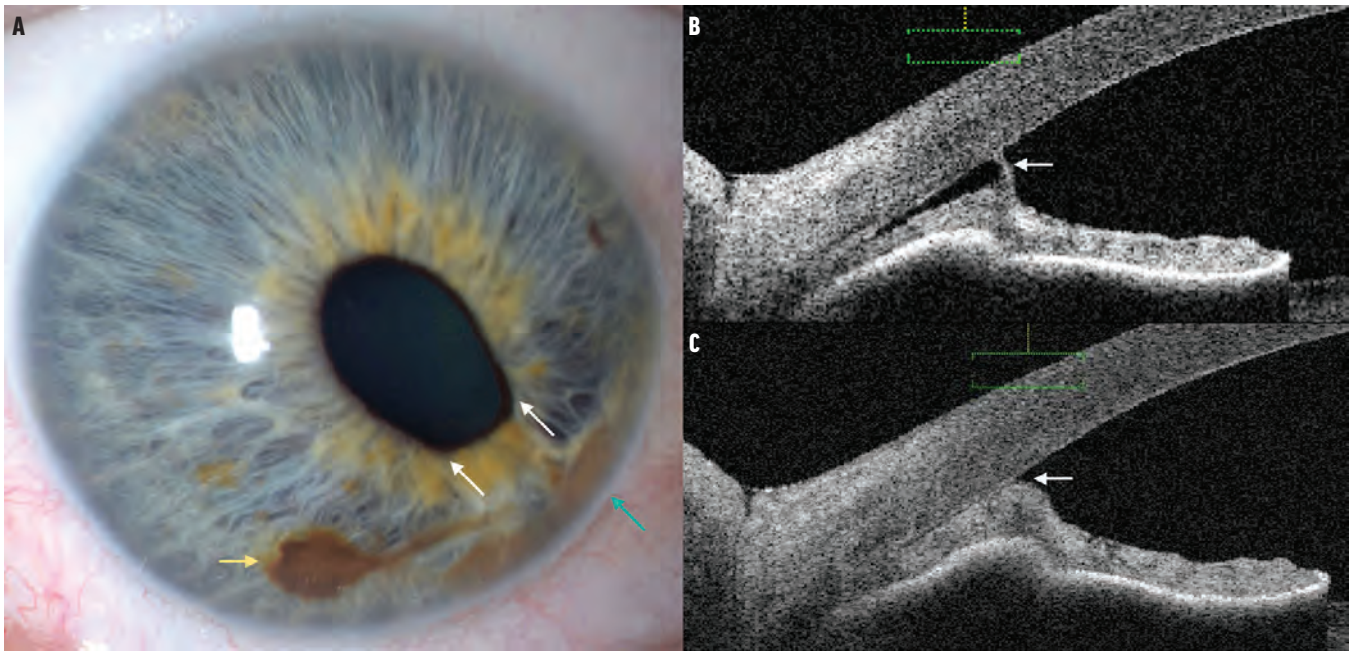

Figure 1. These images depict ICE syndrome masquerading as a suspicious iris nevus in the right eye. Slit lamp photography demonstrates two pigmented iris lesions with classic iris nevus (yellow arrow) and iridocorneal endothelial adhesion (green arrow; A). Note that there is two-point iris traction (white arrows), more consistent with ICE syndrome than iris nevus or melanoma. On AS-OCT there is focal (B) and diffuse (C) iris adhesion to the corneal endothelium with draping of the iris. Note that the iris is otherwise of normal thickness and the iris pigment epithelium is intact without tumor.

Pathogenesis and Treatment

The hypothesized pathogenesis of ICE syndrome is corneal endothelial cell proliferation triggered by herpes simplex virus or Epstein-Barr virus infection.[7,8] Proliferating endothelial cells migrate toward the iridocorneal angle and onto the iris, precipitating corneal, iris, angle, and pupillary abnormalities. Most believe that ICE syndrome is sporadic, unilateral, and more prevalent among middle-aged women.[2,9] The location and degree of pathology differentiates the three ICE syndrome subtypes—Chandler syndrome, Cogan-Reese syndrome, and progressive iris atrophy. ICE syndrome is well documented to mimic malignancy, especially iris melanoma, and assessment by an ocular oncologist is often necessary.

THE COINCIDENTAL FINDING OF AN UNRELATED IRIS NEVUS IN THIS EYE WITH ICE SYNDROME CREATED A DIAGNOSTIC CHALLENGE.

Several cohort studies and case reports support the use of in vivo confocal microscopy as a diagnostic tool for ICE syndrome, particularly in borderline presentations or in cases where corneal edema precludes visualization by specular microscopy.[10-12] In a study of 12 patients with unilateral ICE syndrome, Le et al showed that affected eyes demonstrated a decrease in the percentage of hexagonal endothelial cells (20.3% vs 63.3%, $P < .05$) and greater variation in endothelial cell size (0.512 vs 0.357, $P < .05$) compared with contralateral healthy eyes, which falls in line with previous studies.[10,13] These findings reflect the transformation of uniform corneal endothelial cells to pleomorphic epithelioid "ICE" cells that underlies the pathogenesis of this syndrome.

Treatment of ICE syndrome primarily involves the management of glaucoma with topical IOP-lowering eye drops and glaucoma surgery, including trabeculectomy with antifibrotic agents, implantation of shunt devices, goniotomy, and ciliary body ablation.[6,14] Management of corneal decompensation includes corneal graft with penetrating keratoplasty, Descemet membrane endothelial keratoplasty, or Descemet stripping automated endothelial keratoplasty.[15,16]

CONCLUSION

ICE syndrome can closely simulate iris melanoma; however, there are special features that suggest ICE syndrome, including the corneal endothelial "beaten metal" appearance of guttatae, iris transillumination defects, multipoint ectropion iris and corectopia, and broad-based

PAS (iridocorneal adhesion). In contrast, iris melanoma tends to demonstrate a solid iris mass, occasionally with iris ectropion or corectopia, but usually single-point and with additional iris stromal seeding, angle seeding, secondary glaucoma, and evidence of growth.[2,4] ■

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(Continued from page 42)

innovations may not only durably restore vision but may also prevent vision loss in patients with good baseline visual acuity who may be more prone to vision loss in the long term. ■

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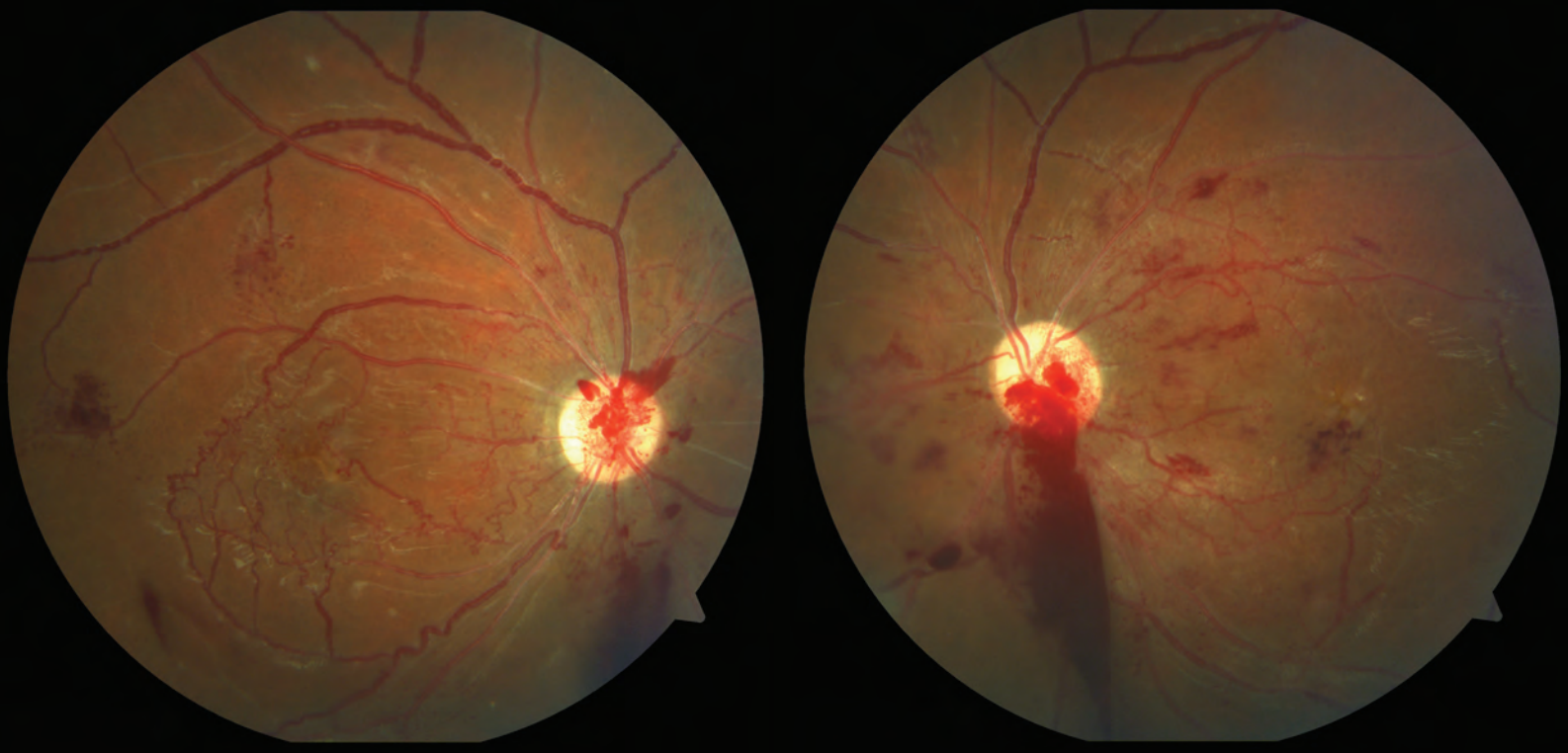


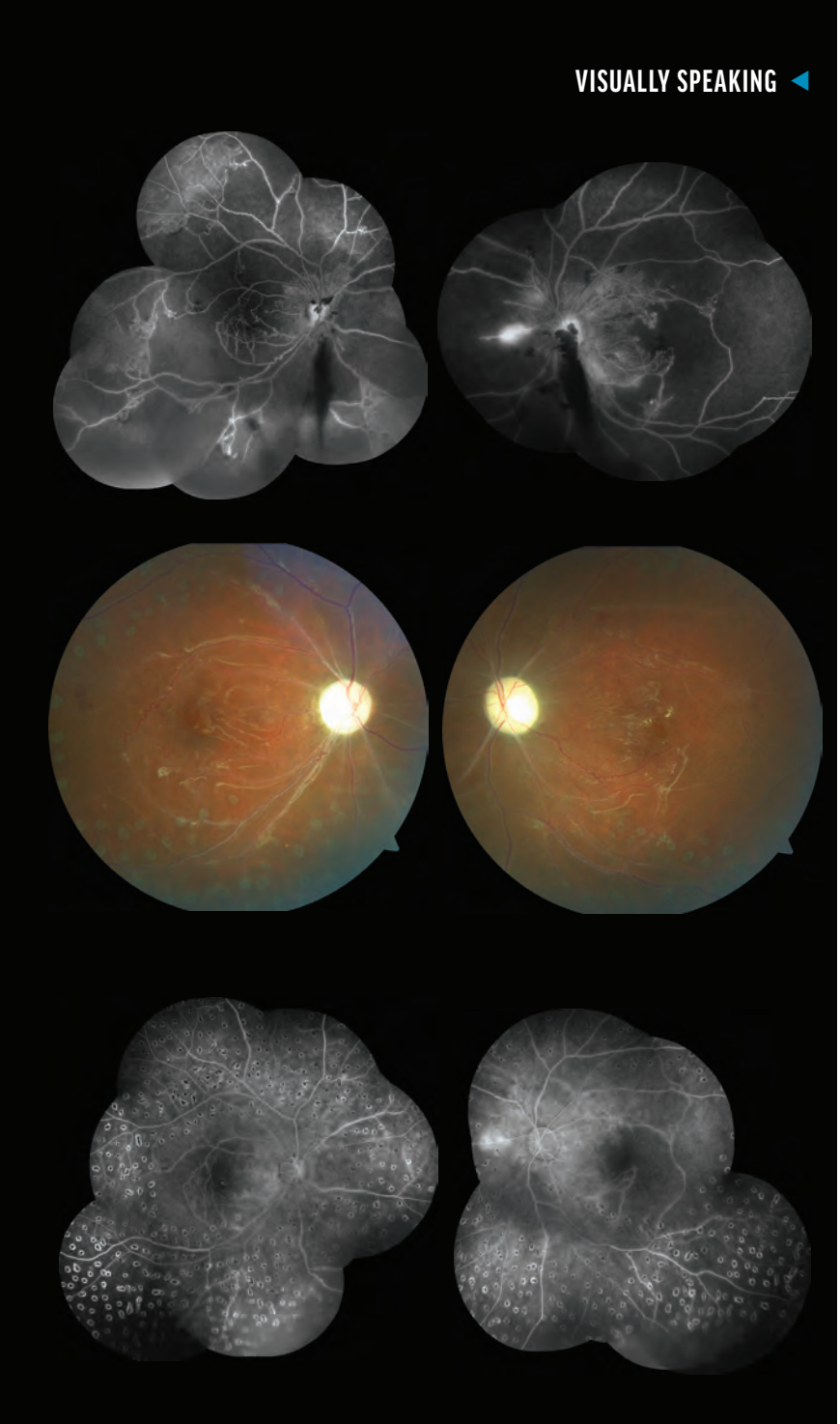
AN AGGRESSIVE PRESENTATION OF PROLIFERATIVE RETINOPATHY

This young patient presented with ocular sequelae of uncontrolled type 1 diabetes and systemic erythematosus lupus.

BY EDUARDO ZANS, MD

A 21-year-old male patient was referred because of progressive vision loss in both eyes for the past 3 months. He had a history of type 1 diabetes and systemic erythematosus lupus, confirmed by a lab test. He had not received any ocular therapies before the consultation. VA was hand motion OD and 20/800 OS. On slit lamp examination, no rubeosis iridis or cataract were noted in either eye. The dilated fundus examination of each eye revealed preretinal vitreous hemorrhage below the optic nerve, neo vessels, venous beading, and intraretinal microvascular abnormality (Main Figure). Fluorescein angiography showed nonperfusion areas in each eye and hyperfluorescence due to neo vessels (Figure, at right, top).

The patient received 3 monthly intraocular injections of bevacizumab (Avastin, Genentech), followed by diode laser pan photocoagulation in each eye (Figure, at right, middle). Macular OCT showed the thin macular tissue as a sequela to nonperfusion severity. The patient had additional posterior pole and periphery diode laser, guided by angiography (Figure, at right, bottom). VA improved to 50 cm counting fingers OD and 20/200 OS. After 6 months of follow up, the patient maintained visual acuity with no new retinal findings. His diabetes and systemic erythematosus lupus are currently well controlled. ■



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DENNIS HAN, MD

When did you first know that you wanted to become a vitreoretinal surgeon?

When I saw my first vitrectomy as an ophthalmology resident at the University of Iowa, I was hooked. The surgery was exciting, challenging, and impactful—everything I wanted in a career.

You specialize in macular disease, macular holes, and epiretinal membranes. What is it about these conditions that interests you the most?

It was exciting to experience the rapid evolution of macular surgery. But more recently, I have chosen to limit my practice to medical retina. So, for me, it is now the intersection between advanced imaging technology and the ever-expanding number of treatment modalities that makes things interesting.

You see a wide range of patients, from infants to seniors. What would you say is one of the biggest differences in treating younger versus older patients?

When performing surgery on infants and young children, retaining an intact crystalline lens is always in the forefront of my mind because of the complexities involving aphakia, amblyopia, and IOL implantation. Also, the stakes are high in children; their whole lives are before them, and both you and the parents know that.

In older children and young adults, an added challenge is working around their educational activities and career plans. I've done a lot of their surgeries over the holidays and academic breaks. Also, I've found that the emotional ups and downs while treating kids can be intense, for both families and physicians. The pediatric retinal surgeons I know are a particularly collegial and supportive group because they all know the pressures. There's a special place in heaven for them.

You loved building and driving soapbox derby cars when you were younger. Is this still a passion of yours? Do you think there are any skills from this hobby that have helped you in the retina world?

As a grade schooler, building and racing soapbox derby cars was something to do during the quiet summers in the rural Upper Peninsula of Michigan. It was exhilarating to steer your self-designed car down a beautifully paved roadway with a competitor beside you, wind rushing by as you hit top speed. But the understanding of spatial relationships, mechanical skills, and dexterity with materials that I learned while building the cars have helped me throughout my career, especially in surgery. I think any activity that involves craftsmanship can be useful for a surgical career—even the arts and crafts that you learn in grade school.

When not in the clinic, Dr. Han enjoys fly-fishing in the Driftless Area of Wisconsin.

What is one of your favorite things about being a professor?

Educating ophthalmology residents and fellows has been my favorite part. Their energy and enthusiasm keep me going. And when you educate others, you educate yourself. ■

DENNIS HAN, MD

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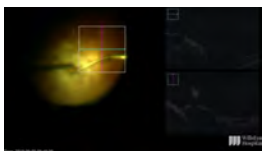
Ajay E. Kuriyan, MD, MS



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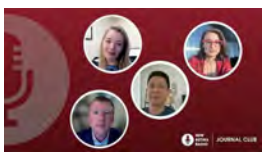

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