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eyetube

DIABETIC EYE DISEASE

A WINDING PATH OF DIAGNOSIS, TREATMENT, AND FOLLOW-UP

STRATEGIES FOR COMBATTING LOSS TO FOLLOW-UP

MANAGING DR ONE CASE AT A TIME

TIPS FOR A SUCCESSFUL DIABETIC TRD SURGERY

DON'T DELAY TREATMENT IN DME

HELP REDUCE INFLAMMATION IN DIABETIC MACULAR EDEMA (DME)

- **Achieved clinically significant 3-line gains in BCVA[1,*]**
- **Suppresses inflammation by inhibiting multiple inflammatory cytokines[2]**

*BCVA = best-corrected visual acuity.

Indications and Usage
Diabetic Macular Edema
OZURDEX® (dexamethasone intravitreal implant) is a corticosteroid indicated for the treatment of diabetic macular edema.

Retinal Vein Occlusion
OZURDEX® is a corticosteroid indicated for the treatment of macular edema following branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO).

Posterior Segment Uveitis
OZURDEX® is indicated for the treatment of noninfectious uveitis affecting the posterior segment of the eye.

IMPORTANT SAFETY INFORMATION
Contraindications
Ocular or Periocular Infections: OZURDEX® (dexamethasone intravitreal implant) is contraindicated in patients with active or suspected ocular or periocular infections including most viral diseases of the cornea and conjunctiva, including active epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections, and fungal diseases.

Glaucoma: OZURDEX® is contraindicated in patients with glaucoma, who have cup to disc ratios of greater than 0.8.

Torn or Ruptured Posterior Lens Capsule: OZURDEX® is contraindicated in patients whose posterior lens capsule is torn or ruptured because of the risk of migration into the anterior chamber. Laser posterior capsulotomy in pseudophakic patients is not a contraindication for OZURDEX® use.

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

IMPORTANT SAFETY INFORMATION (continued)
Warnings and Precautions
Intravitreal Injection-related Effects: Intravitreal injections, including those with OZURDEX® (dexamethasone intravitreal implant), have been associated with endophthalmitis, eye inflammation, increased intraocular pressure, and retinal detachments. Patients should be monitored regularly following the injection.

Steroid-related Effects: Use of corticosteroids including OZURDEX® may produce posterior subcapsular cataracts, increased intraocular pressure, glaucoma, and 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.

Adverse Reactions
Diabetic Macular Edema
Ocular adverse reactions reported by greater than or equal to 1% of patients in the two combined 3-year clinical trials following injection of OZURDEX® for diabetic macular edema include: cataract (68%), conjunctival hemorrhage (23%), visual acuity reduced (9%), conjunctivitis (6%), vitreous floaters (5%), conjunctival edema (5%), dry eye (5%), vitreous detachment (4%), vitreous opacities (3%), retinal aneurysm (3%), foreign body sensation (2%), corneal erosion (2%), keratitis (2%), anterior chamber inflammation (2%), retinal tear (2%), eyelid ptosis (2%). Non-ocular adverse reactions reported by greater than or equal to 5% of patients include: hypertension (13%) and bronchitis (5%).

Increased Intraocular Pressure: IOP elevation greater than or equal to 10 mm Hg from baseline at any visit was seen in 28% of OZURDEX® patients versus 4% of sham patients. 42% of the patients who received OZURDEX® were subsequently treated with IOP-lowering medications during the study versus 10% of sham patients.

The increase in mean IOP was seen with each treatment cycle, and the mean IOP generally returned to baseline between treatment cycles (at the end of the 6-month period).

Cataracts and Cataract Surgery: The incidence of cataract development in patients who had a phakic study eye was higher in the OZURDEX® group (68%) compared with Sham (21%). The median time of cataract being reported as an adverse event was approximately 15 months in the OZURDEX® group and 12 months in the Sham group. Among these patients, 61% of OZURDEX® subjects versus 8% of sham-controlled subjects underwent cataract surgery, generally between Month 18 and Month 39 (Median Month 21 for OZURDEX® group and 20 for Sham) of the studies.

Retinal Vein Occlusion and Posterior Segment Uveitis
Adverse reactions reported by greater than 2% of patients in the first 6 months following injection of OZURDEX® for retinal vein occlusion and posterior segment uveitis include: intraocular pressure increased (25%), conjunctival hemorrhage (22%), eye pain (8%), conjunctival hyperemia (7%), ocular hypertension (5%), cataract (5%), vitreous detachment (2%), and headache (4%).

Increased IOP with OZURDEX® peaked at approximately week 8. During the initial treatment period, 1% (3/421) of the patients who received OZURDEX® required surgical procedures for management of elevated IOP.

Dosage and Administration
FOR OPHTHALMIC INTRAVITREAL INJECTION. The intravitreal injection procedure should be carried out under controlled aseptic conditions. Following the intravitreal injection, patients should be monitored for elevation in intraocular pressure and for endophthalmitis. Patients should be instructed to report any symptoms suggestive of endophthalmitis without delay.

Please see Brief Summary of full Prescribing Information on adjacent page.

References: 1. Data on file, Allergan. **2.** OZURDEX® Prescribing Information.

Ozurdex®
(dexamethasone intravitreal implant) 0.7 mg

Allergan
an AbbVie company

Ozurdex.com OZU144337 02/21 008782

OZURDEX®

(dexamethasone intravitreal implant) 0.7 mg

Brief Summary—Please see the OZURDEX® package insert for full Prescribing Information.

INDICATIONS AND USAGE

Retinal Vein Occlusion: OZURDEX® (dexamethasone intravitreal implant) is a corticosteroid indicated for the treatment of macular edema following branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO).

Posterior Segment Uveitis: OZURDEX® is indicated for the treatment of non-infectious uveitis affecting the posterior segment of the eye.

Diabetic Macular Edema

OZURDEX® is indicated for the treatment of diabetic macular edema.

CONTRAINDICATIONS

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

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Hypersensitivity: OZURDEX® is contraindicated in patients with known hypersensitivity to any components of this product *[see Adverse Reactions]*.

WARNINGS AND PRECAUTIONS

Intravitreal Injection-related Effects: Intravitreal injections, including those with OZURDEX®, have been associated with endophthalmitis, eye inflammation, increased intraocular pressure, and retinal detachments.

Patients should be monitored regularly following the injection *[see Patient Counseling Information]*.

Steroid-related Effects: Use of corticosteroids including OZURDEX® may produce posterior subcapsular cataracts, increased intraocular pressure, glaucoma, and may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses *[see Adverse Reactions]*.

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.

ADVERSE REACTIONS

Clinical Trials Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adverse reactions associated with ophthalmic steroids including OZURDEX® include elevated intraocular pressure, which may be associated with optic nerve damage, visual acuity and field defects, posterior subcapsular cataract formation, secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera.

Retinal Vein Occlusion and Posterior Segment Uveitis

The following information is based on the combined clinical trial results from 3 initial, randomized, 6-month, sham-controlled trials (2 for retinal vein occlusion and 1 for posterior segment uveitis):

Adverse Reactions Reported by Greater than 2% of Patients

MedDRA Term	OZURDEX® N=497 (%)	Sham N=498 (%)
Intraocular pressure increased	125 (25%)	10 (2%)
Conjunctival hemorrhage	108 (22%)	79 (16%)
Eye pain	40 (8%)	26 (5%)
Conjunctival hyperemia	33 (7%)	27 (5%)
Ocular hypertension	23 (5%)	3 (1%)
Cataract	24 (5%)	10 (2%)
Vitreous detachment	12 (2%)	8 (2%)
Headache	19 (4%)	12 (2%)

Increased IOP with OZURDEX® peaked at approximately week 8. During the initial treatment period, 1% (3/421) of the patients who received OZURDEX® required surgical procedures for management of elevated IOP.

Following a second injection of OZURDEX® (dexamethasone intravitreal implant) in cases where a second injection was indicated, the overall incidence of cataracts was higher after 1 year.

In a 2-year observational study, among patients who received >2 injections, the most frequent adverse reaction was cataract 54% (n=96 out of 178 phakic eyes at baseline). Other frequent adverse reactions from the 283 treated eyes, regardless of lens status at baseline, were increased IOP 24% (n=68) and vitreous hemorrhage 6.0% (n=17).

Diabetic Macular Edema

The following information is based on the combined clinical trial results from 2 randomized, 3-year, sham-controlled studies in patients with diabetic macular edema. Discontinuation rates due to the adverse reactions listed in the table below were 3% in the OZURDEX® group and 1% in the Sham group. The most common ocular (study eye) and non-ocular adverse reactions are as follows:

Ocular Adverse Reactions Reported by ≥ 1% of Patients and Non-ocular Adverse Reactions Reported by ≥ 5% of Patients

MedDRA Term	OZURDEX® N=324 (%)	Sham N=328 (%)
Ocular		
Cataract[1]	166/243[2] (68%)	49/230 (21%)
Conjunctival hemorrhage	73 (23%)	44 (13%)
Visual acuity reduced	28 (9%)	13 (4%)
Conjunctivitis	19 (6%)	8 (2%)
Vitreous floaters	16 (5%)	6 (2%)
Conjunctival edema	15 (5%)	4 (1%)
Dry eye	15 (5%)	7 (2%)
Vitreous detachment	14 (4%)	8 (2%)
Vitreous opacities	11 (3%)	3 (1%)
Retinal aneurysm	10 (3%)	5 (2%)
Foreign body sensation	7 (2%)	4 (1%)
Corneal erosion	7 (2%)	3 (1%)
Keratitis	6 (2%)	3 (1%)
Anterior Chamber Inflammation	6 (2%)	0 (0%)
Retinal tear	5 (2%)	2 (1%)
Eyelid ptosis	5 (2%)	2 (1%)
Non-ocular		
Hypertension	41 (13%)	21 (6%)
Bronchitis	15 (5%)	8 (2%)

[1] Includes cataract, cataract nuclear, cataract subcapsular, lenticular opacities in patients who were phakic at baseline. Among these patients, 61% of OZURDEX® subjects vs. 8% of sham-controlled subjects underwent cataract surgery.

[2] 243 of the 324 OZURDEX® subjects were phakic at baseline; 230 of 328 sham-controlled subjects were phakic at baseline.

Increased Intraocular Pressure

Summary of Elevated IOP Related Adverse Reactions

	Treatment: N (%)	
IOP	**OZURDEX®** N=324	**Sham** N=328
IOP elevation ≥10 mm Hg from Baseline at any visit	91 (28%)	13 (4%)
≥30 mm Hg IOP at any visit	50 (15%)	5 (2%)
Any IOP lowering medication	136 (42%)	32 (10%)
Any surgical intervention for elevated IOP*	4 (1.2%)	1 (0.3%)

* OZURDEX®: 1 surgical trabeculectomy for steroid-induced IOP increase, 1 surgical trabeculectomy for iris neovascularization,1 laser iridotomy, 1 surgical iridectomy
Sham: 1 laser iridotomy

The increase in mean IOP was seen with each treatment cycle, and the mean IOP generally returned to baseline between treatment cycles (at the end of the 6 month period).

Cataracts and Cataract Surgery

At baseline, 243 of the 324 OZURDEX® subjects were phakic; 230 of 328 sham-controlled subjects were phakic. The incidence of cataract development in patients who had a phakic study eye was higher in the OZURDEX® group (68%) compared with Sham (21%). The median time of cataract being reported as an adverse event was approximately 15 months in the OZURDEX® group and 12 months in the Sham group. Among these patients, 61% of OZURDEX® subjects vs.

8% of sham-controlled subjects underwent cataract surgery, generally between Month 18 and Month 39 (Median Month 21 for OZURDEX® group and 20 for Sham) of the studies.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

There are no adequate and well-controlled studies with OZURDEX® in pregnant women. Topical ocular administration of dexamethasone in mice and rabbits during the period of organogenesis produced cleft palate and embryofetal death in mice, and malformations of the abdominal wall/intestines and kidneys in rabbits at doses 5 and 4 times higher than the recommended human ophthalmic dose (RHOD) of OZURDEX® (0.7 milligrams dexamethasone), respectively.

In the US 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.

Data

Animal Data

Topical ocular administration of 0.15% dexamethasone (0.75 mg/kg/day) on gestational days 10 to 13 produced embryofetal lethality and a high incidence of cleft palate in mice. A dose of 0.75 mg/kg/day in the mouse is approximately 5 times an OZURDEX® injection in humans (0.7 mg dexamethasone) on a mg/m^2 basis. In rabbits, topical ocular administration of 0.1% dexamethasone throughout organogenesis (0.20 mg/kg/day, on gestational day 6 followed by 0.13 mg/kg/day on gestational days 7-18) produced intestinal anomalies, intestinal aplasia, gastroschisis and hypoplastic kidneys. A dose of 0.13 mg/kg/day in the rabbit is approximately 4 times an OZURDEX® injection in humans (0.7 mg dexamethasone) on a mg/m^2 basis. A no-observed-adverse-effect-level (NOAEL) was not identified in the mouse or rabbit studies.

Lactation

Risk Summary

Systemically administered corticosteroids are present in human milk and can suppress growth and interfere with endogenous corticosteroid production or cause other unwanted effects. There is no information regarding the presence of dexamethasone in human milk, the effects on the breastfed infants, or the effects on milk production to inform risk of OZURDEX® to an infant during lactation. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for OZURDEX® and any potential adverse effects on the breastfed child from OZURDEX®.

Pediatric Use: Safety and effectiveness of OZURDEX® in pediatric patients have not been established.

Geriatric Use: No overall differences in safety or effectiveness have been observed between elderly and younger patients.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Animal studies have not been conducted to determine whether OZURDEX® (dexamethasone intravitreal implant) has the potential for carcinogenesis or mutagenesis. Fertility studies have not been conducted in animals.

PATIENT COUNSELING INFORMATION

Steroid-related Effects

Advise patients that a cataract may occur after repeated treatment with OZURDEX®. If this occurs, advise patients that their vision will decrease, and they will need an operation to remove the cataract and restore their vision.

Advise patients that they may develop increased intraocular pressure with OZURDEX® treatment, and the increased IOP will need to be managed with eye drops, and, rarely, with surgery.

Intravitreal Injection-related Effects

Advise patients that in the days following intravitreal injection of OZURDEX®, patients are at risk for potential complications including in particular, but not limited to, the development of endophthalmitis or elevated intraocular pressure.

When to Seek Physician Advice

Advise patients that if the eye becomes red, sensitive to light, painful, or develops a change in vision, they should seek immediate care from an ophthalmologist.

Driving and Using Machines

Inform patients that they may experience temporary visual blurring after receiving an intravitreal injection. Advise patients not to drive or use machines until this has been resolved.

Rx only

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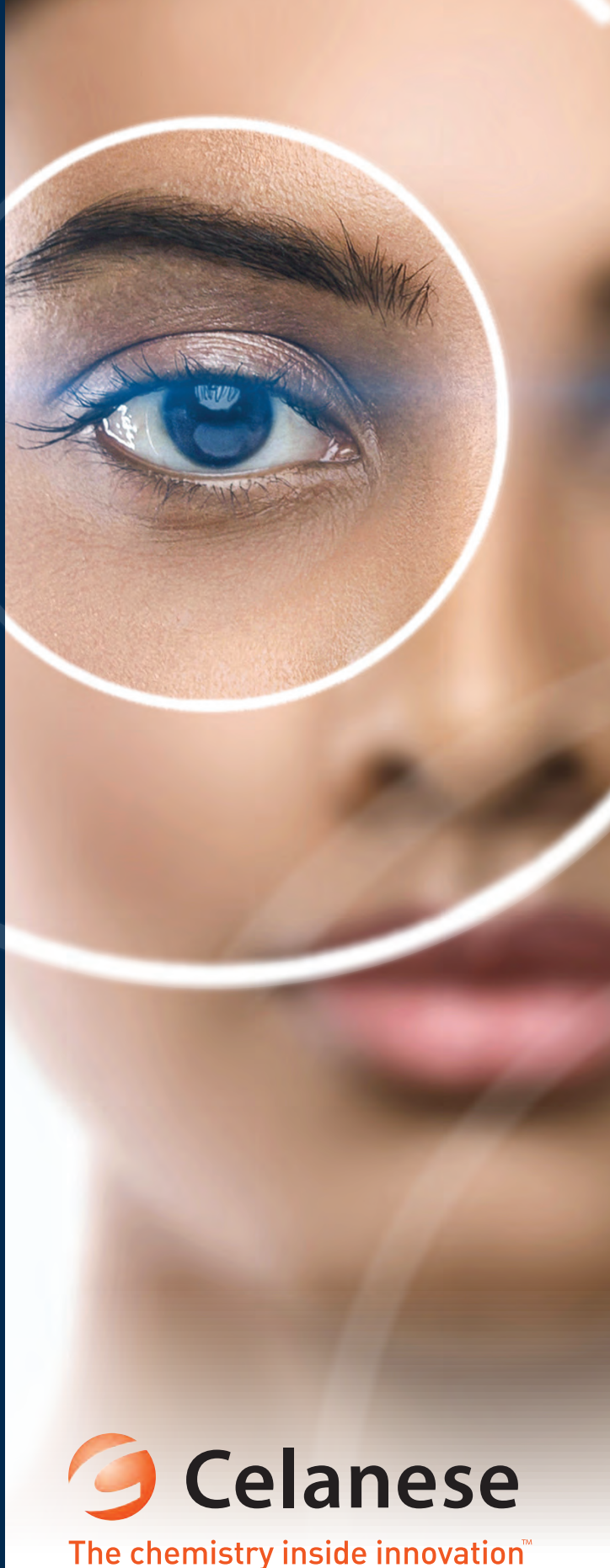
Versatile, innovative platform for ocular drug delivery



Our VitalDose® EVA technology is a drug delivery platform providing controlled release through implant and insert dosage forms. The VitalDose® EVA platform has proven biocompatibility and achieves >6 months release of **mAbs, peptides, small molecules, and fixed dose combination therapies**. We partner with you to enable innovation within your desired delivery profile.

The Celanese Development & Feasibility Lab offers the following support:

- Material selection
- Formulation and R&D prototype development
- Drug release testing
- Tech transfer

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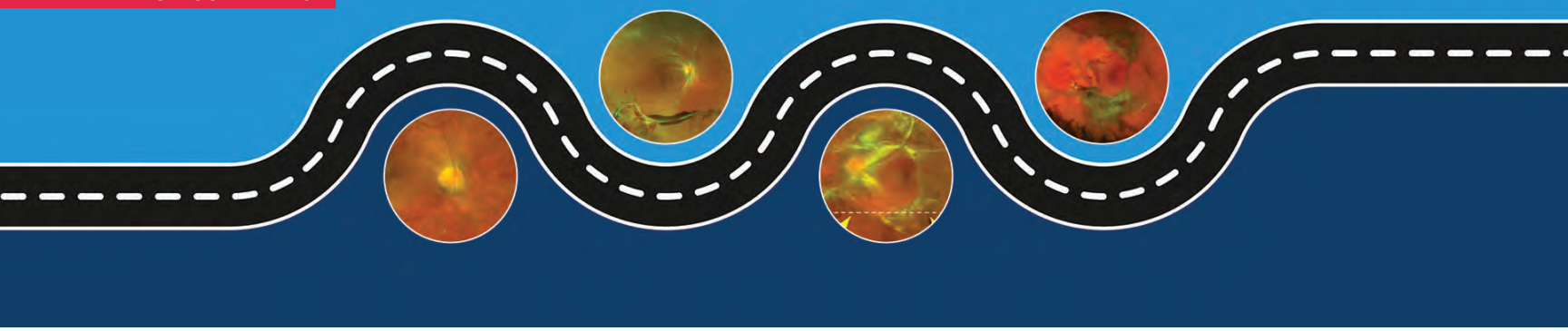

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DEPARTMENTS

PROGRESSION IN GEOGRAPHIC ATROPHY IS RELENTLESS AND IRREVERSIBLE[1-4]

While GA progression may appear to move slowly, it can affect your patients faster than you think[1,4-6]

The consequences of Geographic Atrophy (GA) are too critical to be ignored[7-9]

IN A MEDIAN OF ONLY 2.5 YEARS,
GA lesions encroached on the fovea according to a prospective AREDS study (N=3640)[2*]

2 OUT OF 3 PATIENTS
lost the ability to drive in a median time of <2 years according to a retrospective study (n=523)[10†]

GA lesions can lead to visual impairment even before they reach the fovea[1,5,6]

See the effect of GA progression on your patients

*Data sourced from the Age-related Eye Disease Study (AREDS) Report #26—a long-term, multicenter, prospective study examining progression of GA area in a cohort of 3640 patients with signs of early and more advanced forms of AMD.

†A retrospective cohort analysis (N=1901) of a multicenter electronic medical record database examining disease burden and progression in patients in the United Kingdom with bilateral GA secondary to AMD.

BCVA=best-corrected visual acuity.

References: 1. Boyer DS et al. *Retina*. 2017;37:819-835. 2. Lindblad AS et al, and AREDS Research Group. *Arch Ophthalmol*. 2009;127(9):1168-1174. 3. Holz FG et al. *Ophthalmology*. 2014;121(5):1079-1091. 4. Sunness JS et al. *Ophthalmology*. 2007;114(2):271-277. 5. Kimel M et al. Invest *Ophthalmol Vis Sci*. 2016;57(14):6298-6304. 6. Sadda SR et al. *Retina*. 2016;36(10):1806-1822. 7. Singh RP et al. *Am J Ophthalmic Clin Trials*. 2019;(1):1-6. doi:10.25259/ajoct-9-2018. 8. Sivaprasad S et al. *Ophthalmol Ther*. 2019;8(1):115-124. 9. Patel PJ et al. *Clin Ophthalmol*. 2020;14:15-28. 10. Chakravarthy U et al. *Ophthalmology*. 2018;125:842-849.

Apellis

PRECISION MEDICINE IS ALREADY HERE


It's just clunkier than we envisioned. Hear us out on this one. Talk of precision medicine—tailoring therapies based on a patient's individual genes, environment, and lifestyle—is all the rage. The possibility that we may one day have therapies that successfully treat common retinal diseases based on a patient's genetic makeup is thrilling. The vision is simple: we see a patient suspected of having a retinal disease, such as AMD, we send out for a genetic test, and the results tell us what's going on—and what treatment would work best. Some patients with Leber congenital amaurosis caused by biallelic *RPE65* mutations already have a small taste of precision medicine.

But we have a long way to go before that's a reality for most people with retinal pathology. For now, we have a slew of "one-size-fits-all" therapeutics that we can recommend—and they work well for most patients. When we see a new patient with signs of wet AMD, it's almost a given that we will recommend intravitreal anti-VEGF injections as the primary treatment. And if a patient walks in with a retinal detachment? It's usually off to the OR for them.

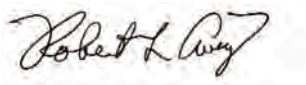
Although the entire clinical picture is important to capture, much of that data is nice to know but doesn't necessarily change our disease management approach all that much; the first step is usually clear.

But when a patient with diabetes walks in with decreased vision, it can feel a little like opening Pandora's box. Depending on the patient's age, disease control, systemic comorbidities, medical and ocular history, clinical examination findings, risk for loss to follow-up, and insurance coverage (to name only a few variables), we might recommend any number of treatment approaches, from intravitreal anti-VEGF injections or steroid injections to panretinal or focal laser treatment to vitrectomy. And *then*, depending on how the patient responds, clinically as well as personally, we might shift between therapeutic approaches to optimize disease control and stave off vision loss. Could you even imagine what a comprehensive decision tree would look like?

But truth be told, each patient already has their own decision tree, and that's what makes caring for patients with diabetes precision medicine at its core. We have robust guidelines to help us (check out the Diabetic Retinopathy Clinical Research Retina Network update on page 42), but at the end of the day, it's the patient's entire story (right down to where they live and their family dynamics) that dictates how we treat them and their potential for ocular complications. We have all chosen panretinal photocoagulation for a patient who would have done just as well with anti-VEGF injections—because we got the sneaking suspicion that they may never pass through our doorway again.

To help you stay focused on the precision care these patients need, this issue addresses the entire experience, from artificial intelligence screening to combatting loss to follow-up, all with the unique patient in mind. As for the treatment approaches themselves, Dilsher S. Dhoot, MD, and Matthew R. Starr, MD, tackle the tough questions of when to intervene and how to proceed based on the patient's changing clinical picture. Once in the OR, David Xu, MD, has some excellent pearls for addressing diabetic tractional retinal detachment. Even surgical intervention for a diabetic patient is more like a series of real-time decisions than a standard approach; "ultimately, it is up to the surgeon to decide how best to manage the unique nuances of each eye," Dr. Xu says in his article on page 53. That just about sums up our entire approach to diabetic eye disease: it depends.

Diabetes is an epidemic and has been for a long time, which means that health care workers and educators have been on a crusade to slow the rising incidence of this (largely) preventable condition for years. By now, we all know that treating these patients isn't enough—we must educate and reinforce healthy habits, over and over. Unfortunately, by the time they are talking to us, it's often too late, and we are on damage control. The best we can do is listen to their story and use all that information to build an individualized treatment plan that works for them—and hopefully preserves their vision. ■

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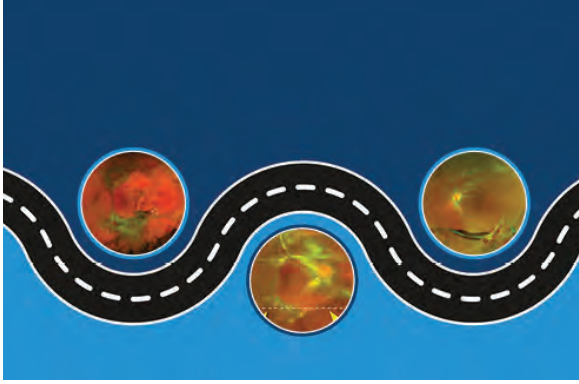


GENDER GAP IN RETINA AUTHORSHIP NARROWS

An analysis of clinical retina research papers published over the last 25 years has found that the percentage of women in first and last authorship positions has significantly increased.[1] The study authors noted in their paper, published in *Ophthalmology Retina*, that there are no studies examining female authorship trends in retina, whereas other specialties, such as cornea and glaucoma, have been individually analyzed.

To fill this gap, researchers at Wills Eye Hospital in Philadelphia assessed the first and last authors of 4,142 original articles published between January 1, 1995, and January 1, 2021, in the *American Journal of Ophthalmology*, *JAMA Ophthalmology* (*Archives of Ophthalmology*), *Ophthalmology*, and *Retina*. They found that the percentage of women in first and last authorship positions increased from 23% to 37.7% ($P < .001$) and 14.2% to 24.6% ($P < .001$) between 1995 and 2021, respectively.[1] In 2020 specifically, 28.2% of the first authors and 22.3% of the last authors of US retina publications were women ($P < .001$ and $P < .001$, respectively). For comparison, 17% of practicing retina specialists in the United States were women in 2020, according to the ASRS directory.[1]

The team also found that papers with women as last authors were more likely to have women as first authors: when the last authors were women, 32.5% of the first authors were women, but when the last authors were men, the percentage of first authors as women dropped to 27.1% ($P = .002$). The overall number of original articles in the field of retina has increased significantly over the last 25 years (from 113 original articles in 1995 to 183 in 2020), possibly due to an increased focus on research productivity as a driver of upward mobility in academia, the authors wrote in their paper. Men still disproportionately outnumber women in first and last author positions in retina research, and "providing women with the opportunities to publish is critical in improving the representation of women in academia and leadership" the authors concluded.

"Closing the gender gap in retina research means giving women an equal opportunity to express their voices in the literature and, therefore, in academic positions," Ankur Nahar, BS, first author of the study, said in a statement to *Retina Today*. "When young women, as medical students, residents, and fellows, see that they are represented, especially in traditionally male-dominated fields like retina, it's inspirational, motivational, and reduces the barrier for entry into the field. A greater representation of women in retina also means a greater diversity of approaches and opinions, which is the engine that pushes research forward."

1. Nahar A, Mahmoudzadeh R, Rama M, et al. Authorship trends of women in retina: a 25-year analysis [Preprint published online August 13, 2022]. *Ophthalmol Retina*.

FIRST PATIENT IN THE NETHERLANDS RECEIVES BIONIC VISION SYSTEM

Pixium Vision announced the successful implantation of the first dry AMD patient in the Netherlands as part of the PRIMAvera pivotal trial. The study's expansion into the Netherlands follows approval by the Dutch Ministry of Health, Welfare and Sport and successful implantations at clinical sites in France, Germany, and the United Kingdom.

The trial is designed to confirm the safety and efficacy of the Prima System for patients with atrophic dry AMD. A total of 38 patients will be enrolled in the open-label, baseline-controlled, non-randomized, multicenter, prospective, single-arm pivotal trial. The primary efficacy endpoint is the number of patients with an improvement of at least 0.2 logMAR from baseline after 12 months; the primary safety endpoint is the number and severity of serious adverse events at 12 months.

The Prima System consists of a subretinal miniature photovoltaic wireless implant, a pair of glasses with a camera and digital projector, and a pocket processor. The company also received regulatory approval for its remote rehabilitation system, allowing study participants to conduct the majority of their rehabilitation sessions from home after completing the initial in-office sessions. The remote rehabilitation uses apps designed for patients enrolled in the PRIMAvera trial and capitalizes on gamification principles to better engage patients and improve efficacy, Lloyd Diamond, chief executive officer of Pixium Vision, said in a press release. "We also expect the remote patient engagement platform, thanks to upcoming additional functionality, to encourage better

communication between patients and their physicians and among patients themselves," he added.

Pixium Vision plans to open additional clinical trial sites in Spain and Italy, with the PRIMAvera read-out expected by the end of 2023.

ADAPTIVE OPTICS REVEAL VARIATIONS IN VITELLIFORM MACULAR DYSTROPHY

Researchers from the National Eye Institute (NEI) have discovered that cell densities surrounding the retinal lesions characteristic of vitelliform macular dystrophy (VMD) vary by gene mutation.[1]

The team used genetic testing and multimodal adaptive optics imaging to assess 11 patients with VMD. All patients showed reduced cone and retinal pigment epithelium (RPE) cell densities within the lesions (37% of normal cone density and 8.4% of normal RPE density). Surrounding the lesions, the cell densities were slightly reduced and varied based on the associated gene mutation. *IMPG1* and *IMPG2* mutations had a greater effect on photoreceptor cell density compared with RPE cell density, while the opposite was true for eyes with *PRPH2* and *BEST1* mutations. This trend held true even in fellow eyes that did not present with a VMD lesion.[1]

"These findings provide insight into the cellular pathogenesis of disease in VMD," the researchers concluded in their paper.[1]

"The NEI's long-term investment in imaging technology is changing our understanding of eye diseases," added NEI Director Michael F. Chiang, MD, in a press release. "This study is just one example of how improved imaging can reveal subtle details about pathology in a rare eye disease that can inform the development of therapeutics."

1. Liu T, Aguilera N, Bower AJ, et al. Photoreceptor and retinal pigment epithelium relationships in eyes with vitelliform macular dystrophy revealed by multimodal adaptive optics imaging. *Invest Ophthalmol Vis Sci*. 2022;63(8):27.

LUMITHERA RELEASES POSITIVE DATA ON PHOTOBIOMODULATION THERAPY

Data from LumiThera's LIGHTSITE III clinical trial showed an improvement in vision for patients with dry AMD treated with photobiomodulation (PBM) using the company's Valeda Light Delivery System.

The phase 3, randomized, double-masked, multicenter trial, which included 100 participants (148 eyes total) and compared BCVA at 13 months, met its primary efficacy endpoints when comparing the PBM group (91 eyes) with a sham treatment group (54 eyes). PBM-treated eyes showed a mean improvement of approximately 5.5 letters from baseline at month 13 ($P < .0001$). In the PBM treatment group responders, 26% achieved an improvement of greater than 10 letters (mean of 12.8 letters).

In addition, PBM-treated eyes demonstrated no significant increase in drusen at the 13-month timepoint compared with baseline, while eyes in the control group did.[1] As for disease progression, 1.8% of sham eyes converted to wet AMD by month 13 compared with 5.4% of PBM-treated eyes. The occurrence of new geographic atrophy was significantly higher in the sham group compared with the PBM group (9.8% of participants vs 1.1%, respectively).[1]

LumiThera plans to follow all participants for up to 24 months to continue to assess safety. To date, the safety data suggest a favorable profile for the PBM therapy.[1] ■

1. LumiThera presents LIGHTSITE III trial data showing improvement in vision in intermediate dry age-related macular degeneration [Press release]. June 22, 2022. Accessed July 21, 2022. www. lumithera.com/lumithera-presents-us-lightsite-iii-trial-data-showingimprovement-in-vision-in-intermediate-dry-age-related-macular-degeneration

Pharma Updates From Eyewire+

This summer has witnessed at least two companies beginning phase 2 clinical trials of investigative products for the treatment of retinal diseases, and others launching approved products into new markets.

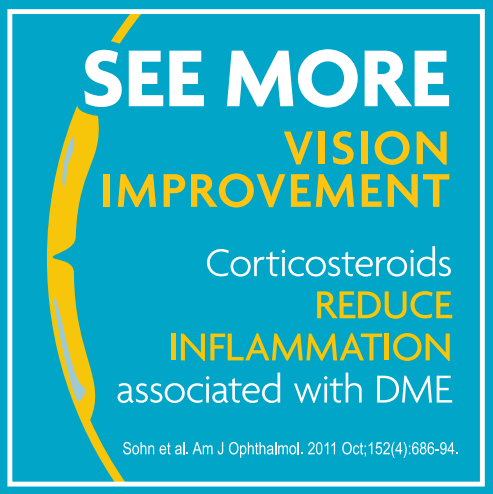
In July, **Alimera Sciences Europe Limited**, an Ireland-based subsidiary of Alimera, announced plans to launch the 0.19 mg fluocinolone acetonide intravitreal sustained release implant (Iluvien) for the treatment of noninfectious posterior uveitis in France in collaboration with its distributor, Horus Pharma SAS. Horus has received pricing and reimbursement approval for this indication from the Economics Committee for Health Products in France, according to a press release.

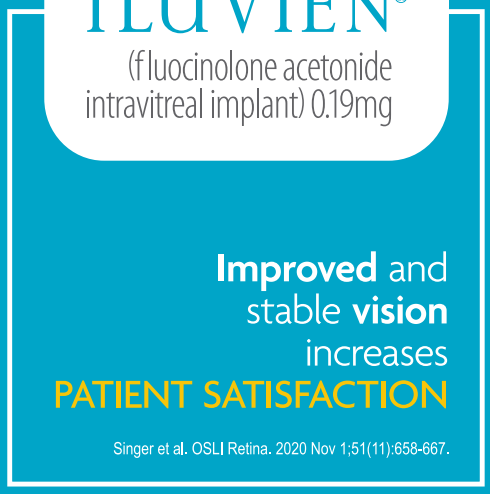
Nanoscope Therapeutics has dosed the first participant of its phase 2 clinical trial of the multicharacteristic opsin (MCO-010) ambient-light activatable optogenetic monotherapy for the treatment of Stargardt disease, according to a press release from the company. The trial will enroll six patients to receive the 1.2E11 gc/eye dose of MCO-010, a single-injection gene therapy that reprograms healthy retinal cells to become photosensitive. Six-month safety and efficacy data from the trial are expected in the first quarter of 2023.

EyePoint Pharmaceuticals began the phase 2 clinical trial of its investigational sustained delivery anti-VEGF maintenance treatment for wet AMD (EYP-1901) with the dosing of the first trial participant, according to a company press release. The trial is expected to enroll 150 patients and will compare 6-month visual acuity gains associated with injection of EYP-1901 with those of an aflibercept (Eylea, Regeneron) control group.

Coherus BioSciences announced in a press release last month the FDA approval of ranibizumab-eqrn (Cimerli), an interchangeable biosimilar to ranibizumab (Lucentis, Genentech/Roche), for the treatment of wet AMD, diabetic macular edema, diabetic retinopathy, retinal vein occlusion, and myopic choroidal neovascularization. It is the first and only biosimilar to ranibizumab that is approved for all five indications, according to the press release. The US commercial launch of this biosimilar is expected in October.

Check out more of the latest eye care news at ***Eyewire+.***





ILUVIEN with CONTINUOUS MICRODOSING™ can reduce the recurrence of edema by treating the underlying inflammation that drives DME.[1,2]

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INDICATION

ILUVIEN® (fluocinolone acetonide intravitreal implant) 0.19 mg is indicated for the treatment of diabetic macular edema (DME) in patients who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure.

Important Safety Information

CONTRAINDICATIONS

- ILUVIEN 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.
- ILUVIEN is contraindicated in patients with glaucoma who have cup to disc ratios of greater than 0.8.
- ILUVIEN is contraindicated in patients with known hypersensitivity to any components of this product.

WARNINGS AND PRECAUTIONS

- Intravitreal injections, including those with ILUVIEN, have been associated with endophthalmitis, eye inflammation, increased intraocular pressure, and retinal detachments. Patients should be monitored following the intravitreal injection.
- Use of corticosteroids including ILUVIEN 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.
- 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 (ILUVIEN 82%; sham 50%) and intraocular pressure elevation of ≥ 10 mm Hg (ILUVIEN 34%; sham 10%).

Please see brief summary of Prescribing Information on the following page. You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

[1]Deuchler SK, et al., Arch Clin Exp Ophthalmol. 2022 Mar 3. doi: 10.1007/s00417-022-05564-2. Epub ahead of print.

[2]Singer M, et al. Ophthalmology. 2022. doi: 10.1016/j.ophtha.2022.01.015. Online ahead of print.

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BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

ILUVIEN® (fluocinolone acetonide intravitreal implant) 0.19 mg
For Intravitreal Injection

INDICATIONS AND USAGE

ILUVIEN® (fluocinolone acetonide intravitreal implant) 0.19 mg is indicated for the treatment of diabetic macular edema in patients who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure.

CONTRAINDICATIONS

Ocular or Periocular Infections: **ILUVIEN** 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.

Glaucoma: **ILUVIEN** is contraindicated in patients with glaucoma who have cup to disc ratios of greater than 0.8.

Hypersensitivity: **ILUVIEN** 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 **ILUVIEN**, have been associated with endophthalmitis, eye inflammation, increased intraocular pressure, and retinal detachments. Patients should be monitored following the intravitreal injection.

Steroid-related Effects: Use of corticosteroids including **ILUVIEN** 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

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 **ILUVIEN** 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.

ILUVIEN was studied in two multicenter, randomized, sham-controlled, masked trials in which patients with diabetic macular edema were treated with either **ILUVIEN** (n=375) or sham (n=185). Table 1 summarizes safety data available when the last subject completed the last 36-month follow-up visit for the two primary **ILUVIEN** trials. In these trials, subjects were eligible for retreatment no earlier than 12 months after study entry. Over the three-year follow-up period, approximately 75% of the **ILUVIEN** treated subjects received only one **ILUVIEN** implant.

Table 1: Ocular Adverse Reactions Reported by ≥1% of Patients and Non-ocular Adverse Reactions Reported by ≥5% of Patients

Adverse Reactions	ILUVIEN (N=375) n (%)	Sham (N=185) n (%)
Ocular		
Cataract[1]	192/235[2] (82%)	61/121[2] (50%)
Myodesopsia	80 (21%)	17 (9%)
Eye pain	57 (15%)	25 (14%)
Conjunctival haemorrhage	50 (13%)	21 (11%)
Posterior capsule opacification	35 (9%)	6 (3%)
Eye irritation	30 (8%)	11 (6%)
Vitreous detachment	26 (7%)	12 (7%)
Conjunctivitis	14 (4%)	5 (3%)
Corneal oedema	13 (4%)	3 (2%)
Foreign body sensation in eyes	12 (3%)	4 (2%)
Eye pruritus	10 (3%)	3 (2%)
Ocular hyperaemia	10 (3%)	3 (2%)
Optic atrophy	9 (2%)	2 (1%)
Ocular discomfort	8 (2%)	1 (1%)
Photophobia	7 (2%)	2 (1%)
Retinal exudates	7 (2%)	0 (0%)
Anterior chamber cell	6 (2%)	1 (1%)
Eye discharge	6 (2%)	1 (1%)

Table 1 (continued)

Adverse Reactions	ILUVIEN (N=375) n (%)	Sham (N=185) n (%)
Non-ocular		
Anemia	40 (11%)	10 (5%)
Headache	33 (9%)	11 (6%)
Renal failure	32 (9%)	10 (5%)
Pneumonia	28 (7%)	8 (4%)

[1] Includes cataract, cataract nuclear, cataract subcapsular, cataract cortical and cataract diabetic in patients who were phakic at baseline. Among these patients, 80% of **ILUVIEN** subjects vs. 27% of sham-controlled subjects underwent cataract surgery.

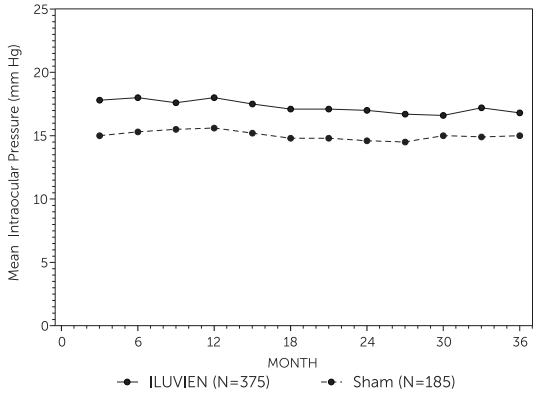
[2] 235 of the 375 **ILUVIEN** subjects were phakic at baseline; 121 of 185 sham-controlled subjects were phakic at baseline.

Increased Intraocular Pressure

Table 2: Summary of Elevated IOP-Related Adverse Reactions

Event	ILUVIEN (N=375) n (%)	Sham (N=185) n (%)
Non-ocular		
IOP elevation ≥ 10 mm Hg from baseline	127 (34%)	18 (10%)
IOP elevation ≥ 30 mm Hg	75 (20%)	8 (4%)
Any IOP-lowering medication	144 (38%)	26 (14%)
Any surgical intervention for elevated intraocular pressure	18 (5%)	1 (1%)

Figure 1: Mean IOP during the study



Cataracts and Cataract Surgery

At baseline, 235 of the 375 **ILUVIEN** subjects were phakic; 121 of 185 sham-controlled subjects were phakic. The incidence of cataract development in patients who had a phakic study eye was higher in the **ILUVIEN** group (82%) compared with sham (50%). The median time of cataract being reported as an adverse event was approximately 12 months in the **ILUVIEN** group and 19 months in the sham group. Among these patients, 80% of **ILUVIEN** subjects vs. 27% of sham-controlled subjects underwent cataract surgery, generally within the first 18 months (Median Month 15 for both **ILUVIEN** group and for sham) of the studies.

Post-marketing Experience: The following reactions have been identified during post-marketing use of **ILUVIEN** in clinical practice. Because they are reported voluntarily, estimates of frequency cannot be made. The reactions, which have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to **ILUVIEN**, or a combination of these factors, include reports of drug administration error and reports of the drug being ineffective.

USE IN SPECIFIC POPULATIONS

Pregnancy: Pregnancy Category C.
There are no adequate and well-controlled studies of **ILUVIEN** in pregnant women. Animal reproduction studies have not been conducted with fluocinolone acetonide. Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. **ILUVIEN** should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Systemically administered corticosteroids are present in human milk and could suppress growth and interfere with endogenous corticosteroid production. The systemic concentration of fluocinolone acetonide following intravitreal treatment with **ILUVIEN** is low. It is not known whether intravitreal treatment with **ILUVIEN** could result in sufficient systemic absorption to produce detectable quantities in human milk. Exercise caution when **ILUVIEN** is administered to a nursing woman.

Pediatric Use: Safety and effectiveness of **ILUVIEN** in pediatric patients have not been established.

Geriatric Use: No overall differences in safety or effectiveness have been observed between elderly and younger patients.

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DUKE FELLOWS AND FACULTY UNITE


The 2022 fellows Advanced Vitreous Surgery course was packed with educational sessions and hands-on learning.

BY JORDAN DEANER, MD, AND HENRY FENG, MD

The Duke Fellows Advanced Vitreous Surgery (fAVS) course was back in person for its 2022 rendition, combining medical and surgical lectures, a robust wet lab experience, and numerous talks on career development. First- and second-year retina and uveitis fellows, along with a few ophthalmology residents, traveled to Durham, North Carolina, to partake in this interactive course led by Lejla Vajzovic, MD; Dilraj S. Grewal, MD; Xi Chen, MD; Durga Borkar, MD; and the Duke retina faculty. Guest faculty included Carl Awh, MD, FASRS; Amani A. Fawzi, MD; Jorge Fortun, MD; Ivana Kim, MD; Szilárd Kiss, MD; Yannek Leiderman, MD, PhD; and Phoebe Lin, MD, PhD.

UVEITIS THERAPIES

Dr. Lin kicked off the course with a discussion of this year's new and emerging therapies for uveitis. She began by discussing the triamcinolone acetonide injectable suspension (Xipere, Bausch + Lomb and Clearside Biomedical), recently FDA-approved for the treatment of uveitic cystoid macular edema (CME). The treatment decreased the risk of glaucoma and cataract formation compared with contemporary therapies, she said. She also presented on future local nonsteroidal options for uveitis, including an intravitreal interleukin-6, intravitreal sirolimus, and electro-transfer of anti-TNF-alpha plasmids into the ciliary body. Dr. Lin finished by reviewing the novel use of systemic immunosuppressive therapies. Tocilizumab (Actemra, Genentech/Roche) has been shown to be effective in the treatment of noninfectious uveitis, particularly when CME is present, she noted. Finally, the JAK/STAT inhibitors (ie, filgotinib, tofacitinib, baricitinib) are small-molecule oral medications that have shown promise in the treatment of noninfectious intraocular inflammation.

DEBATES

The fAVS debates were a highlight of this year's conference. The sparring began between Dr. Fawzi and Dr. Grewal, who debated on the utility of OCT angiography (OCTA). Dr. Fawzi began by stating, "OCTA is indispensable in the clinic," and remarked on its ability to identify and localize macular neovascularization (MNV) with much greater resolution than fluorescein angiography (FA). Similarly, OCTA can identify

Image courtesy of Kevin Caldwell.

Figure. Course attendees got the chance to try the Zeiss Rescan system with the Artevo 3D heads-up display (Carl Zeiss Meditec) during the fAVS wet lab. Guiding the station was Phoebe Lin, MD, PhD, (left of the surgeon) and Glenn J. Jaffe, MD (right).

nonexudative MNV and differentiate MNV from posterior uveitis, both of which can be missed on FA. Dr. Grewal took the opposing viewpoint, noting that OCTA is peppered with weaknesses that cripple it as a reliable imaging tool, including poor repeatability, poor scan quality, numerous artifacts that can simulate vascular lesions, lack of standard nomenclature, and an inability to quantify leakage. Additionally, OCTA image acquisition times are long, and, frequently, the unique pathologies that can only be detected by OCTA (ie, nonexudative MNV) don't result in a change in patient management.

The second debate pitted Dr. Liederman against Dr. Kiss on the topic of artificial intelligence (AI) in retina. In support of AI, Dr. Liederman began by describing the rise and future direction of AI with a particular focus on diagnostics. He noted that AI tools for detecting diabetic retinopathy (DR) have become increasingly accurate in correctly identifying and grading DR. AI can pick up on patterns that we are unable to see or detect, Dr. Liederman said. In one study of ultra-widefield fundus photos, AI was able to accurately predict gender and risk of a major cardiac event. Dr. Liederman imagined a future in which AI analyzes live surgeries and provides active feedback to help surgeons avoid errors.

Dr. Kiss began his counter-argument by noting that AI successes make great headlines, but that AI's efficacy in the real world is often disappointing. He pointed out several

high-profile medical AI programs that ultimately failed when released for real-world use, including IBM Watson, EPIC's predictive sepsis model, and Google Health—all of which were very successful in tightly controlled lab environments but were underwhelming in clinical practice.

TOUGH SURGERIES

Dr. Chen presented her experience managing difficult diabetic vitrectomies and the lessons learned over the past few years. She started by emphasizing that diabetics are a difficult patient population with a high risk of loss to follow-up; they often present late in the disease process and are hesitant to pursue surgery. Once in the OR, it is imperative to first release as much anterior-posterior traction as possible and then segment and peel the fibrovascular proliferation. Dr. Chen deliberated about how much dissection is required to attain macular anatomic success and noted that she has fluctuated throughout her career. "You must peel enough to relieve traction off the macula, but not too much that you create a break unnecessarily," she said. Dr. Chen emphasized that early conversion to bimanual surgery will ultimately save time in these challenging cases.

DATA DISCOVERY

Dr. Borkar highlighted the power of leveraging real-world evidence and large data for clinical discovery. She described early epidemiologic studies with an emphasis on structured ophthalmologic data such as vision, pressure, and diagnosis codes. While ICD-10 codes and structured data may be useful in common diseases such as AMD and DR, other databases, such as claims data and FDA adverse events, may also be analyzed, as was done in the discovery of pentosan polysulfate maculopathy. She emphasized that clinical trial design may be influenced by large data resources and, importantly, data quality must be considered carefully when planning studies involving real-world evidence and data registries.

HANDS-ON LEARNING

The fAVS course is known for hosting one of the most immersive wet lab experiences available to trainees. Fellows can trial vitreoretinal surgical instruments, viewing systems, and techniques guided by expert faculty and industry representatives. Sharon Fekrat, MD, demonstrated the installation of the port delivery system with ranibizumab (Genentech/Roche), a surgical solution that may decrease injection burden and allow for more stable drug concentrations. Nearby, Dr. Fortun amazed fellows with the Beyeonics One (Beyeonics Surgical), a virtual reality viewing system that may be an ergonomic and intuitive alternative to microscope-based viewing systems for vitreoretinal surgery.

Glenn J. Jaffe, MD, and Dr. Lin demonstrated intraoperative OCT on the Zeiss Rescan system with the Artevo 3D heads-up display (Carl Zeiss Meditec) and highlighted surgical pearls for tumor biopsy and diagnostic vitrectomy (Figure). In a similar vein, we showcased Duke's custom swept-source intraoperative OCT system integrated with the Alcon Ngenuity 3D head-up display and guided fellows in membrane peeling using a variety of vitreoretinal forceps. Dr. Kiss and Tso-Ting Lai, MD, showcased subretinal delivery using the MedOne microinjector, and Dr. Leiderman and Dr. Kim demonstrated tips for solo surgery, emphasizing the versatility of the chandelier light when performing peripheral vitreous shaving. Dr. Awh and Eric Postel, MD, highlighted pearls for retinal detachment (RD) repair using the Bausch + Lomb Stellaris Elite system with a bi-blade cutter.

LIGHTNING ROUNDS

One of the most exciting and longstanding traditions of Duke fAVS is the fellow-run Machemer vitreoretinal surgical rounds. The panelists offered their approaches, tips, and pearls on a variety of complex surgical cases submitted by fellow attendees. Ishrat Ahmed, MD, PhD, from Massachusetts Eye and Ear Infirmary, presented a complex repair of a funnel RD with proliferative vitreoretinopathy in a monocular patient. Tedi Begaj, MD, from Associated Retinal Consultants/Beaumont Hospital, showcased the repair of a chronic large macular hole with an amniotic membrane graft in a patient with multiple prior RD surgeries. Samuel Hobbs, MD, from the University of California Los Angeles, showed a macula-on rhegmatogenous RD repair using a primary scleral buckle technique and a tire segment, encircling band, and subretinal fluid drainage. Grant Justin, MD, from Duke, presented a case of coloboma-associated RD with fibrin gluing of the intercalary membrane, endolaser of the coloboma edges, and C_3F_8 tamponade. Michael Simmons, MD, from the University of Minnesota, demonstrated a complex case of pars plana lensectomy and intraocular foreign body removal with a foreign body magnet in the setting of multidrug resistant *Acinetobacter* endophthalmitis. Delu Song, MD, from the University of California San Diego's Shiley Eye Institute, presented a case of recurrent exudative RD in a nanophthalmic eye treated with scleral windows and adjunctive mitomycin C. ■

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LIFETIME MENTORSHIP AWARD: A VBS TRADITION

This year's lecture by Julia A. Haller, MD, focused on diversity, equity, and inclusion in retina.

BY THOMAS LAZZARINI, MD

As is tradition, the 10th annual Vit-Buckle Society (VBS) meeting didn't shy away from the tough conversations that are necessary to move the field of retina forward. This year's Lifetime Mentorship lecture, given by the 2022 Lifetime Mentorship Award honoree, Julia A. Haller, MD, centered on diversity, equity, and inclusion (Figure). Here's what she had to say.

A LIFETIME OF ADVICE

Dr. Haller began her lecture with a lighthearted story about being a woman in the field retina. She recounted that 30 years ago she was the first female member of the American Society of Retina Specialists and received a certificate commemorating "his role in the advancement of vitreoretinal surgery." As honored as she was to become a member, she joked that the time had come for her to come out as a female in retina. Amid the many responses to her questioning the certificate's wording, the one from Jerald A. Bovino, MD, stood out to her. He sarcastically joked that the simplest way to fix the problem was for Dr. Haller to change her sex and go by "Julian" because there was room on the certificate for an "n" and there would be no need to reprint the document.

This was one small personal example of a longstanding lack of and need for sensitivity to equity in the field of retina and elsewhere in medicine, Dr. Haller stated.

To move the needle on diversity, equity, and inclusion, we need more than public demonstrations of support—we must tip the balance through research, evidence, and hard work, she said. The benefits of diversity are well-documented in the clinic, the classroom, and the boardroom. Dr. Haller cited a Wharton School of Business course by Deputy Dean Nancy Rothbard, PhD, during which she emphasized that diversity in the boardroom can be uncomfortable and can take time to implement but is more inclusive of a broader set of stakeholders and yields higher quality decisions.

Perhaps the slight discomfort of being in an unfamiliar group helps with deliberation and decision making, she mused. One key insight that has been borne out in research is that participants come to board meetings better prepared when the board is diverse. Additionally, according to the literature, diverse groups demonstrate more decision-making accuracy, according to Dr. Haller.

Image courtesy of Kevin Caldwell.

Figure. The VBS leadership presented Dr. Haller with the 2022 Lifetime Mentorship Award. Pictured here [left to right]: Back row: Jayanth Sridhar, MD, and Basil K. Williams Jr, MD. Front row: Mrinali Gupta, MD; Yoshihiro Yonekawa, MD; Avni P. Finn, MD, MBA; Dr. Haller, Nika Bagheri, MD; Priya Vakharia, MD; and Charles C. Wykoff, MD, PhD.

RESEARCH ROUNDUP

The quest for gender and racial equity in academic medicine is ongoing, and retina has made some strides, Dr. Haller admitted. She dove into the literature to share examples and demonstrate that the playing field is still far from level. She noted that female residents have fewer cases than male residents, and more female researchers are first or junior authors, but still lag significantly in senior authorship.[1,2] When the last author of a paper is a woman, the first author is far more likely to be a woman than when the last author is a man, she added.[2] The good news is that, in 2020, women authored more papers and were more frequently the senior author than their representation in the field in general.[2]

Despite the increased attention to the importance of gender equity over the last few decades and the progress made, there is still significant room for improvement. Women have fewer industry ties and are paid less regardless of the role, whether that's honoraria, speaking opportunities, or consultancies. In a recent study, women were found to occupy fewer than one in four faculty roles at academic meetings.[3] However, when at least one woman *was* included as a member of the program committee, more female faculty members were invited. Between 2015 and 2019, female editorial authorship increased 68%, but women still represented only 5% of all editorial authors.

Unlike gender diversity, ethnic and socioeconomic diversity has mostly been ignored by academic medicine, Dr. Haller noted. She discussed a study recently published by Soares et al that looked at geographic disparities and access to neovascular AMD trials.[4] Soares and her team identified 42 trials and 829 unique trial sites and matched them with the surrounding census data. The researchers found that patients in the Midwest and South had longer drives to the clinical trial sites; longer distance travelled was associated with rural populations, lower education levels, and identifying as an ethnic minority. The data suggest that the benefits of medical research—in terms of treatment, education, and engagement—is more readily available to some groups compared with others. It's no surprise that researchers are working harder to better understand how diverse groups of patients differ with respect to various ophthalmic conditions and treatments.

Dr. Haller then touched on data presented by M. Ali Khan, MD, who reported that Black patients have less visual acuity improvement than White patients when treated with ranibizumab (Lucentis, Genentech/Roche) for diabetic macular edema.[5] He was unable to analyze the relative efficacy for Asian or Hispanic patients because the trials did not include enough patients from these groups.

Komodo Health looked at larger numbers of patients to assess the relationship between patient care and patient race and ethnicity, Dr. Haller said. Preliminary data from 242,000 patients demonstrated that Black, Hispanic, and Asian patients were all less likely to receive anti-VEGF treatments than their White counterparts. Even among patients who were treated with anti-VEGF therapy, the likelihood that patients received off-label bevacizumab (Avastin, Genentech/Roche) compared with a branded medication was significantly greater among racial and ethnic minorities compared with White patients, Dr. Haller noted.

Unfortunately, an important disconnect remains in academic medicine, according to Dr. Haller. Research is clear that the number one cause of blindness among working-age people is diabetic eye disease, which disproportionately affects racial and ethnic minorities.[6,7] Despite this, racial and ethnic minority enrollment in clinical trials remains unacceptably low, making it challenging, if not impossible, to evaluate differences in response to therapy. In the real-world clinical setting, we know that racial minorities have worse access to care and are treated less frequently and with different drugs, Dr. Haller explained.

WAYS TO MAKE PROGRESS

She concluded by addressing several avenues toward a more diverse and inclusive field. There must be an emphasis on the recruitment of diverse patient populations into large clinical trials, and researchers must identify strategies to circumvent any barriers. Leaders must also emphasis the importance of training health care professionals who are representative of the patient population they serve. Now is the time to harness the outrage and determination unleashed by the events of the last few years to develop treatments and data to help our patients, Dr. Haller said.

To ensure a more equitable future, women and minorities must occupy positions of power—not just on the team, but leaders of the team, Dr. Haller emphasized. Stereotypes matter, she added; words like "bossy" can change the ambitions of girls and women. By their teenage years, many young women are not interested in leadership roles because they don't want to be labeled as "bossy." Women must know that it is OK to be ambitious. Dr. Haller suggested a turn-of-phrase to help: "I am not bossy, I am the boss."

Dr. Haller ended the way she began, with a personal touch. We all need heroes, teammates, and mentors, she said—for her that's Carol L. Shields, MD, and Marlene R. Moster, MD, among many others. Women and minorities in medicine need networking and mentorship, and the VBS is an inspiring example of that. "The organization has taken the ball and run with it over the past 10 years. Thank you for your hard work and hospitality," Dr. Haller concluded. "I look forward to continued collaboration." ■

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■ Financial disclosure: Consultant (Genentech/Roche, Regenxbio)

FERHINA S. ALI, MD, MPH

Please share with us your background.

My parents and three older siblings immigrated to the United States from India, and I was born and raised in New York. Observing my parents repeat their medical training while juggling a busy family life in a new country made a lasting impression and demonstrated how rewarding the field of medicine is. I pursued my undergraduate studies at the University of Rochester through the Rochester Early Medical Scholars Program and completed medical school at Johns Hopkins.

When did you know that you wanted to be a retina specialist?

During my residency at the University of California San Francisco (UCSF), I completed a retina rotation at the San Francisco Veterans Affairs. I worked closely with Daniel Schwartz, MD, who was instrumental in guiding and mentoring me as an ophthalmologist and retina specialist. He taught me how to think critically and holistically and impressed upon me the unique privilege and opportunity it is to train to become an ophthalmologist; he also shared with me how innovative and rewarding the field of retina is!

Who are your mentors?

I have been fortunate to have extraordinarily supportive mentors. My journey in ophthalmology was first inspired by my time with David Friedman, MD, PhD, MPH, who encouraged me to "think big" and to be creative with my potential career path. During residency, the rigorous yet warm environment created by the entire UCSF faculty shaped my early experiences in ophthalmology. Eugene de Juan, MD, in particular, continues to have a lasting effect on my personal and professional growth with his ongoing support, guidance, and generosity. During my retina fellowship at Wills Eye Hospital, I had a diverse experience learning from more than 15 exceptional retina mentors (I wish I could list them all here!). Nearly every day I am reminded of and grateful for the breadth and depth of the training I received at Wills and the obvious dedication and discipline that was imparted onto me. Last, but not least, borne out of the Wills fellowship are my "peer mentors"—a group chat of alums who are a sounding board for all things retina and otherwise.

Describe your current position.

I serve on the retina faculty at New York Medical College, a relatively new ophthalmology department led by Kelly Hutcheson, MD, MBA, with the rare opportunity to help shape the retina division, resident education, and clinical research. I also take care of patients at Westchester Medical Center, the only level 1 trauma center in the region and a safety net hospital. These practice settings allow me to take care of a diverse range of patients, agnostic of health insurance and background, including complex referrals and trauma cases. With time, I also hope to develop a clinical trials unit at New York Medical College, bringing the latest potential treatments to the patients in this region, who have historically been underserved.

What has been a memorable experience in your career?

After my fellowship, I was recruited by Geoffrey Tabin, MD, to serve as retina faculty and fellowship instructor for the Himalayan Cataract Project's Retina Fellowship Program. I spent time in Nepal working with Sisay Bekele, MD, who is now one of only a handful of vitreoretinal surgeons in the entire country of Ethiopia. I remain in awe of his persevering journey to become a retina specialist, and his commitment to bringing much-needed specialty care to his patients. I look forward to further developing this fellowship curriculum once travel to these regions is more feasible.

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

Choose a career path that will cement your training through a busy clinical and surgical practice early on. The learning process is ongoing, but once you've established credibility and consistency in your patient care and outcomes, you can focus on how you want to shape your career. Career development opportunities can be serendipitous, so it is important to stay openminded and connected. There is no preset prototype of a practicing retina specialist, so think broadly when developing the vision for your career, something I too am working on! ■

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DIAGNOSING EXOPHYTIC RETINAL CAPILLARY HEMANGIOBLASTOMA

Multimodal imaging is crucial when identifying this choroidal neovascularization masquerader.

BY JONATHAN F. RUSSELL, MD, PHD; VICTOR M. VILLEGAS, MD; PHILIP J. ROSENFELD, MD, PHD; AND J. WILLIAM HARBOUR, MD

Retinal capillary hemangioblastoma (RCH) is a rare tumor of the retinal vasculature that can occur sporadically or as part of von Hippel-Lindau (VHL) syndrome.[1] Identifying an RCH can lead to the diagnosis of VHL, an autosomal-dominant and potentially life-threatening multi-organ neoplastic syndrome. Most RCHs are endophytic, meaning they grow inward toward the vitreous cavity, resulting in a characteristic red-orange, nodular, vascularized mass with dilated feeder vessels that are usually straightforward to diagnose. However, exophytic RCHs grow in the direction of the subretinal space, resulting in a subtle ophthalmoscopic appearance that is more challenging to diagnose, particularly when located near the optic disc.[2] Exophytic juxtapapillary RCHs (JRCHs) can simulate more common conditions such as optic disc edema or peripapillary choroidal neovascularization (CNV).[2,3]

JRCH CASES

We recently published a retrospective case series describing the role of multimodal imaging for diagnosing exophytic JRCH (Figures 1-3).[4] Of the 12 patients with exophytic JRCH, six were male, and the average age was 54 years. Five patients had been previously diagnosed with VHL syndrome, while the other seven had negative clinical and genetic workups for VHL.

The initial referring diagnoses included JRCH (in those with known VHL), peripapillary CNV (three patients), neuroretinitis (two patients), optic disc metastasis (one patient), and branch retinal vein occlusion (one patient). Multiple RCHs were present in three of the five patients with VHL, and none of the patients without VHL had multiple lesions. Treatments included photodynamic therapy (PDT), intravitreal anti-VEGF injections, laser photocoagulation, intravitreal or sub-Tenon's triamcinolone, and observation.

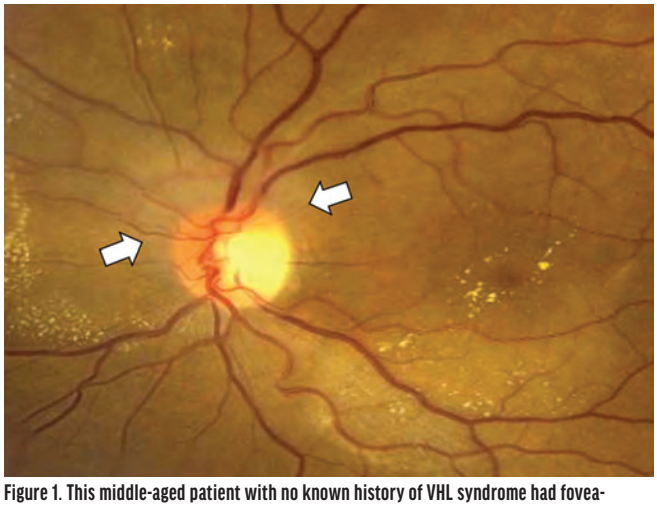

Figure 1. This middle-aged patient with no known history of VHL syndrome had fovea-involving exudation with decreased visual acuity. There was subtle opacification of the superior juxtapapillary retina, blurring of the superior disc margin (arrows), and remote hard exudates. The referral diagnosis was peripapillary CNV, but the macular edema had not responded to anti-VEGF injections. The patient was diagnosed with an exophytic JRCH.

THE CLINICAL PICTURE

The most common features of exophytic JRCHs are pink or red color (66%), lipid exudates (83%), and intraretinal fluid (92%).[4] OCT in all exophytic JRCHs showed hyperreflective lesions in the outer retina with choroidal shadowing. On fluorescein angiography (FA), all cases showed early hyperfluorescence with late leakage and staining. OCT angiography (OCTA) showed abnormal vasculature within the middle and outer retinal layers. The lesions were hypoautofluorescent, and on B-scan they were hyperechoic and vascularized.

Clinical examination alone was inadequate to confidently diagnose exophytic JRCH. Ophthalmoscopically, the lesions manifested as a subtle bulge at the disc margin, often with

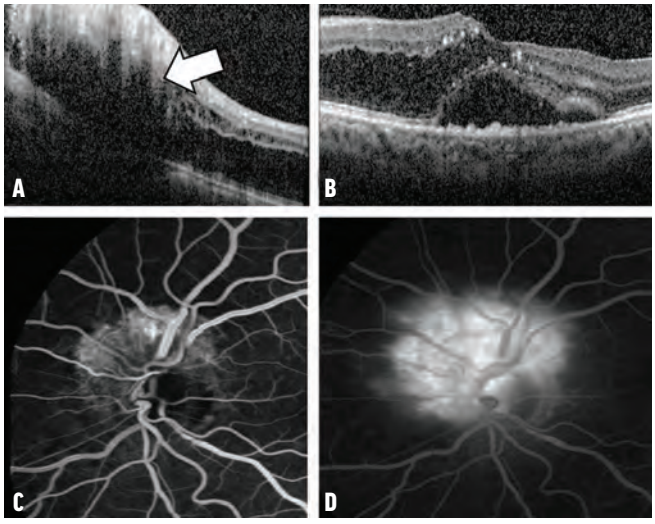

Figure 2. OCT through the juxtapapillary lesion in Figure 1 revealed a hyperreflective lesion (arrow) in the middle/outer retinal layers with outer retinal and choroidal shadowing and adjacent intraretinal fluid (A). Foveal OCT showed intraretinal fluid tracking from the disc and subretinal fluid (B). Early-frame FA showed hyperfluorescence of a juxtapapillary vascular lesion deep to the retinal vessels (C). Late-frame FA showed leakage/staining of the lesion (D).

remote lipid exudation. Lesions with a pink/red color were often mistaken for peripapillary CNV or a small subretinal hemorrhage. If they obscured the disc margin, they often mimicked optic disc edema or neuroretinitis. When the lesion caused pseudo-disc edema, the blurred disc margin was sectoral with hard exudates located farther from the disc than in papillitis or neuroretinitis. The differential diagnoses included combined hamartoma of the retina and retinal pigment epithelium, astrocytic hamartoma, and optic disc granuloma or metastasis.

IMAGING OPTIONS

Multimodal imaging is essential to differentiate these entities. For example, OCT of a peripapillary CNV will show a pigment epithelial detachment (PED) with associated subretinal vasculature, whereas exophytic JRCHs have no PED, and the abnormal vasculature resides in the middle/outer retinal layers. CNV tends to have more subretinal fluid than intraretinal fluid; the opposite is true for exophytic JRCH.

On FA, an eye with disc edema may have engorged disc vessels that are typically localized to the disc borders and encompass the entire disc, whereas the vessels of an exophytic JRCH extend beyond the disc border and only involve a segment of the disc. Swept-source (SS) OCTA can pinpoint the distribution and depth of abnormal vasculature, eliminating the need for dye-based angiography.[5]

HOW TO TREAT

Asymptomatic exophytic JRCHs require no treatment, but exudation can progress to threaten the fovea, so patients need to be monitored closely. Exophytic JRCHs in the papillomacular bundle are more likely to have macular exudation and vision loss.

We prefer full-fluence PDT as an initial treatment, sometimes supplemented with intravitreal anti-VEGF agents and intravitreal/periocular corticosteroids. Multiple PDT sessions may be necessary. Lesions outside of the papillomacular bundle can often be successfully treated with laser photocoagulation alone. Anti-VEGF therapy alone is generally inadequate to induce regression, although we recently used serial SS-OCTA imaging to demonstrate decreased vascular

(Continued on page 61)

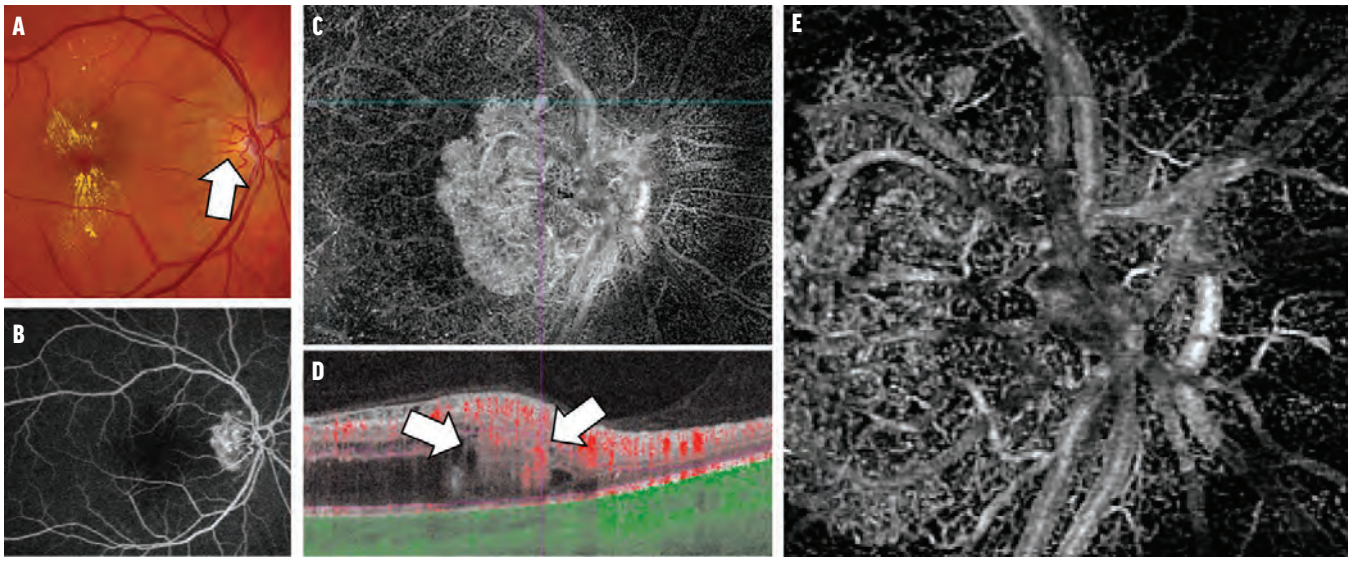

Figure 3. This patient with no known history of VHL syndrome had subtle thickening of the temporal juxtapapillary retina with sectoral blurring of the disc margin, dilated draining veins (arrow), remote hard exudates, and foveal macular edema that had not responded to 18 monthly anti-VEGF injections (A). The early-frame FA showed hyperfluorescence of a juxtapapillary vascular lesion deep to the retinal vessels (B). A 9x9 mm SS-OCTA image confirmed an intraretinal juxtapapillary vascular lesion (C). The corresponding B-scan showed a hyperreflective lesion (arrows) within the outer retinal layers and no PED (D). A 3x3 mm SS-OCTA image of the lesion characterized the individual vessels of the lesion in high resolution (E). The patient was diagnosed with exophytic JRCH.

WHAT COULD THEY SEE THIS YEAR?

EYLEA® (aflibercept) Injection
For Intravitreal Injection

10 years & COUNTING
FDA approved 2011

Inspired by real patients with Wet AMD, MEfRVO, and DME.

- **First-line efficacy and safety data from 8 clinical trials[1]**
- **Dosing flexibility across several FDA-approved indications[1]**
- **>20 million doses administered to >1.6 million eyes since launch[2]**
- **Broad first-line coverage and dedicated support with EYLEA4U®[2]**

EXPLORE THE DATA
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IMPORTANT SAFETY INFORMATION
CONTRAINDICATIONS

- EYLEA is contraindicated in patients with ocular or periocular infections, active intraocular inflammation, or known hypersensitivity to aflibercept or to any of the excipients in EYLEA.

WARNINGS AND PRECAUTIONS

- Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately. Intraocular inflammation has been reported with the use of EYLEA.
- Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with VEGF inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately.
- There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA compared with 1.5% (9 out of 595) in patients treated with ranibizumab; through 96 weeks, the incidence was 3.3% (60 out of 1824) in the EYLEA group compared with 3.2% (19 out of 595) in the ranibizumab group. The incidence in the DME studies from baseline to week 52 was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

ADVERSE REACTIONS

- Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment.
- The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and intraocular pressure increased.
- Patients may experience temporary visual disturbances after an intravitreal injection with EYLEA and the associated eye examinations. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

INDICATIONS

EYLEA® (aflibercept) Injection 2 mg (0.05 mL) is indicated for the treatment of patients with Neovascular (Wet) Age-related Macular Degeneration (AMD), Macular Edema following Retinal Vein Occlusion (RVO), Diabetic Macular Edema (DME), and Diabetic Retinopathy (DR).

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

References: 1. EYLEA® (aflibercept) Injection full U.S. Prescribing Information. Regeneron Pharmaceuticals, Inc. June 2021. **2.** Data on file. Regeneron Pharmaceuticals, Inc.

REGENERON®

777 Old Saw Mill River Road, Tarrytown, NY 10591 06/2022 EYL.22.05.0005

EYLEA® (aflibercept) Injection
For Intravitreal Injection

BRIEF SUMMARY—Please see the EYLEA full Prescribing Information available on HCP.EYLEA.US for additional product information.

1 INDICATIONS AND USAGE
EYLEA is a vascular endothelial growth factor (VEGF) inhibitor indicated for the treatment of patients with:

Neovascular (Wet) Age-Related Macular Degeneration (AMD), Macular Edema Following Retinal Vein Occlusion (RVO), Diabetic Macular Edema (DME), Diabetic Retinopathy (DR).

4 CONTRAINDICATIONS

4.1 Ocular or Periocular Infections
EYLEA is contraindicated in patients with ocular or periocular infections.

4.2 Active Intraocular Inflammation
EYLEA is contraindicated in patients with active intraocular inflammation.

4.3 Hypersensitivity
EYLEA is contraindicated in patients with known hypersensitivity to aflibercept or any of the excipients in EYLEA. Hypersensitivity reactions may manifest as rash, pruritus, urticaria, severe anaphylactic/anaphylactoid reactions, or severe intraocular inflammation.

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis and Retinal Detachments
Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments [*see Adverse Reactions (6.1)*]. Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately [*see Patient Counseling Information (17)*].

5.2 Increase in Intraocular Pressure
Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA [*see Adverse Reactions (6.1)*]. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with vascular endothelial growth factor (VEGF) inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately.

5.3 Thromboembolic Events
There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA compared with 1.5% (9 out of 595) in patients treated with ranibizumab; through 96 weeks, the incidence was 3.3% (60 out of 1824) in the EYLEA group compared with 3.2% (19 out of 595) in the ranibizumab group. The incidence in the DME studies from baseline to week 52 was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

6 ADVERSE REACTIONS
The following potentially serious adverse reactions are described elsewhere in the labeling:
- Hypersensitivity [*see Contraindications (4.3)*]
- Endophthalmitis and retinal detachments [*see Warnings and Precautions (5.1)*]
- Increase in intraocular pressure [*see Warnings and Precautions (5.2)*]
- Thromboembolic events [*see Warnings and Precautions (5.3)*]

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in other clinical trials of the same or another drug and may not reflect the rates observed in practice.
A total of 2980 patients treated with EYLEA constituted the safety population in eight phase 3 studies. Among those, 2379 patients were treated with the recommended dose of 2 mg. Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment. The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and intraocular pressure increased.

Neovascular (Wet) Age-Related Macular Degeneration (AMD). The data described below reflect exposure to EYLEA in 1824 patients with wet AMD, including 1223 patients treated with the 2-mg dose, in 2 double-masked, controlled clinical studies (VIEW1 and VIEW2) for 24 months (with active control in year 1).
Safety data observed in the EYLEA group in a 52-week, double-masked, Phase 2 study were consistent with these results.

Table 1: Most Common Adverse Reactions (≥1%) in Wet AMD Studies

	Baseline to Week 52		Baseline to Week 96	
Adverse Reactions	EYLEA (N=1824)	Active Control (ranibizumab) (N=595)	EYLEA (N=1824)	Control (ranibizumab) (N=595)
Conjunctival hemorrhage	25%	28%	27%	30%
Eye pain	9%	9%	10%	10%
Cataract	7%	7%	13%	10%
Vitreous detachment	6%	6%	8%	8%
Vitreous floaters	6%	7%	8%	10%
Intraocular pressure increased	5%	7%	7%	11%
Ocular hyperemia	4%	8%	5%	10%
Corneal epithelium defect	4%	5%	5%	6%
Detachment of the retinal pigment epithelium	3%	3%	5%	5%
Injection site pain	3%	3%	3%	4%
Foreign body sensation in eyes	3%	4%	4%	4%
Lacrimation increased	3%	1%	4%	2%
Vision blurred	2%	2%	4%	3%
Intraocular inflammation	2%	3%	3%	4%
Retinal pigment epithelium tear	2%	1%	2%	2%
Injection site hemorrhage	1%	2%	2%	2%
Eyelid edema	1%	2%	2%	3%
Corneal edema	1%	1%	1%	1%
Retinal detachment	<1%	<1%	1%	1%

Less common serious adverse reactions reported in <1% of the patients treated with EYLEA were hypersensitivity, retinal tear, and endophthalmitis.

Macular Edema Following Retinal Vein Occlusion (RVO). The data described below reflect 6 months exposure to EYLEA with a monthly 2 mg dose in 218 patients following central retinal vein occlusion (CRVO) in 2 clinical studies (COPERNICUS and GALILEO) and 91 patients following branch retinal vein occlusion (BRVO) in one clinical study (VIBRANT).

Table 2: Most Common Adverse Reactions (≥1%) in RVO Studies

	CRVO		BRVO	
Adverse Reactions	EYLEA (N=218)	Control (N=142)	EYLEA (N=91)	Control (N=92)
Eye pain	13%	5%	4%	5%
Conjunctival hemorrhage	12%	11%	20%	4%
Intraocular pressure increased	8%	6%	2%	0%
Corneal epithelium defect	5%	4%	2%	0%
Vitreous floaters	5%	1%	1%	0%
Ocular hyperemia	5%	3%	2%	2%
Foreign body sensation in eyes	3%	5%	3%	0%
Vitreous detachment	3%	4%	2%	0%
Lacrimation increased	3%	4%	3%	0%
Injection site pain	3%	1%	1%	0%
Vision blurred	1%	<1%	1%	1%
Intraocular inflammation	1%	1%	0%	0%
Cataract	<1%	1%	5%	0%
Eyelid edema	<1%	1%	1%	0%

Less common adverse reactions reported in <1% of the patients treated with EYLEA in the CRVO studies were corneal edema, retinal tear, hypersensitivity, and endophthalmitis.

Diabetic Macular Edema (DME) and Diabetic Retinopathy (DR). The data described below reflect exposure to EYLEA in 578 patients with DME treated with the 2-mg dose in 2 double-masked, controlled clinical studies (VIVID and VISTA) from baseline to week 52 and from baseline to week 100.

Table 3: Most Common Adverse Reactions (≥1%) in DME Studies

	Baseline to Week 52		Baseline to Week 100	
Adverse Reactions	EYLEA (N=578)	Control (N=287)	EYLEA (N=578)	Control (N=287)
Conjunctival hemorrhage	28%	17%	31%	21%
Eye pain	9%	6%	11%	9%
Cataract	8%	9%	19%	17%
Vitreous floaters	6%	3%	8%	6%
Corneal epithelium defect	5%	3%	7%	5%
Intraocular pressure increased	5%	3%	9%	5%
Ocular hyperemia	5%	6%	5%	6%
Vitreous detachment	3%	3%	8%	6%
Foreign body sensation in eyes	3%	3%	3%	3%
Lacrimation increased	3%	2%	4%	2%
Vision blurred	2%	2%	3%	4%
Intraocular inflammation	2%	<1%	3%	1%
Injection site pain	2%	<1%	2%	<1%
Eyelid edema	<1%	1%	2%	1%

Less common adverse reactions reported in <1% of the patients treated with EYLEA were hypersensitivity, retinal detachment, retinal tear, corneal edema, and injection site hemorrhage.
Safety data observed in 269 patients with nonproliferative diabetic retinopathy (NPDR) through week 52 in the PANORAMA trial were consistent with those seen in the phase 3 VIVID and VISTA trials (see Table 3 above).

6.2 Immunogenicity
As with all therapeutic proteins, there is a potential for an immune response in patients treated with EYLEA. The immunogenicity of EYLEA was evaluated in serum samples. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to EYLEA in immunoassays. The detection of an immune response is highly dependent on the sensitivity and specificity of the assays used, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to EYLEA with the incidence of antibodies to other products may be misleading.
In the wet AMD, RVO, and DME studies, the pre-treatment incidence of immunoreactivity to EYLEA was approximately 1% to 3% across treatment groups. After dosing with EYLEA for 24-100 weeks, antibodies to EYLEA were detected in a similar percentage range of patients. There were no differences in efficacy or safety between patients with or without immunoreactivity.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Risk Summary
Adequate and well-controlled studies with EYLEA have not been conducted in pregnant women. Aflibercept produced adverse embryofetal effects in rabbits, including external, visceral, and skeletal malformations. A fetal No Observed Adverse Effect Level (NOAEL) was not identified. At the lowest dose shown to produce adverse embryofetal effects, systemic exposures (based on AUC for free aflibercept) were approximately 6 times higher than AUC values observed in humans after a single intravitreal treatment at the recommended clinical dose [*see Animal Data*].
Animal reproduction studies are not always predictive of human response, and it is not known whether EYLEA can cause fetal harm when administered to a pregnant woman. Based on the anti-VEGF mechanism of action for aflibercept, treatment with EYLEA may pose a risk to human embryofetal development. EYLEA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.
Data
Animal Data
In two embryofetal development studies, aflibercept produced adverse embryofetal effects when administered every three days during organogenesis to pregnant rabbits at intravenous doses ≥3 mg per kg, or every six days during organogenesis at subcutaneous doses ≥0.1 mg per kg.
Adverse embryofetal effects included increased incidences of postimplantation loss and fetal malformations, including anasarca, umbilical hernia, diaphragmatic hernia, gastroschisis, cleft palate, ectrodactyly, intestinal atresia, spina bifida, encephalomeningocele, heart and major vessel defects, and skeletal malformations (fused vertebrae, sternebrae, and ribs; supernumerary vertebral arches and ribs; and incomplete ossification). The maternal No Observed Adverse Effect Level (NOAEL) in these studies was 3 mg per kg. Aflibercept produced fetal malformations at all doses assessed in rabbits and the fetal NOAEL was not identified. At the lowest dose shown to produce adverse embryofetal effects in rabbits (0.1 mg per kg), systemic exposure (AUC) of free aflibercept was approximately 6 times higher than systemic exposure (AUC) observed in humans after a single intravitreal dose of 2 mg.

8.2 Lactation
Risk Summary
There is no information regarding the presence of aflibercept in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production/excretion. Because many drugs are excreted in human milk, and because the potential for absorption and harm to infant growth and development exists, EYLEA is not recommended during breastfeeding.
The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for EYLEA and any potential adverse effects on the breastfed child from EYLEA.

8.3 Females and Males of Reproductive Potential
Contraception
Females of reproductive potential are advised to use effective contraception prior to the initial dose, during treatment, and for at least 3 months after the last intravitreal injection of EYLEA.

Infertility
There are no data regarding the effects of EYLEA on human fertility. Aflibercept adversely affected female and male reproductive systems in cynomolgus monkeys when administered by intravenous injection at a dose approximately 1500 times higher than the systemic level observed humans with an intravitreal dose of 2 mg. A No Observed Adverse Effect Level (NOAEL) was not identified. These findings were reversible within 20 weeks after cessation of treatment.

8.4 Pediatric Use
The safety and effectiveness of EYLEA in pediatric patients have not been established.

8.5 Geriatric Use
In the clinical studies, approximately 76% (2049/2701) of patients randomized to treatment with EYLEA were ≥65 years of age and approximately 46% (1250/2701) were ≥75 years of age. No significant differences in efficacy or safety were seen with increasing age in these studies.

17 PATIENT COUNSELING INFORMATION
In the days following EYLEA administration, patients are at risk of developing endophthalmitis or retinal detachment. If the eye becomes red, sensitive to light, painful, or develops a change in vision, advise patients to seek immediate care from an ophthalmologist [*see Warnings and Precautions (5.1)*].
Patients may experience temporary visual disturbances after an intravitreal injection with EYLEA and the associated eye examinations [*see Adverse Reactions (6)*]. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

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SURGICAL OPTIONS FOR REFRACTORY MACULAR HOLES

A case presentation and brief review can help you tackle challenging full-thickness macular holes.

BY JORDAN MANDELL, BS; LAUREN KIRYAKOZA, MD; AND JAYANTH SRIDHAR, MD

Primary full-thickness macular holes (FTMHs) most commonly develop in elderly patients without apparent underlying retinal diseases. Recent studies that include OCT imaging have attributed the formation of an idiopathic FTMH to the persistent adherence of the cortical vitreous to the fovea, which causes vitreoretinal separation.[1-3] The resulting traction on the fovea is also thought to contribute to cystoid degeneration and dissolution of inner retinal layers, which may lead to foveal detachment or dehiscence and FTMH formation.[4-6]

Another proposed mechanism of FTMH involves tangential traction from an adherent posterior hyaloid or from the presence of an epiretinal membrane, which can exert tangential traction on the fovea and generate an FTMH.[7,8]

The current standard surgical management for primary FTMH is pars plana vitrectomy (PPV) with internal limiting membrane (ILM) peeling and the use of a tamponade agent, which achieves a closure rate of greater than 90%.[9,10]

If the macular hole does not close with the standard approach, there are several unique strategies that can help, including the inverted ILM flap with or without adjuvant blood products, lens capsule flap transplantation, human amniotic membrane, and autologous retinal transplantation (ART).[10-12] Here we present an example of a refractory FTMH successfully closed after multiple failed surgeries, leading to meaningful visual acuity improvement.

CASE PRESENTATION

A 60-year-old man with a medical history of diabetes, hyperlipidemia, hypertension, and neovascular glaucoma in the left eye presented for a second opinion. He had developed an FTMH in his only seeing eye—the right eye—3 months prior and had undergone three unsuccessful PPV procedures with ILM peel and gas tamponade. His VA was counting fingers OD. OCT demonstrated an FTMH measuring approximately 1,000 µm with underlying retinal pigment epithelium (RPE) atrophy and no visible posterior hyaloid face (Figure 1). Alternative surgical options were discussed with the patient.

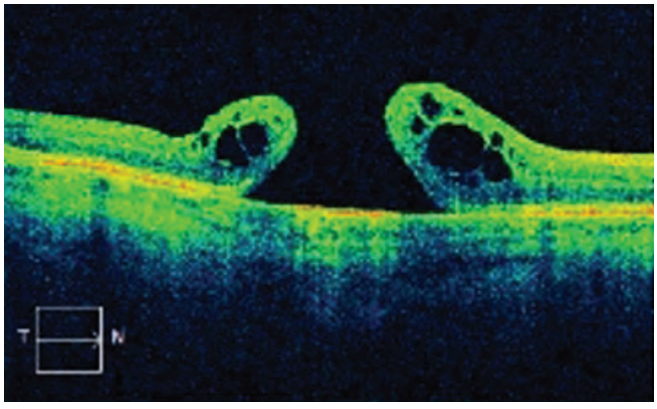

Figure 1. OCT imaging showed a refractory primary FTMH of approximately 1,000 µm in the right eye of a 60-year-old man with a VA of counting fingers.

TREATMENT OPTIONS

The inverted ILM flap technique involves performing a core vitrectomy and trypan blue staining followed by peeling any epiretinal membrane; ILM forceps are used to peel the membrane in a circular fashion around the macular hole.[13] While performing the circumferential peeling, the surgeon aims to leave the ILM attached to the edges of the macular hole. The rolled segment of the peeled ILM is massaged gently over the macular hole until the ILM is inverted so the surface that normally faces the vitreous body now faces the RPE.[13] Michalewska et al reported great success with this technique; they stated that the technique was able to achieve a high closure rate in myopic macular holes and led

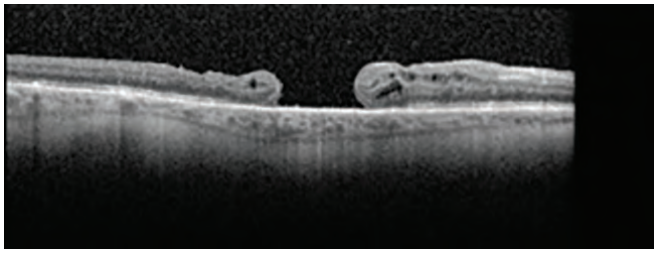

Figure 2. The postoperative day 1 OCT scan showed the FTMH without anatomic closure.

to a mean improvement in VA of 6 logMAR lines.[13]

Lens capsule flap transplantation involves harvesting a piece of the anterior or posterior lens capsule and placing it into the hole to help facilitate hole closure.[14] Chen at el found that the macular hole was closed in all 10 eyes undergoing anterior capsular flap transplantation. Comparatively, in the 10 patients who underwent posterior capsular flap transplantation, five holes were closed, three were partially closed, and two were not closed.[14] Peng et al recently described the long-term outcomes of lens capsule flap transplantation as a primary treatment for large macular holes and found promising results.[15]

Consequently, not only can lens capsule flap transplantation be effective in treating refractory macular holes, but it also may help improve the closure rate and visual outcomes when used as the primary treatment for large macular holes.[15]

Human amniotic membrane use has been proposed as a method to address failed macular hole closure.[16] Amniotic membrane has a wide variety of biomedical applications, but its use in the treatment of refractory macular holes has not been studied extensively.[17] Several case reports and small series show promising initial results for the use of amniotic membrane in the closure of refractory macular holes.[18-21]

Several studies have described ART as an effective option for FTMH closure.[12,22-25] The surgical technique involves selecting an appropriate graft size, depending on the FTMH defect size, and neurosensory retina harvest site, typically in the midperiphery superior to the superotemporal arcade. Once the harvest site is selected according to surgeon preference in the superior, temporal, or nasal location beyond the arcade, diathermy is used to mark the autograft site. Vertical scissors are used to free the graft tissue, and endolaser barricade is applied in a circular manner around the graft site. PFO is then injected, and the graft is moved toward the macular hole with grasping forceps and positioned with a loop scraper. The patient is positioned supine postoperatively, and PFO is removed 7 to 10 days later. In clinical studies, the ART technique offered a high degree of anatomic closure of refractory macular holes, with closure rates ranging from 87% and 89% to 100%.[12,22-25]

Several studies have examined the use of adjunctive treatments, such as recombinant TGF-ß2 or platelet products such as autologous platelets, platelet-rich plasma, and platelet-derived growth factor.[11,26-28] The results of one study examining recombinant TGF-ß2 demonstrated no difference between the application of TGF-ß2 and placebo in closing FTMHs; however, platelet-derived products have proven to be efficacious as an adjunctive treatment for closure of macular holes.[26-28]

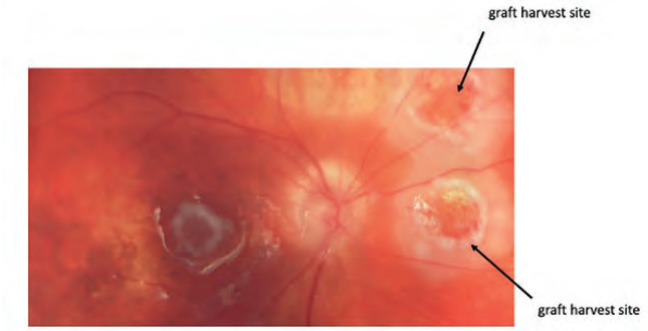

Figure 3. The color fundus photograph obtained 1 day after the second surgery depicted two graft harvest sites with the macular hole adequately covered by the graft and PFO present in the eye. The patient's VA was 3/200 OD.

PREOPERATIVE DISCUSSIONS ARE A MUST TO ENSURE PATIENTS UNDERSTAND THE IMPORTANCE OF ADHERING TO POSTOPERATIVE POSITIONING INSTRUCTIONS TO MINIMIZE THE CHANCES OF GRAFT DISLOCATION.

SURGICAL OUTCOME

The patient presented here elected to undergo ART for refractory primary FTMH. He failed to position as instructed, and on postoperative day 1, the patient had a VA of 20/250 with a dislocated graft and a persistent FTMH (Figure 2).

The patient was eager to undergo a second attempt, which was performed 1 week later. Imaging obtained 1 day after the second ART procedure showed the hole to be adequately

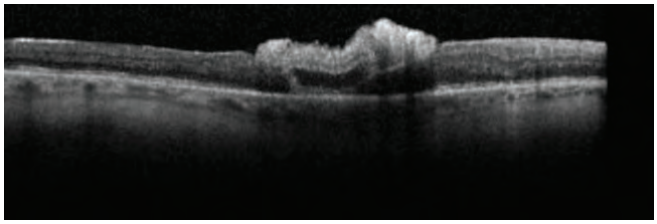

Figure 4. OCT imaging 1 day after the second procedure depicted the graft in an adequate position and a closed macular hole.

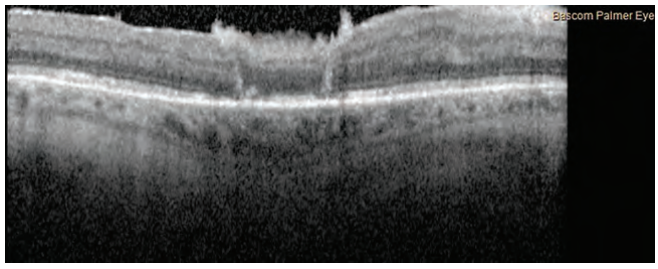

Figure 5. OCT imaging obtained 13 days after the procedure and staged PFO removal demonstrates that the macular hole remained closed. The patient's VA was 20/70 OD.

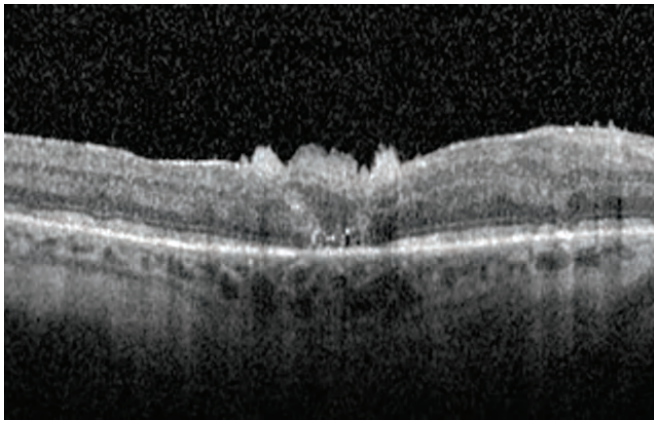

Figure 6. OCT imaging obtained 31 days after the second procedure showed that the macular hole remained closed. The patient's VA was 20/50.

covered by the graft under PFO tamponade (Figure 3). His VA was 3/200 OD. Repeat OCT demonstrated an adequately positioned graft and closed macular hole (Figure 4).

On postoperative day 13, after staged PFO removal, repeat OCT demonstrated that the macular hole remained closed, and the patient's VA was 20/70 OD (Figure 5).

One month after the second surgery, the macular hole remained closed, and the patient's VA had improved to 20/50 OD (Figure 6).

This case demonstrates the effectiveness of ART in patients with refractory macular holes after undergoing PPV with or without ILM peeling. Preoperative discussions are a must to ensure patients understand the importance of adhering to postoperative positioning instructions to minimize the chances of graft dislocation. With appropriate patient selection, ART may be a viable option for closure of refractory FTMHs. ■

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CIMERLI™ (ranibizumab-eqrn), a vascular endothelial growth factor (VEGF) inhibitor, is indicated for the treatment of patients with:

- Neovascular (Wet) Age-Related Macular Degeneration (AMD)
- Macular Edema Following Retinal Vein Occlusion (RVO)
- Diabetic Macular Edema (DME)
- Diabetic Retinopathy (DR)
- Myopic Choroidal Neovascularization (mCNV)

CONTRAINDICATIONS

- CIMERLI™ is contraindicated in patients with ocular or periocular infections or known hypersensitivity to ranibizumab products or any of the excipients in CIMERLI™. Hypersensitivity reactions may manifest as severe intraocular inflammation

WARNINGS AND PRECAUTIONS

- **Endophthalmitis and Retinal Detachments:** Intravitreal injections, including those with ranibizumab products, have been associated with endophthalmitis and retinal detachments. Proper aseptic injection technique should always be utilized when administering CIMERLI™. Patients should be monitored following the injection to permit early treatment, should an infection occur
- **Increases in Intraocular Pressure:** Increases in intraocular pressure (IOP) have been noted both pre-injection and post-injection (at 60 minutes) with ranibizumab products. Monitor intraocular pressure prior to and following intravitreal injection with CIMERLI™ and manage appropriately
- **Thromboembolic Events:** Although there was a low rate of arterial thromboembolic events (ATEs) observed in the ranibizumab clinical trials, there is a potential risk of ATEs following intravitreal use of VEGF inhibitors. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause)

Neovascular (wet) age-related macular degeneration

- The ATE rate in the 3 controlled neovascular AMD studies during the first year was 1.9% (17 of 874) in the combined group of patients treated with 0.3 mg or 0.5 mg ranibizumab compared with 1.1% (5 of 441) in patients from the control arms. In the second year of Studies AMD-1 and AMD-2, the ATE rate was 2.6% (19 of 721) in the combined group of ranibizumab-treated patients compared with 2.9% (10 of 344) in patients from the control arms. In Study AMD-4, the ATE rates observed in the 0.5 mg arms during the first and second year were similar to rates observed in Studies AMD-1, AMD-2, and AMD-3
- In a pooled analysis of 2-year controlled studies (AMD-1, AMD-2, and a study of ranibizumab used adjunctively with verteporfin photodynamic therapy), the stroke rate (including both ischemic and hemorrhagic stroke) was 2.7% (13 of 484) in patients treated with 0.5 mg ranibizumab compared to 1.1% (5 of 435) in patients in the control arms (odds ratio 2.2 [95% confidence interval (0.8-7.1)])

Macular edema following retinal vein occlusion

- The ATE rate in the 2 controlled RVO studies during the first 6 months was 0.8% in both the ranibizumab and control arms of the studies (4 of 525 in the combined group of patients treated with 0.3 mg or 0.5 mg ranibizumab and 2 of 260 in the control arms). The stroke rate was 0.2% (1 of 525) in the combined group of ranibizumab-treated patients compared to 0.4% (1 of 260) in the control arms

Diabetic macular edema and Diabetic Retinopathy

- In a pooled analysis of Studies D-1 and D-2, the ATE rate at 2 years was 7.2% (18 of 250) with 0.5 mg ranibizumab, 5.6% (14 of 250) with 0.3 mg ranibizumab, and 5.2% (13 of 250) with control. The stroke rate

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at 2 years was 3.2% (8 of 250) with 0.5 mg ranibizumab, 1.2% (3 of 250) with 0.3 mg ranibizumab, and 1.6% (4 of 250) with control. At 3 years, the ATE rate was 10.4% (26 of 249) with 0.5 mg ranibizumab and 10.8% (27 of 250) with 0.3 mg ranibizumab; the stroke rate was 4.8% (12 of 249) with 0.5 mg ranibizumab and 2.0% (5 of 250) with 0.3 mg ranibizumab

- **Fatal events in patients with diabetic macular edema and diabetic retinopathy at baseline:** A pooled analysis of Studies D-1 and D-2 showed that fatalities in the first 2 years occurred in 4.4% (11 of 250) of patients treated with 0.5 mg ranibizumab, in 2.8% (7 of 250) of patients treated with 0.3 mg ranibizumab, and in 1.2% (3 of 250) of control patients. Over 3 years, fatalities occurred in 6.4% (16 of 249) of patients treated with 0.5 mg ranibizumab and in 4.4% (11 of 250) of patients treated with 0.3 mg ranibizumab. Although the rate of fatal events was low and included causes of death typical of patients with advanced diabetic complications, a potential relationship between these events and intravitreal use of VEGF inhibitors cannot be excluded

ADVERSE REACTIONS

- Serious adverse events related to the injection procedure have occurred in <0.1% of intravitreal injections, including endophthalmitis, rhegmatogenous retinal detachment, and iatrogenic traumatic cataract
- In ranibizumab-treated patients compared with the control group, the most common ocular side effects included conjunctival hemorrhage, eye pain, vitreous floaters, and intraocular pressure. The most common non-ocular side effects included nasopharyngitis, anemia, nausea, and cough
- As with all therapeutic proteins, there is the potential for an immune response in patients treated with ranibizumab products. The clinical significance of immunoreactivity to ranibizumab products is unclear at this time

Postmarketing Experience

The following adverse reaction has been identified during post-approval use of ranibizumab products:

- Ocular: Tear of retinal pigment epithelium among patients with neovascular AMD

*An interchangeable product (IP) is a biological product that is approved based on data demonstrating that it is highly similar to an FDA-approved reference product (RP) and that there are no clinically meaningful differences between the products; it can be expected to produce the same clinical result as the RP in any given patient; and if administered more than once to a patient, the risk in terms of safety or diminished efficacy from alternating or switching between use of the RP and IP is not greater than that from the RP without such alternation or switch. Interchangeability of CIMERLI™ has been demonstrated for the condition(s) of use, strength(s), dosage form(s), and route(s) of administration described in its Full Prescribing Information

References: 1. CIMERLI™ (ranibizumab-eqrn) prescribing information. Redwood City, CA: Coherus BioSciences, Inc. **2.** Data on file. Coherus BioSciences, Inc.

To report SUSPECTED ADVERSE REACTIONS, contact Coherus BioSciences at 1-800-483-3692 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see additional Important Safety Information and Brief Summary of Full Prescribing Information on the following page.

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BRIEF SUMMARY—please review the full Prescribing Information prior to prescribing CIMERLI™. CIMERLI™ is interchangeable with LUCENTIS® (ranibizumab injection).

1 INDICATIONS AND USAGE

CIMERLI is indicated for the treatment of patients with:

1.1 Neovascular (Wet) Age-Related Macular Degeneration (AMD)

1.2 Macular Edema Following Retinal Vein Occlusion (RVO)

1.3 Diabetic Macular Edema (DME)

1.4 Diabetic Retinopathy (DR)

1.5 Myopic Choroidal Neovascularization (mCNV)

4 CONTRAINDICATIONS

4.1 Ocular or Periocular Infections

CIMERLI is contraindicated in patients with ocular or periocular infections.

4.2 Hypersensitivity

CIMERLI is contraindicated in patients with known hypersensitivity to ranibizumab products or any of the excipients in CIMERLI. Hypersensitivity reactions may manifest as severe intraocular inflammation.

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis and Retinal Detachments

Intravitreal injections, including those with ranibizumab products, have been associated with endophthalmitis and retinal detachments. Proper aseptic injection technique should always be used when administering CIMERLI. In addition, patients should be monitored following the injection to permit early treatment should an infection occur [*see Dosage and Administration (2.6, 2.7) in the Full Prescribing Information*].

5.2 Increases in Intraocular Pressure

Increases in intraocular pressure have been noted both pre-injection and post-injection (at 60 minutes) while being treated with ranibizumab products. Monitor intraocular pressure prior to and following intravitreal injection with CIMERLI and manage appropriately [*see Dosage and Administration (2.7) in the Full Prescribing Information*].

5.3 Thromboembolic Events

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

Neovascular (Wet) Age-Related Macular Degeneration

The ATE rate in the three controlled neovascular AMD studies (AMD-1, AMD-2, AMD-3) during the first year was 1.9% (17 of 874) in the combined group of patients treated with 0.3 mg or 0.5 mg ranibizumab compared with 1.1% (5 of 441) in patients from the control arms [*see Clinical Studies (14.1)*]. In the second year of Studies AMD-1 and AMD-2, the ATE rate was 2.6% (19 of 721) in the combined group of ranibizumab-treated patients compared with 2.9% (10 of 344) in patients from the control arms. In Study AMD-4, the ATE rates observed in the 0.5 mg arms during the first and second year were similar to rates observed in Studies AMD-1, AMD-2, and AMD-3.

In a pooled analysis of 2-year controlled studies [AMD-1, AMD-2, and a study of ranibizumab used adjunctively with verteporfin photodynamic therapy (PDT)], the stroke rate (including both ischemic and hemorrhagic stroke) was 2.7% (13 of 484) in patients treated with 0.5 mg ranibizumab compared to 1.1% (5 of 435) in patients in the control arms [odds ratio 2.2 (95% confidence interval (0.8-7.1)].

Macular Edema Following Retinal Vein Occlusion

The ATE rate in the two controlled RVO studies during the first 6 months was 0.8% in both the ranibizumab and control arms of the studies (4 of 525 in the combined group of patients treated with 0.3 mg or 0.5 mg ranibizumab and 2 of 260 in the control arms) [*see Clinical Studies (14.2)*]. The stroke rate was 0.2% (1 of 525) in the combined group of ranibizumab-treated patients compared to 0.4% (1 of 260) in the control arms.

Diabetic Macular Edema and Diabetic Retinopathy

Safety data are derived from studies D-1 and D-2. All enrolled patients had DME and DR at baseline [*see Clinical Studies (14.3, 14.4)*].

In a pooled analysis of Studies D-1 and D-2 [*see Clinical Studies (14.3)*], the ATE rate at 2 years was 7.2% (18 of 250) with 0.5 mg ranibizumab, 5.6% (14 of 250) with 0.3 mg ranibizumab, and 5.2% (13 of 250) with control. The stroke rate at 2 years was 3.2% (8 of 250) with 0.5 mg ranibizumab, 1.2% (3 of 250) with 0.3 mg ranibizumab, and 1.6% (4 of 250) with control. At 3 years, the ATE rate was 10.4% (26 of 249) with 0.5 mg ranibizumab and 10.8% (27 of 250) with 0.3 mg ranibizumab; the stroke rate was 4.8% (12 of 249) with 0.5 mg ranibizumab and 2.0% (5 of 250) with 0.3 mg ranibizumab.

5.4 Fatal Events in Patients with Diabetic Macular Edema and Diabetic Retinopathy at Baseline

Diabetic Macular Edema and Diabetic Retinopathy

Safety data are derived from studies D-1 and D-2. All enrolled patients had DME and DR at baseline [*see Clinical Studies (14.3, 14.4)*].

A pooled analysis of Studies D-1 and D-2 [*see Clinical Studies (14.3)*], showed that fatalities in the first 2 years occurred in 4.4% (11 of 250) of patients treated with 0.5 mg ranibizumab, in 2.8% (7 of 250) of patients treated with 0.3 mg ranibizumab, and in 1.2% (3 of 250) of control patients. Over 3 years, fatalities occurred in 6.4% (16 of 249) of patients treated with 0.5 mg ranibizumab and in 4.4% (11 of 250) of patients treated with 0.3 mg ranibizumab. Although the rate of fatal events was low and included causes of death typical of patients with advanced diabetic complications, a potential relationship between these events and intravitreal use of VEGF inhibitors cannot be excluded.

6 ADVERSE REACTIONS

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

- Endophthalmitis and Retinal Detachments [*see Warnings and Precautions (5.1)*]
- Increases in Intraocular Pressure [*see Warnings and Precautions (5.2)*]
- Thromboembolic Events [*see Warnings and Precautions (5.3)*]
- Fatal Events in patients with DME and DR at baseline [*see Warnings and Precautions (5.4)*]

6.1 Injection Procedure

Serious adverse reactions related to the injection procedure have occurred in < 0.1% of intravitreal injections, including endophthalmitis [*see Warnings and Precautions (5.1)*], rhegmatogenous retinal detachment, and iatrogenic traumatic cataract.

6.2 Clinical Trials Experience

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

The data below reflect exposure to 0.5 mg ranibizumab in 440 patients with neovascular AMD in Studies AMD-1, AMD-2, and AMD-3; in 259 patients with macular edema following RVO. The data also reflect exposure to 0.3 mg ranibizumab in 250 patients with DME and DR at baseline [*see Clinical Studies (14)*].

Safety data observed in 224 patients with mCNV, as well as Studies AMD-4 and D-3, were consistent with these results. On average, the rates and types of adverse reactions in patients were not significantly affected by dosing regimen.

Ocular Reactions

Table 1 shows frequently reported ocular adverse reactions in ranibizumab-treated patients compared with the control group.

Table 1

Ocular Reactions in the DME and DR, AMD, and RVO Studies

Adverse Reaction	DME and DR 2-year		AMD 2-year		AMD 1-year		RVO 6-month	
	Ranibizumab 0.3 mg	Control	Ranibizumab 0.5 mg	Control	Ranibizumab 0.5 mg	Control	Ranibizumab 0.5 mg	Control
	n=250	n=250	n=379	n=379	n=440	n=441	n=259	n=260
Conjunctival hemorrhage	47%	32%	74%	60%	64%	50%	48%	37%
Eye pain	17%	13%	35%	30%	26%	20%	17%	12%
Vitreous floaters	10%	4%	27%	8%	19%	5%	7%	2%
Intraocular pressure increased	18%	7%	24%	7%	17%	5%	7%	2%
Vitreous detachment	11%	15%	21%	19%	15%	15%	4%	2%
Intraocular inflammation	4%	3%	18%	8%	13%	7%	1%	3%
Cataract	28%	32%	17%	14%	11%	9%	2%	2%
Foreign body sensation in eyes	10%	5%	16%	14%	13%	10%	7%	5%
Eye irritation	8%	5%	15%	15%	13%	12%	7%	6%
Lacrimation increased	5%	4%	14%	12%	8%	8%	2%	3%
Blepharitis	3%	2%	12%	8%	8%	5%	0%	1%
Dry eye	5%	3%	12%	7%	7%	7%	3%	3%
Visual disturbance or vision blurred	8%	4%	18%	15%	13%	10%	5%	3%
Eye pruritis	4%	4%	12%	11%	9%	7%	1%	2%
Ocular hyperemia	9%	9%	11%	8%	7%	4%	5%	3%
Retinal disorder	2%	2%	10%	7%	8%	4%	2%	1%
Maculopathy	5%	7%	9%	9%	6%	6%	11%	7%
Retinal degeneration	1%	0%	8%	6%	5%	3%	1%	0%
Ocular discomfort	2%	1%	7%	4%	5%	2%	2%	2%
Conjunctival hyperemia	1%	2%	7%	6%	5%	4%	0%	0%
Posterior capsule opacification	4%	3%	7%	4%	2%	2%	0%	1%
Injection site hemorrhage	1%	0%	5%	2%	3%	1%	0%	0%

Non-Ocular Reactions

Non-ocular adverse reactions with an incidence of ≥ 5% in patients receiving ranibizumab for DR, DME, AMD, and/or RVO and which occurred at a ≥ 1% higher frequency in patients treated with ranibizumab compared to control are shown in Table 2. Though less common, wound healing complications were also observed in some studies.

Table 2

Non-Ocular Reactions in the DME and DR, AMD, and RVO Studies

Adverse Reaction	DME and DR 2-year		AMD 2-year		AMD 1-year		RVO 6-month	
	Ranibizumab 0.3 mg	Control	Ranibizumab 0.5 mg	Control	Ranibizumab 0.5 mg	Control	Ranibizumab 0.5 mg	Control
	n=250	n=250	n=379	n=379	n=440	n=441	n=259	n=260
Nasopharyngitis	12%	6%	16%	13%	8%	9%	5%	4%
Anemia	11%	10%	8%	7%	4%	3%	1%	1%
Nausea	10%	9%	9%	6%	5%	5%	1%	2%
Cough	9%	4%	9%	8%	5%	4%	1%	2%
Constipation	8%	4%	5%	7%	3%	4%	0%	1%
Seasonal allergy	8%	4%	4%	4%	2%	2%	0%	2%
Hypercholesterolemia	7%	5%	5%	5%	3%	2%	1%	1%
Influenza	7%	3%	7%	5%	3%	2%	3%	2%
Renal failure	7%	6%	1%	1%	0%	0%	0%	0%
Upper respiratory tract infection	7%	7%	9%	8%	5%	5%	2%	2%
Gastroesophageal reflux disease	6%	4%	4%	6%	3%	4%	1%	0%
Headache	6%	8%	12%	9%	6%	5%	3%	3%
Edema peripheral	6%	4%	3%	5%	2%	3%	0%	1%
Renal failure chronic	6%	2%	0%	1%	0%	0%	0%	0%
Neuropathy peripheral	5%	3%	1%	1%	1%	0%	0%	0%
Sinusitis	5%	8%	8%	7%	5%	5%	3%	2%
Bronchitis	4%	4%	11%	9%	6%	5%	0%	2%
Atrial fibrillation	3%	3%	5%	4%	2%	2%	1%	0%
Arthralgia	3%	3%	11%	9%	5%	5%	2%	1%
Chronic obstructive pulmonary disease	1%	1%	6%	3%	3%	1%	0%	0%
Wound healing complications	1%	0%	1%	1%	1%	0%	0%	0%

6.3 Immunogenicity

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

The pre-treatment incidence of immunoreactivity to ranibizumab was 0%-5% across treatment groups. After monthly dosing with ranibizumab for 6 to 24 months, antibodies to ranibizumab were detected in approximately 1%-9% of patients.

The clinical significance of immunoreactivity to ranibizumab products are unclear at this time. Among neovascular AMD patients with the highest levels of immunoreactivity, some were noted to have iritis or vitritis. Intraocular inflammation was not observed in patients with DME and DR at baseline, or RVO patients with the highest levels of immunoreactivity.

6.4 Postmarketing Experience

The following adverse reaction has been identified during post-approval use of ranibizumab products. Because this reaction was reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure.

• Ocular: Tear of retinal pigment epithelium among patients with neovascular AMD

7 DRUG INTERACTIONS

Drug interaction studies have not been conducted with ranibizumab products.

Ranibizumab intravitreal injection has been used adjunctively with PDT. Twelve of 105 (11%) patients with neovascular AMD developed serious intraocular inflammation; in 10 of the 12 patients, this occurred when ranibizumab was administered 7 days (± 2 days) after PDT.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate and well-controlled studies of ranibizumab products administered in pregnant women.

Administration of ranibizumab to pregnant monkeys throughout the period of organogenesis resulted in a low incidence of skeletal abnormalities at intravitreal doses 13-times the predicted human exposure (based on maximal serum trough levels [C_{max}]) after a single eye treatment at the recommended clinical dose. No skeletal abnormalities were observed at serum trough levels equivalent to the predicted human exposure after a single eye treatment at the recommended clinical dose [*see Animal Data*].

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

CIMERLI should be given to a pregnant woman only if clearly needed.

Data

Animal Data

An embryo-fetal developmental toxicity study was performed on pregnant cynomolgus monkeys. Pregnant animals received intravitreal injections of ranibizumab every 14 days starting on Day 20 of gestation, until Day 62 at doses of 0, 0.125, and 1 mg/eye. Skeletal abnormalities including incomplete and/or irregular ossification of bones in the skull, vertebral column, and hindlimbs and shortened supernumerary ribs were seen at a low incidence in fetuses from animals treated with 1 mg/eye of ranibizumab. The 1 mg/eye dose resulted in trough serum ranibizumab levels up to 13 times higher than predicted C_{max} levels with single eye treatment in humans. No skeletal abnormalities were seen at the lower dose of 0.125 mg/eye, a dose which resulted in trough exposures equivalent to single eye treatment in humans. No effect on the weight or structure of the placenta, maternal toxicity, or embryotoxicity was observed.

8.2 Lactation

Risk Summary

There are no data available on the presence of ranibizumab products in human milk, the effects of ranibizumab products on the breastfed infant or the effects of ranibizumab products on milk production/excretion.

Because many drugs are excreted in human milk, and because the potential for absorption and harm to infant growth and development exists, caution should be exercised when CIMERLI is administered to a nursing woman.

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

8.3 Females and Males of Reproductive Potential

Infertility

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

8.4 Pediatric Use

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

8.5 Geriatric Use

In the clinical studies, approximately 76% (2449 of 3227) of patients randomized to treatment with ranibizumab were ≥ 65 years of age and approximately 51% (1644 of 3227) were ≥ 75 years of age [*see Clinical Studies (14)*]. No notable differences in efficacy or safety were seen with increasing age in these studies. Age did not have a significant effect on systemic exposure.

10 OVERDOSAGE

More concentrated doses as high as 2 mg ranibizumab in 0.05 mL have been administered to patients. No additional unexpected adverse reactions were seen.

17 PATIENT COUNSELING INFORMATION

Advise patients that in the days following CIMERLI administration, patients are at risk of developing endophthalmitis. If the eye becomes red, sensitive to light, painful, or develops a change in vision, advise the patient to seek immediate care from an ophthalmologist [*see Warnings and Precautions (5.1)*].

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A 'SEROUS' FLOATER

A rare case of an ocular parasite requires surgical intervention to confirm the diagnosis.

BY RIYAZ Y. BHIKOO, MBCHB, FRANZCO

A 49-year-old Cambodian man was referred to the Royal Perth Hospital in Perth, Australia, with a 2-day history of right eye pain, photophobia, and floaters. He had no significant ophthalmic or medical history. He had immigrated to Australia in 2004 and last travelled to Cambodia 3 years earlier.

On examination, VA was 20/25 OD and 20/20 OS and IOP was 14 mm Hg OD and 16 mm Hg OS. A low-grade panuveitis with fine keratic precipitates was observed in the right eye with a mobile worm-like opacity present within the inferior vitreous chamber (Figure 1A). A serous macular detachment was also present, and a round, punched-out chorioretinal scar was noted above the superotemporal arcade (Figure 1B). The left eye appeared normal on ophthalmoscopy. OCT imaging demonstrated subretinal fluid (SF) at the maculae (Figure 1C and D).

Fluorescein angiography showed a smokestack pattern of hyperfluorescence in the right macula and a minimally expanding focus of hyperfluorescence in the left macula (Figure 1E and F). Laboratory investigations revealed a mild eosinophilia; however, we could not identify the worm on either stool or serology testing (*Schistosoma*, *Strongyloides*, and *Toxocara* were negative), so we proceeded to a diagnostic and therapeutic vitrectomy.

SURGERY

This procedure was performed using a three-port 25-gauge system. A small peritomy was fashioned superotemporally, in anticipation that the 25-gauge sclerostomy would need to be extended to remove the intraocular worm. A posterior vitreous detachment was induced, and a core vitrectomy was performed. Attention was then focused on the inferior fundus, and the worm was observed to be tangled within the prominent sheets of the vitreous (Figure 2A).

Significant care was taken to detangle the worm from the vitreous without damaging its structural integrity. The superotemporal sclerostomy was enlarged using a 20-gauge microvitreoretinal blade, and end-grasping forceps were used to extract the foreign body (Figure 2B-D). The mechanical manipulation caused a reflex movement by the worm, indicating that it was alive. Laser was applied to the retinal hole that was thought to be the worm's route of entry. An air-fluid exchange was performed to complete the surgery.

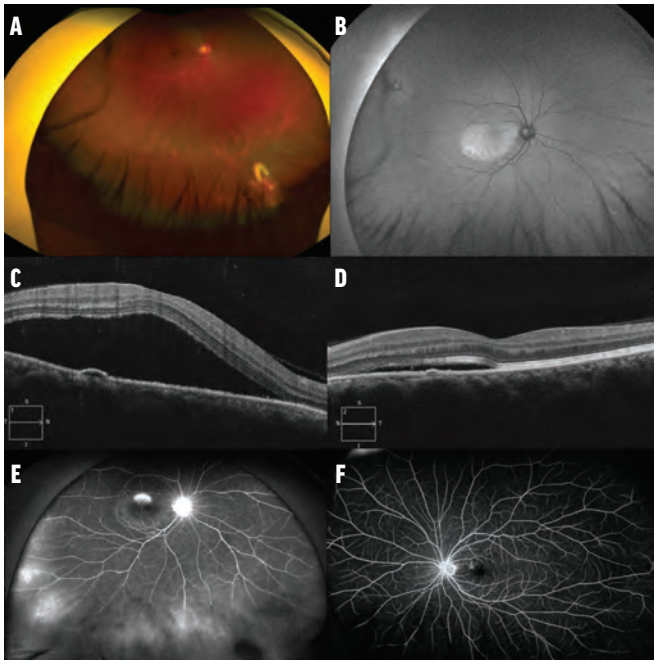

Figure 1. Widefield color photography of the inferior retina showed a yellow S-shaped opacity within the vitreous chamber (A). Fundus autofluorescence revealed hyperautofluorescence at the right macula due to subretinal fluid (B). A round hyperautofluorescent focus with an outer ring of hypoautofluorescence was seen above the superotemporal arcade, which may represent the parasite's entry into the eye. OCT showed a large serous detachment of the right macula (C) with a shallower detachment in the uninflamed left eye (D) with a pigment epithelial detachment in each eye. A widefield fluorescein angiogram of the right eye showed disc and peripheral vascular leakage consistent with intraocular inflammation, and a smokestack pattern of hyperfluorescence was seen at the macula (E). Mild fluorescein leakage was seen at the left macula (F).

POSTOPERATIVE COURSE

The worm was identified as the third-stage larvae of the roundworm *Gnathostoma (G.) spinigerum* (Figure 3). The patient was reviewed by the Infectious Diseases Service at the Royal Perth Hospital and underwent abdominal and neuroimaging, which came back normal. Despite no evidence of meningoencephalitis, they felt it was appropriate that he receive a 7-day course of oral ivermectin at a dose of 200 mg/kg/day, with concurrent oral prednisone.

The worsening of his serous macula detachments complicated his visual recovery, which resolved after cessation of

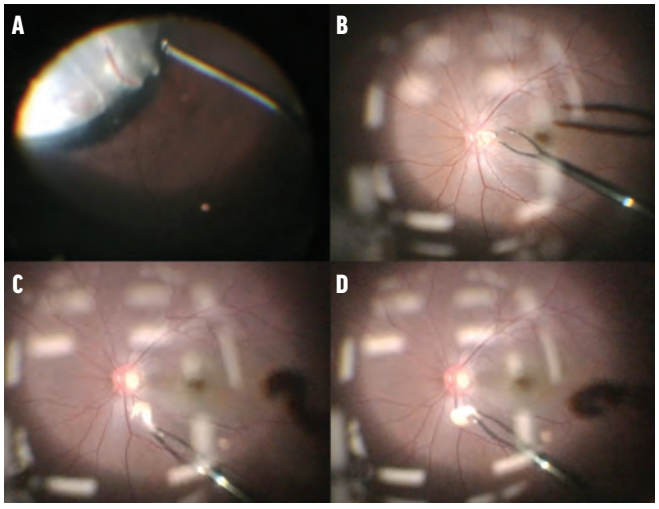

Figure 2. Intraoperatively, the vitrector was used to isolate the worm, which was encapsulated within the inferior vitreous (A). Once separated, the worm drifted posteriorly and settled over the optic nerve (B). End-grasping forceps were used to remove the worm (C and D).

oral and topical steroids. One year after the vitrectomy, the patient underwent routine cataract surgery for the right eye. He achieved unaided VA of 20/25 OD and 20/20 OS, with no recurrence of intraocular inflammation or SF.

DISCUSSION

Although recognized as an endemic parasitic nematode in Southeast Asia and parts of Latin America, *G. spinigerum* is growing increasingly problematic among travellers. *G. spinigerum* larvae migrate through the gastric wall and can survive inside of humans for up to 12 years, although they do not reach reproductive maturity. The most common manifestation of gnathostomiasis is recurrent migratory swellings under the skin, with involvement of visceral organs and the central nervous system being less common.[1-3]

Definitive diagnosis of gnathostomiasis is only possible by direct identification of the larva; however, this is seldom possible. Therefore, the diagnosis of systemic gnathostomiasis is typically based on the classic triad of a history of ingesting undercooked protein while living in or visiting endemic areas, migratory skin edema, and eosinophilia. Eosinophilia is less commonly reported in cases of ocular gnathostomiasis than in cutaneous or visceral infections.[4,5] Serology testing using enzyme-linked immunosorbent assay or immunoblot for IgG detection of *G. spinigerum* has reported sensitivity of 47% to 100% and specificity of 70% to 100%. However, such testing is not available in the United States, and traditionally, samples have been sent to specific international laboratories in Japan and Thailand (more details available through the Centers for Disease Control and Prevention).[6]

The route by which this parasite enters the eye remains unclear. More than 80 cases of ocular gnathostomiasis have been reported in the literature, with the majority involving

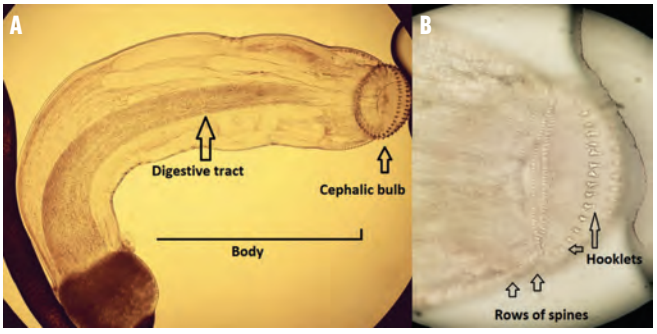

Figure 3. Scanning electron microscopy showed a third-stage larva with a prominent bulb, body, and digestive tract (A). The head of the worm contains hooklets and a grinding apparatus that is reminiscent of a tunnel drill machine (B).

the anterior segment.[4,5] Vitreoretinal involvement has also been reported and manifests as diffuse unilateral subacute neuroretinitis. Although serous retinal detachments are associated with several uveitic diseases, the findings in this case were more typical of central serous chorioretinopathy; the worsening of the serous detachments with commencement of high-dose oral steroids supports this diagnosis.

Given the rarity of such ocular parasitic cases, there is no consensus on the treatment approach.[1,4,5] Albendazole (Albenza, IMPAX Labs) or ivermectin are commonly prescribed when other organ systems are involved, but they are not considered to be the most effective treatments in ocular cases. Periocular or systemic steroids are used to manage inflammatory sequelae. Some have found laser photocoagulation to be effective, but the most definitive treatment and method of diagnosis is surgical extraction; however, due to the parasite's mobility, this may not always be feasible.

A POSITIVE OUTCOME

The case presented here is an example of positive visual recovery following treatment of ocular gnathostomiasis. Patients traveling to endemic areas should be reminded to avoid raw or undercooked protein and to ensure the food they consume has been handled safely. ■

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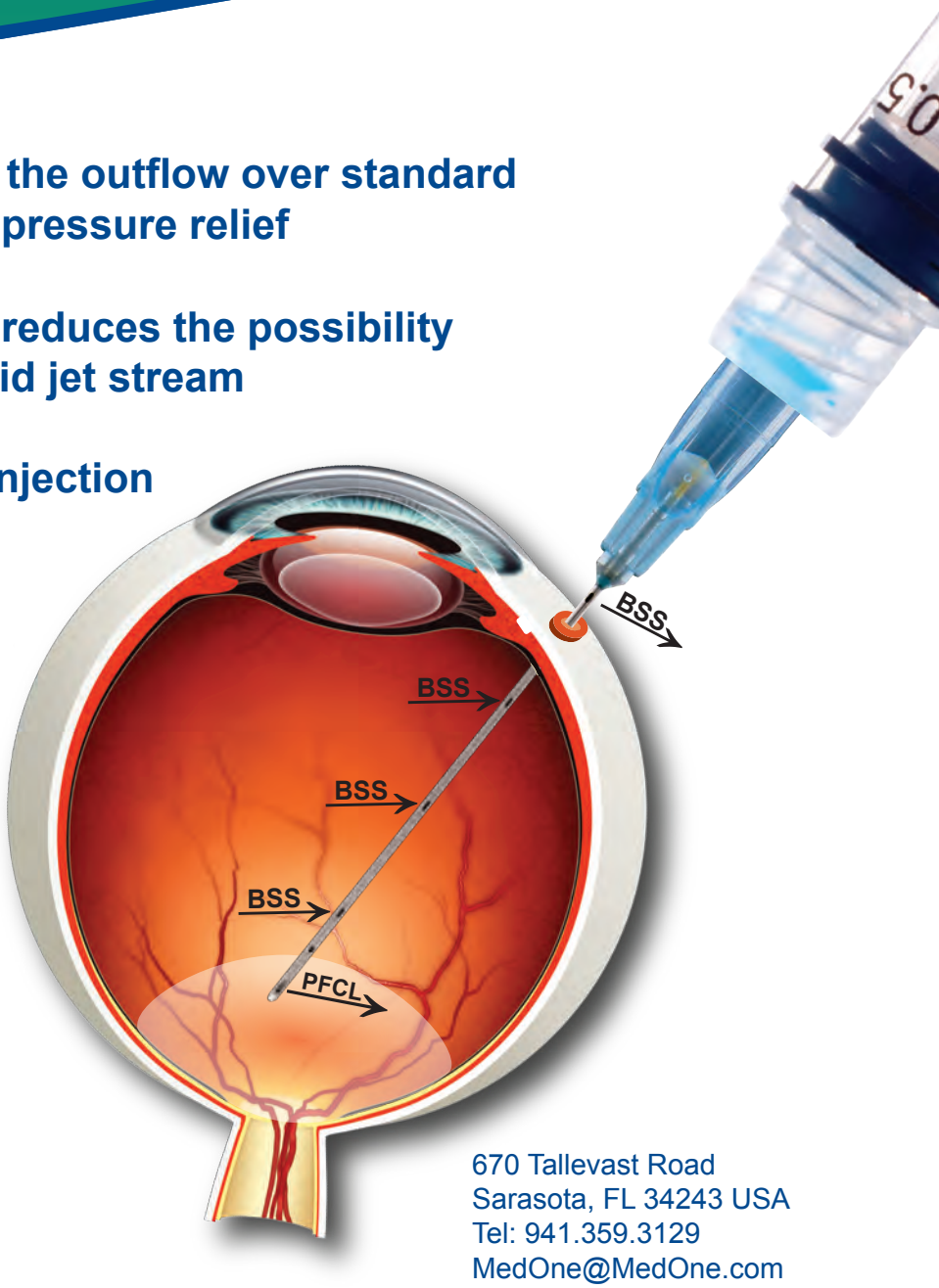

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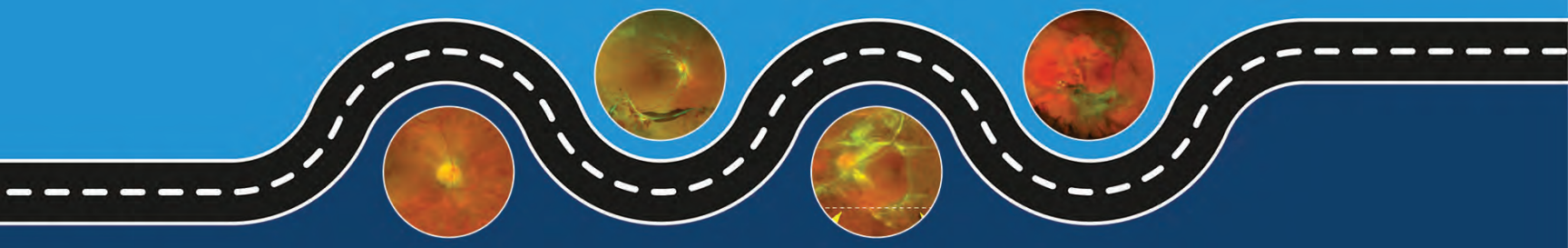


STRATEGIES FOR COMBATTING LTFU

Experts share why follow-up is crucial for patients with diabetes and how you can keep patients on the schedule.

BY RAHUL N. KHURANA, MD, FASRS; KATHERINE TALCOTT, MD; AND JASON HSU, MD



RETINA TODAY: HOW DOES LOSS TO FOLLOW-UP (LTFU) AFFECT THE DIABETES PATIENT POPULATION?

Jason Hsu, MD: The issue of LTFU is huge in the diabetic population. Unfortunately, to develop more severe diabetic retinopathy (DR), there is often some element of noncompliance with physician recommendations and nonadherence to treatment regimens.

I have seen too many patients who have unforeseen circumstances, such as an extended hospitalization, loss of insurance, or problems getting transportation, that lead them to delay returning for eye care. As expected, the prognosis for some of these patients can be abysmal.

Patients who are LTFU generally have worse visual outcomes. However, some of this depends on past treatments. For example, patients with proliferative DR (PDR) who were treated with panretinal photocoagulation (PRP) and were then LTFU had a lower rate of long-term adverse outcomes compared with patients who were treated only with anti-VEGF injections.[1] More recently, we found that patients who had been receiving anti-VEGF injections for diabetic macular edema (DME) were, on average, able to recover vision after a period of LTFU.[2] While this is reassuring, it does not address the fact that these patients may have gained even more vision had they stayed on regular treatments, rather than missing appointments.

Katherine Talcott, MD: Even in clinical trials where patients have the support of research coordinators and are often compensated for transportation, long lapses in care are common, as was demonstrated in the Diabetic Retinopathy Clinical Research Retina Network's Protocol S.[3] There are visual consequences associated with these lapses, especially in patients undergoing treatment for PDR, where the goal of treatment is often to slow vision loss.

When DR patients are LTFU, they are at an increases risk of disease progression or experiencing a vision-threatening complication. In the case of PDR, it can mean that neovascularization or fibrovascular proliferation worsens and leads to vitreous hemorrhage, neovascular glaucoma, or a tractional retinal detachment (Figures 1 and 2). These complications require more interventions for the patient, including more intravitreal injections or PRP, but can also mean retina or glaucoma surgery. Additionally, it may increase the risk of further and permanent vision loss. This obviously affects patients' vision but can also impact their ability to work or take care of themselves or their families.

RT: WHAT DO WE KNOW ABOUT THE PREVALENCE OF LTFU FROM THE LITERATURE?

Dr. Hsu: At Wills Eye Hospital, we performed many of the early studies exploring risk factors for LTFU in patients with diabetes receiving intravitreal anti-VEGF injections. In our offices, the major risk factors included younger age;

AT A GLANCE

- New research suggests approximately 10% of patients with proliferative diabetic retinopathy are lost to follow-up.
- Risk factors for loss to follow-up include older age, male sex, Black or Latinx race/ethnicity, unilateral disease, and having private insurance.
- Retinal imaging can be helpful to explain–and show–the concerning findings and improve patient engagement.

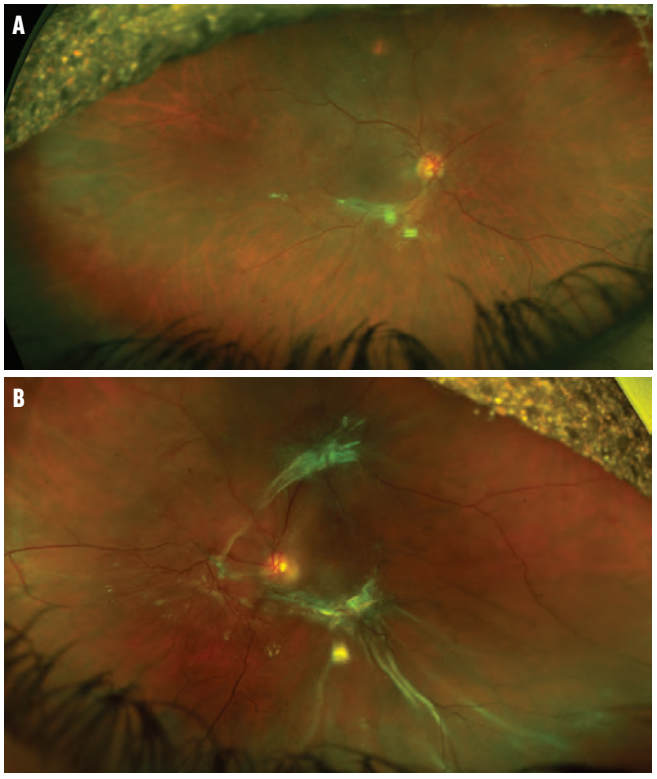


Figure 1. This 58-year-old woman with diabetes was LTFU for 4 years. When she returned to the office, she had developed PDR in each eye. Note the traction and a full-thickness macular hole in the right eye (A) and a tractional retinal detachment in the left eye (B).

identifying as Black, Hispanic, or not reporting race; having worse baseline visual acuity; and living in a zip code with a lower average adjusted gross income.[1,4]

Risk factors in other studies include older age (unlike what we found), poor mobility, need for transportation assistance, insurance status, and having multiple comorbidities. However, what I've learned is that you can never be certain who is going to be LTFU, as patients don't follow a manual.

Rahul N. Khurana, MD, FASRS: A few single-institution studies have shown that anywhere from 25% to 51% of patients with PDR are LTFU after their first treatment.[4,5] These rates of LTFU vary for each institution and clinic, so my group wanted to see what was true on a national level for patients with PDR treated with only anti-VEGF therapy, only PRP, or a combination of both.[6] We used the IRIS Registry from the American Academy of Ophthalmology, which offers access to a huge number of patients to help eliminate bias introduced by single-site studies (ie, single sites may list patients as LTFU if they are seeing another clinician and not truly lost).[6]

We found nearly 300,000 patients who were newly diagnosed with PDR between 2013 and 2015. After applying various exclusion criteria, we separated them into three treatment groups: anti-VEGF therapy alone (approximately 40,000 patients), PRP alone (approximately 32,000 patients),

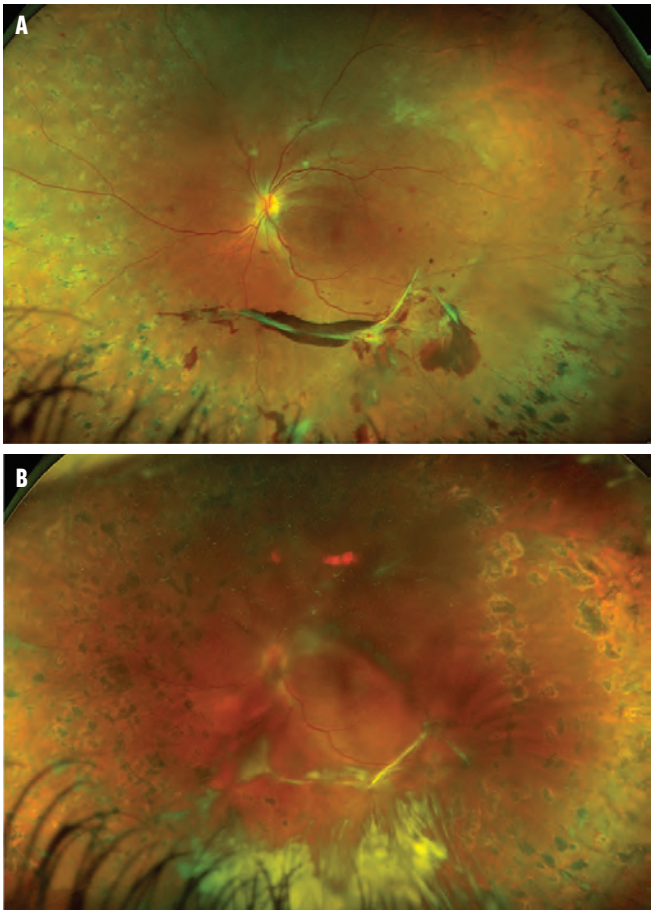


Figure 2. This 32-year-old woman with PDR presented with a vitreous hemorrhage (A). She was LTFU for 6 months and eventually returned with worsening traction and vitreous hemorrhage (B).

and combined anti-VEGF therapy and PRP (approximately 33,000 patients).[6]

We found that 10.7% of patients treated with anti-VEGF therapy alone were LTFU (defined as a visit more than 12 months after the last treatment), 9.5% of patients treated with PRP alone were LTFU, and 9.8% of patients treated with combination therapy were LTFU. The difference between the anti-VEGF therapy and both PRP and the combination therapy arms was statistically significant.[6]

When we initiated this study, I thought that the LTFU number would be higher because the LTFU rates were so high for other institutions, but that's one of the issues with determining this rate from a single site or even a single system. Patients move and see other providers, and they aren't really LTFU, but they are counted as such in a single-institution study. The national registry provides a much more accurate number, even though it still doesn't capture all ophthalmologists. Regardless, the 10% number we found is still an unacceptably high number.

As for demographics, patients who were older were more likely to be LTFU when they were treated with anti-VEGF

therapy alone. We also found that women were less likely to be LTFU in both the anti-VEGF and the PRP arms. We noticed that Black and Latinx patients were more likely to be LTFU in each of the three treatment groups compared with White patients. We also noted that patients who had unilateral disease had a nearly twofold higher rate of LTFU compared with those with bilateral disease. Finally, when we looked at insurance, we found that patients with private insurance were more likely to be LTFU compared with patients who had Medicare.[6]

RT: HOW DOES THIS DATA AFFECT CLINICAL PRACTICE?

Dr. Khurana: One of the most important findings in our study was the demographics at risk for LTFU. We need to emphasize the importance of following up for all patients, but for certain groups that are at a higher riskf for LTFU, it makes sense to spend even more time explaining why treatment is important and why coming back is a must.

Dr. Hsu: It would be great if we had a formula to calculate each patient's risk for LTFU. We could then tailor an intervention to each individual. For example, if a patient has PDR and is calculated to have a high risk of LTFU, then PRP would be the go-to treatment. On the flip side, if they have a low risk of LTFU, then anti-VEGF therapy might be better, which requires ongoing treatments to ensure optimal outcomes. However, we cannot create a formula that has any degree of certainty in predicting who is going to be LTFU. While certain risk factors are evident, they do not hold true across the board. Therefore, just using those factors to tailor treatment is risky. As a result, I basically assume that everyone is equally at risk of LTFU and treat them with that in mind.

Dr. Talcott: If I'm worried that a patient may be at risk for a lapse in care, I make management decisions that may help lessen the burden of follow-up or could help to maintain vision if they have a lapse in care, whether that's treating DME with longer-acting agents or opting for PRP for patients with PDR. This may require taking them to the OR for PRP or working with my ophthalmology colleagues to do PRP in the OR in conjunction with another procedure.

RT: ANY TIPS FOR IMPROVING ADHERENCE TO FOLLOW-UP?

Dr. Khurana: All clinics have a variety of tools to help, whether it's a phone call or reminder cards. Furthermore, monitoring patients who miss treatment follow-up visits is even more crucial; having programs in place to do that is important in the clinical system. These simple measures are helpful, but when we look at other chronic diseases and conditions, those physicians usually have other people on the team whose sole job is to educate and motivate patients. We as a community are going to have to think about adding those components in our retina practices as we deal with these chronic conditions in the future.

Dr. Hsu: Patient education is paramount. Helping them understand the nature of their disease and the benefits of ongoing follow-up and treatment is critical. The availability of digital imaging, including OCT and fundus photography, has allowed us to show patients what is going on in their eyes, which helps augment the educational discussions.

Tracking these high-risk patients is also important. Our practice instituted a call-back system where patients who have received treatment are carefully tracked. If they miss a visit, a staff member contacts them immediately. If they continue to miss visits or cannot be reached, we send them a certified letter explaining our concern and the risks they may face by not being seen and treated.

Dr. Talcott: This is the biggest challenge. It's one thing to understand why a patient might be LTFU or the visual consequences associated with it, but it's an entirely different issue to prevent it. Patients with diabetes face a lot of issues that put them at risk for LTFU. Compared with most of our retina patients, they tend to be younger and are often balancing retina appointments with work and family responsibilities. Patients with diabetes with retina pathology often have concomitant end-organ damage and have multiple medical appointments with other specialties or even frequent hospital admissions.

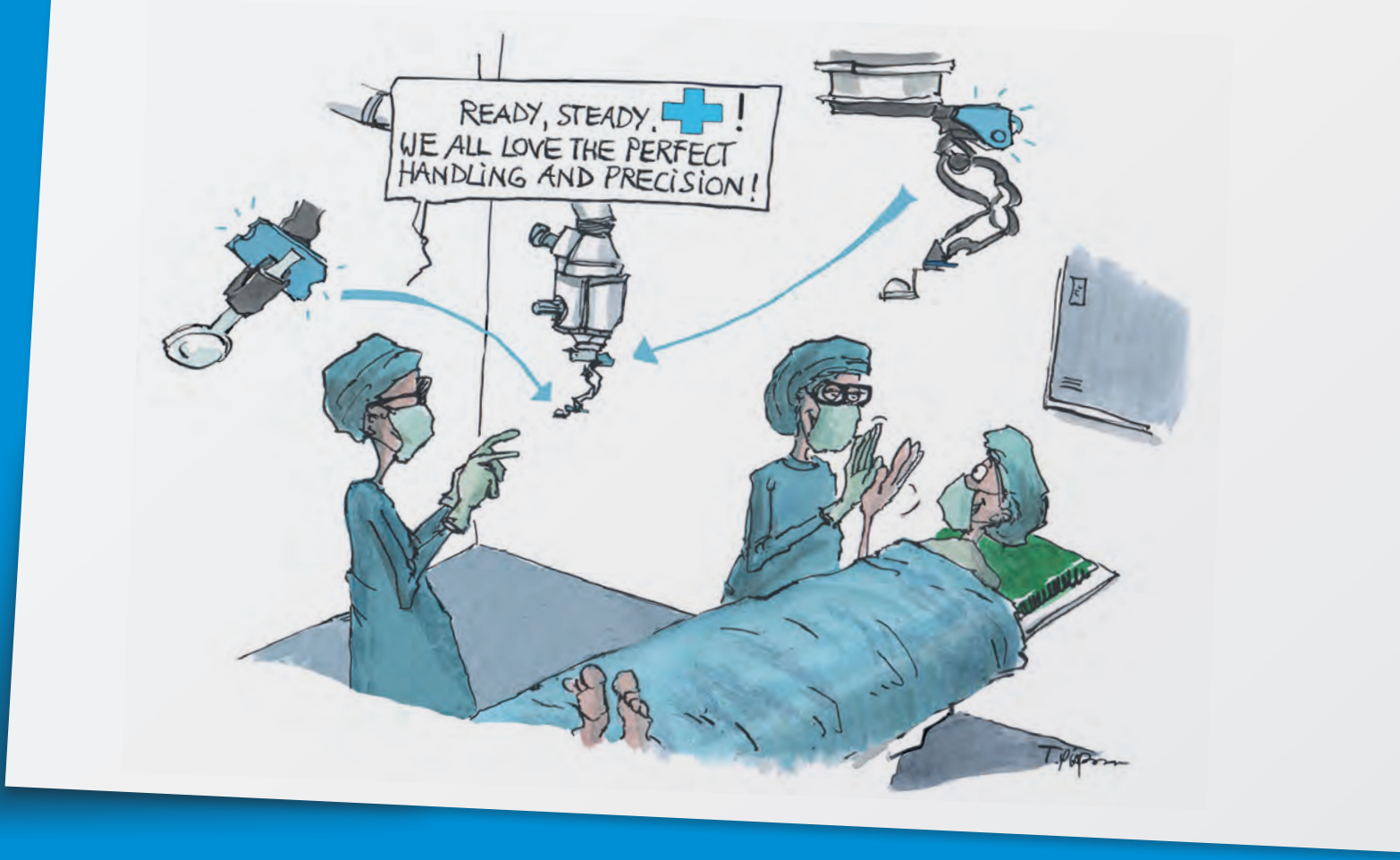
I stress the importance of regular follow-up with all my patients with DR and any family members who accompany them. I try to get a sense of a patient's social support because involved family members can be critical to help the patient get to their appointments. I try to engage the patient and their caregiver (if appropriate) from our first visit by carefully explaining their disease and what could happen if it progresses. Imaging, including wide-angle fundus photography or fluorescein angiography at baseline, can be helpful to explain and show the concerning findings. Additionally, the treatment approach is important because PRP may help prevent vision-threatening complications if patients are LTFU.

RT: WHAT ARE SOME CHANGES THAT MIGHT HELP MITIGATE THESE RISKS FOR LTFU?

Dr. Hsu: There are two avenues that need to be developed. The first is improving communication and patient education. Our clinics are busier than ever as more therapies are becoming available to treat retinal diseases. Better integrating patient education in a way that helps patients understand their condition and treatment plan will likely help to improve patient adherence. More innovative educational experiences, both office-based and mobile, may be one route. Smartphone applications that assist with education, help detect visual issues, and even remind patients that they are overdue for an appointment may be useful tools.

The second is extended-duration therapies, which I believe will ultimately play the largest role in improving outcomes.

(Continued on page 58)



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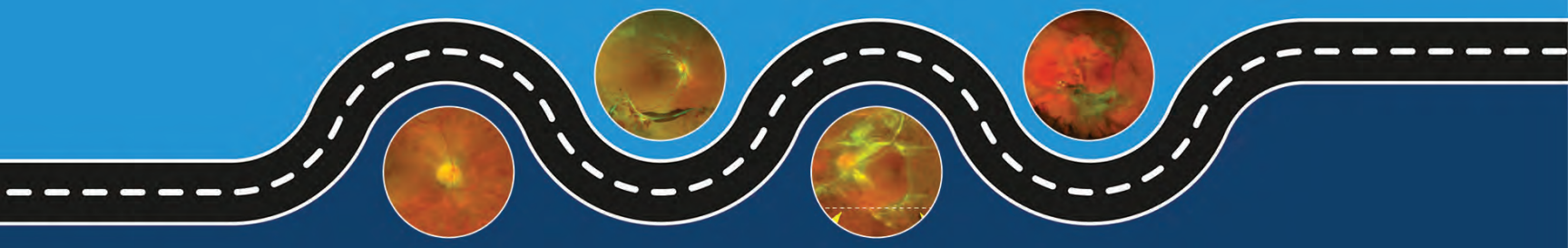

WIDEFIELD OCTA: A NEW WAY TO STAGE DIABETIC RETINOPATHY

Our current system isn't harnessing the power of recent advances. This approach does.

BY JONATHAN F. RUSSELL, MD, PHD, AND IAN C. HAN, MD


Diabetic retinopathy (DR) remains the leading cause of blindness among adults of working age in developed countries, and the prevalence of DR continues to increase.[1,2] This massive disease burden necessitates the development and implementation of effective and efficient strategies for screening, staging, and managing DR.

For more than 50 years, DR has been classified based on vascular abnormalities visible with conventional fundus photography.[3] Although widely used, the current system relies on decades-old technology (ie, montaged 30° color fundus photographs) and does not harness the capabilities of modern retinal imaging. For this reason, current DR staging has many limitations, including the following:

- a limited field of view compared with modern photography that allows up to 200° in a single frame,
- a lack of angiography to define the extent of retinal ischemia or differentiate intraretinal microvascular abnormalities (IRMA) from neovascularization (NV), and
- no cross-sectional imaging to identify structural changes such as diabetic macular edema (DME) or areas of traction.[4]

Moreover, traditional DR staging is limited to clinically apparent abnormalities of the retinal vasculature—it does not address structural changes in the inner retina, such as retinal nerve fiber layer/ganglion cell layer thinning, vascular loss in the choriocapillaris/choroid, or vitreoretinal interface abnormalities such as tractional retinal detachment.

To account for advances in our understanding of DR, multiple people have called for the development of new DR staging systems.[5-9] There is at least one large, multidisciplinary working group attempting to create one, although this group is still in preliminary discussions.[8,10]

A NEW WAY TO SEE

Over the past 2 decades, OCT has become an ubiquitous technology that enables visualization of retinal changes such as DME and atrophy. OCT angiography (OCTA) is a more recent advance that images both retinal structures and vascularity well beyond the ability of conventional fundus photography. We recently proposed a new staging system for DR based solely on OCT/OCTA scans (Figure 1).[4] Our system leverages the current DR staging system but overcomes many of the limitations by visualizing the entire posterior pole with a single scan and by incorporating both angiographic and structural information. An OCTA-based system has a few other advantages, including an ability to:

- image the choroid and any tractional retinal detachment (TRD),
- differentiate between active versus quiescent proliferative DR (PDR), and

AT A GLANCE

- The current diabetic retinopathy staging system relies on decades-old technology and does not harness the capabilities of modern retinal imaging.
- A new staging system based solely on OCT/OCT angiography overcomes many of the current system's limitations.
- Barriers to adoption include the learning curve for OCT angiography interpretation and the cost of implementation.

- register scans for direct comparison between visits.

This system encompasses all the clinically useful information needed for staging and managing DR.

The proposed OCTA-based system consists of six stages[4]:

No DR: This stage is defined as a normal widefield (WF) OCTA of the posterior pole.

Subclinical DR: This stage is defined as small areas of decreased vascular density without distinct vascular abnormalities (ie, microaneurysms, IRMA, or NV). With the current DR staging methods, eyes with subclinical DR are mistakenly labelled as normal, whereas OCTA clearly reveals signs of early disease.[11]

Nonproliferative DR (NPDR): The new staging system compresses mild and moderate NPDR into a single category that features microaneurysms and/or larger areas of capillary ischemia.

Severe NPDR: This is an important clinical threshold for clinicians to recognize because of the risk of progression to NV and its associated complications.

In the OCTA-based system, severe NPDR is replaced with a new category called preproliferative DR. This stage is defined by OCTA evidence of IRMA but not NV. Because IRMAs have been shown to be the vascular precursor to NV,[12] IRMAs are the defining feature of the preproliferative stage.

PDR: This stage is defined by OCTA evidence of NV (Figure 2).[13] Unlike fluorescein angiography, OCTA captures vascular flow in a binary fashion (either present or absent) and lacks the ability to evaluate dynamic transit of dye and leakage over time. However, OCTA's ability to correlate vascular information with structural details facilitates the differentiation of NV from IRMA based on the location of the lesion (preretinal vs intraretinal, respectively). Moreover, OCTA can distinguish active versus quiescent NV based on the caliber and density of vessels within the neovascular complex.[13]

TRD: The final stage is defined by RD with traction from active or quiescent NV or fibrosis.[14] TRD substages are defined based on location: extramacular, macular (but not foveal), or foveal detachment. DME remains an off-axis parameter that is imaged and potentially quantifiable with every OCTA scan, unlike in the current staging system.

In contrast to current DR staging, this OCTA-based system intentionally does not include intraretinal hemorrhages, which are readily apparent on fundus photography but less distinguishable on OCTA and typically not visually significant. Because hemorrhages are secondary to vascular

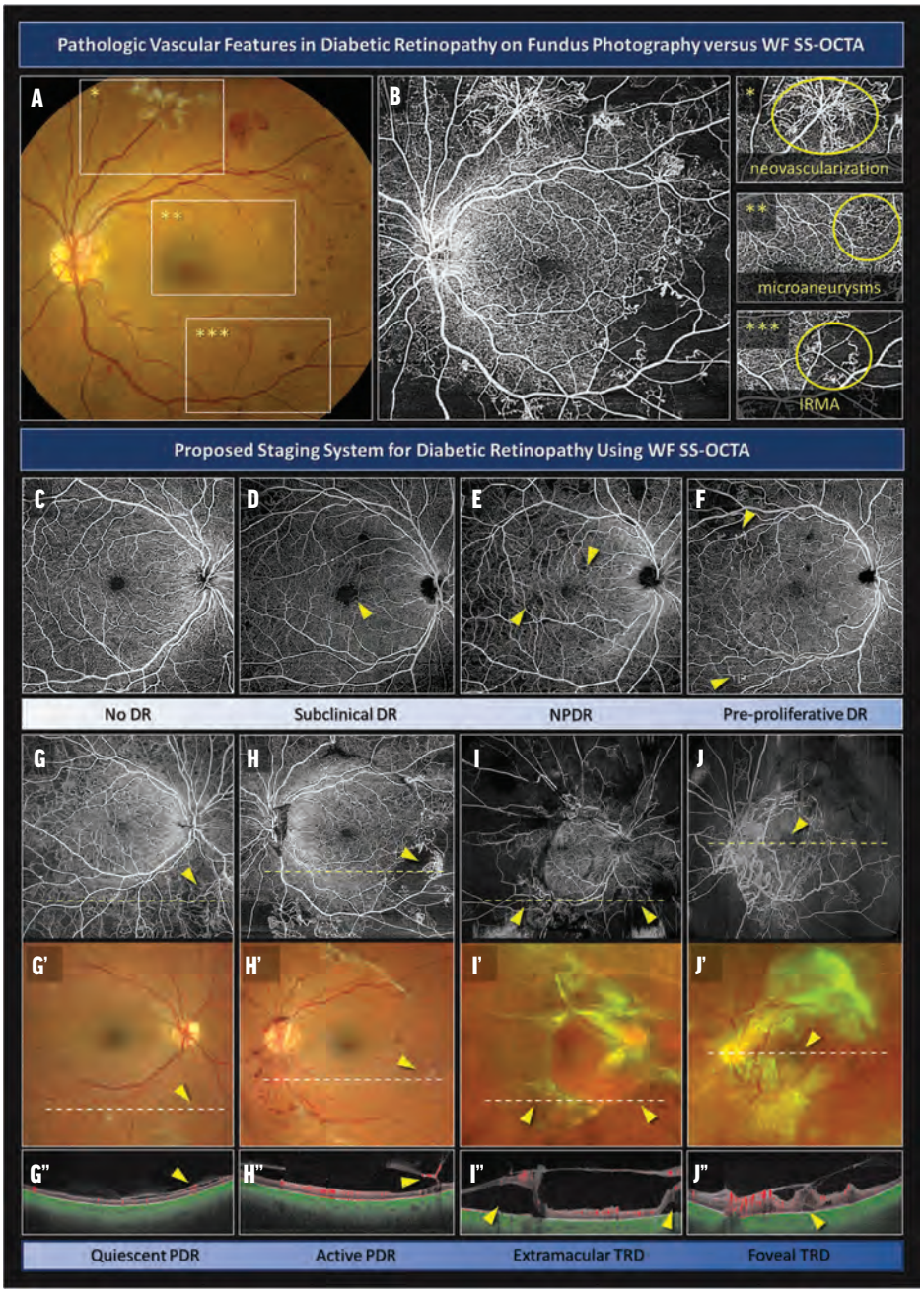

Figure 1. Proposed OCTA-based DR staging system. Reprinted with permission from Russell et al.[4]

compromise, eyes with hemorrhages always have other vascular features of DR on OCTA. Moreover, the lack of hemorrhages can deceive a clinician into undergrading diabetic eyes. Specifically, some eyes with a featureless fundus with few or no hemorrhages may have severe ischemia and, often, NV.

As such, our system was designed to focus on other, more clinically relevant lesions, such as IRMA, NV, and DME. The goal of a staging system should be to guide the clinician on how to help the patient see better, not to make the fundus look better.

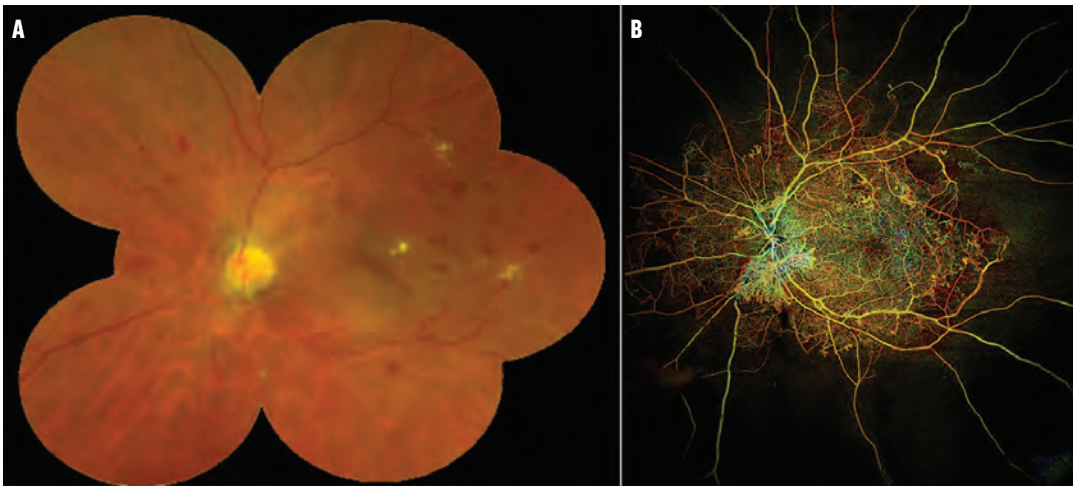

Figure 2. An eye with PDR imaged with fundus photography (A) and WF OCTA (B). The ultra-widefield photograph is cropped to reflect the field of view with current DR staging protocols. The WF OCTA image captures a larger field of view and reveals retinal ischemia and vascular abnormalities such as NV of the disc.

HURDLES

An OCTA-based staging system for DR faces several potential barriers to adoption in the clinic and for clinical research purposes. For one, there is a learning curve for OCTA interpretation that can intimidate some technicians and clinicians. This curve is not steep for DR, however, because research shows that trainees and retina specialists can identify PDR on WF OCTA images with similar accuracy as for fluorescein angiograms.[15]

Another barrier is that the instruments required for WF OCTA are not universally available and are costly (on par with an ultra-widefield fundus camera), and current insurers do not reimburse OCTA interpretation separately from OCT. Finally, the large data files of WF OCTA present challenges in the amount of data storage required and the ease of real-time, in-clinic evaluation. Further technological improvements should help overcome these limitations.

TIME TO MODERNIZE

A new system that uses the advantages of WF OCTA can modernize the DR staging system to include all structural and vascular aspects of DR. For example, WF OCTA enables detection of all clinically relevant features of DR and builds upon current DR staging methods while overcoming their primary limitations.

The new OCTA-based system can be used for staging DR in routine clinical practice and can be standardized for research studies. Incorporation in future clinical trials is necessary to demonstrate the efficacy of this new staging system for preventing vision loss from DR. ■

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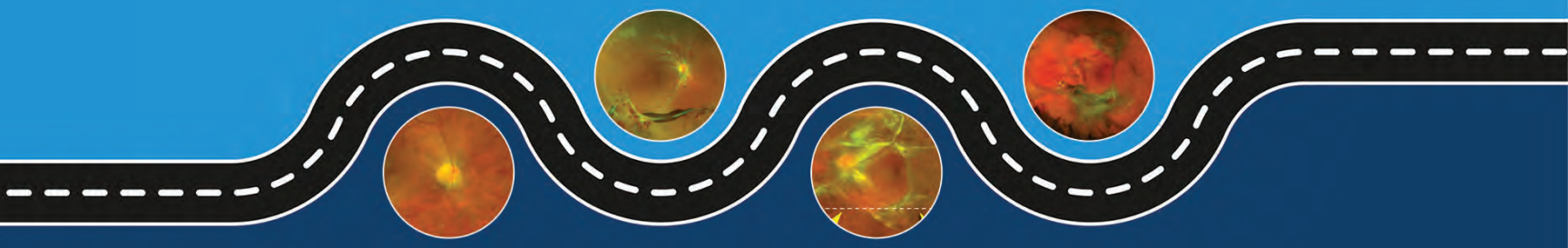

A DRCR RETINA NETWORK UPDATE A TO Z

This research group tackles myriad questions surrounding the optimal treatment approach for patients with diabetic eye disease.

BY SALEEMA KHERANI, MD, MPH, AND JUDY E. KIM, MD, FARVO, FASRS

Over the last 2 decades, the Diabetic Retinopathy Clinical Research (DRCR) Retina Network has completed more than 30 multicenter studies in diabetic retinopathy (DR) in collaboration with more than 160 participating clinical sites throughout the United States and Canada. These studies have played a pivotal role in advancing the care of diabetic eye diseases. For example, DRCR Retina Network studies helped establish anti-VEGF therapy as a first-line treatment for vision-threatening center-involving diabetic macular edema (CI-DME) and an effective alternative to panretinal photocoagulation (PRP) for the treatment of proliferative DR (PDR).

In recent years, the DRCR Retina Network has expanded its studies to include other retinal diseases beyond DR. Here is a look at the DRCR Retina Network's recently published and ongoing trials.

RECENT FINDINGS

Protocol T compared aflibercept (Eylea, Regeneron), bevacizumab (Avastin, Genentech/Roche), and ranibizumab (Lucentis, Genentech/Roche) for eyes with visual impairment due to CI-DME (Figure 1). At the end of the 2-year study period, there were no differences between the agents with regards to the mean change in VA from baseline, if baseline VA was between 20/32 and 20/40. However, among patients with a baseline VA between 20/50 and 20/320, aflibercept was superior to bevacizumab and ranibizumab at 1 year, and to bevacizumab at 2 years.[1]

Patients from Protocol T were asked to follow up for a single visit at 5 years as part of the Protocol T extension study, **Protocol TX**, to assess clinical outcomes. A total of 317 of 463 patients completed the 5-year follow-up; 68% received at least one anti-VEGF injection between years 2 and 5 (median [range]: 4 [0-12]). The mean VA at 5 years improved by 7.4 letters from baseline but was 4.7 letters less than year 2. Overall, mean central subfield thickness (CST) stayed stable between years 2 and 5.[2]

Protocol V evaluated three treatment strategies for patients with good vision (20/25 or better) and CI-DME: intravitreal aflibercept as frequently as every 4 weeks, focal/grid laser therapy with deferred aflibercept, or observation with deferred aflibercept. The primary outcome was at least

AT A GLANCE

- The Diabetic Retinopathy Clinical Research (DRCR) Retina Network has completed more than 30 multicenter studies in diabetic retinopathy.
- The recently published Protocol AC study created a real-world scenario to investigate the anti-VEGF cost burden for patients and insurance companies.
- Since 2002, the DRCR Retina Network has made substantial contributions to the way retina specialists manage diabetic eye disease, both medically and surgically.
- In recent years, the DRCR Retina Network has expanded its studies to include all retinal diseases in addition to diabetic retinopathy.

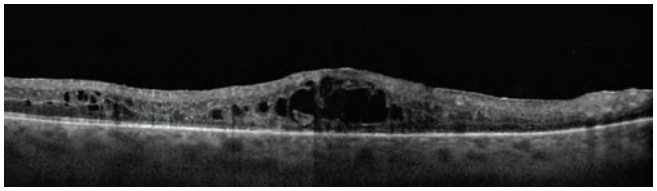

Figure 1. The DRCR Retina Network studies were integral to the shift toward anti-VEGF as the first-line treatment for CI-DME, as seen here.

a 5-letter VA decrease from baseline at 2 years.[3]

At 2 years, there was no statistically significant difference in the percentage of patients who lost at least 5 letters between the three groups, whether they were initially treated with aflibercept or received aflibercept as a rescue when visual acuity worsened, for those assigned to the laser or observation groups. The researchers concluded that observation may be a reasonable initial strategy for patients with good vision and CI-DME until visual acuity worsens.[3]

In a post-hoc analysis of Protocol V's observation group, 80 of 236 (34%) patients received treatment with aflibercept during the 2-year follow-up. Patients with a CST ≥ 300 µm, more severe DR stage, or fellow non-study eye receiving treatment for DME within 4 months of randomization were more likely to receive rescue treatment with aflibercept. Eyes that were treated with initial observation and then with aflibercept if visual acuity worsened maintained good vision at 2 years.[4]

Protocol W evaluated the effect of intravitreal anti-VEGF aflibercept versus sham for the prevention of vision-threatening complications of moderate to severe nonproliferative DR (NPDR). Patients were randomly assigned to receive intravitreal aflibercept injection or sham at baseline, at months 1, 2, and 4, and then every 4 months through 2 years. Between years 2 and 4, aflibercept was administered if patients developed CI-DME with vision loss or high-risk PDR. The primary outcome of the study was the development of vision-threatening CI-DME or PDR.[5]

At 2 years, the cumulative probability of developing PDR was 13.5% and 33.2% and CI-DME with vision loss was 4.1% and 14.8% in the aflibercept and sham groups, respectively. Although periodic treatment with aflibercept reduced the development of vision-reducing CI-DME and PDR, it did not have any statistically significant visual acuity benefits at the end of 2 years.[5] The 4-year results will be revealed near the end of 2022 and will give us long-term assessment of whether prevention of vision-threatening CI-DME and PDR with aflibercept results in long-term visual benefits.[5]

Protocol AA compared ultra-widefield (UWF) imaging with Early Treatment Diabetic Retinopathy Study (ETDRS) 7-standard-field imaging for the assessment of peripheral lesions, DR severity, and rates of DR worsening over time. This 4-year study evaluated the association of retinal nonperfusion on UWF fluorescein angiography (FA) with DR severity and predominantly peripheral lesions (Figure 2).

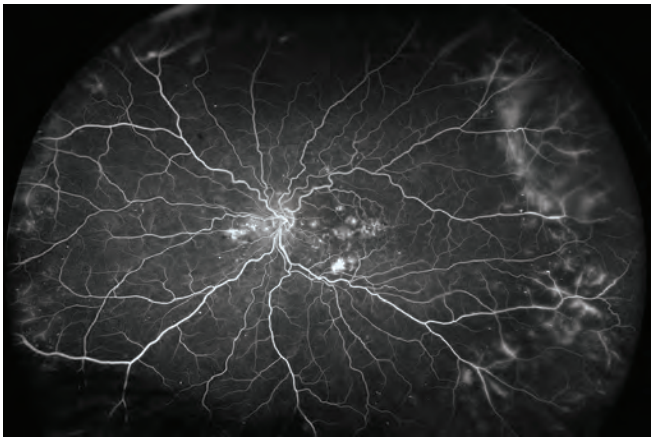

Figure 2. UWF-FA imaging, as seen here, may better predict progression of DR compared with 7-standard-fields imaging, according to DRCR Retina Network's Protocol AA.

The study concluded that 70% of the nonperfusion in diabetic eyes involves the peripheral retina and suggested that UWF-FA may better predict progression of DR compared with 7-standard-fields imaging, as increased nonperfusion on UWF-FA is associated with the presence of predominantly peripheral lesions.[6]

Protocol AB compared the initial treatment for vitreous hemorrhage from PDR with intravitreal aflibercept versus vitrectomy with PRP. Patients were randomly assigned to aflibercept (4 monthly injections) or vitrectomy with PRP. The primary outcome was mean visual acuity at 24-weeks and the secondary outcome was mean visual acuity at 2 years.[7] There was no statistically significant difference in the mean visual acuity at 24 weeks or 2 years between the two groups. Over 2 years, 33% of patients in the aflibercept group required vitrectomy and 32% in vitrectomy with PRP group received subsequent aflibercept injections. The researchers concluded that the study may have been underpowered to detect a clinical benefit in favor of initial vitrectomy with PRP.[7]

Protocol AC compared the efficacy of intravitreal aflibercept monotherapy versus intravitreal bevacizumab first with a switch to aflibercept beginning at week 12 if protocol-specific criteria were met in eyes with visual impairment (BCVA between 20/50 and 20/320) from CI-DME. The study concluded that there was no significant difference in visual outcomes over 2 years in eyes treated with aflibercept monotherapy versus those switched from bevacizumab to aflibercept due to suboptimal clinical response. It was suggested that initiating treatment with bevacizumab and switching to aflibercept is a safe and effective alternative to aflibercept monotherapy in diabetic eyes with moderate visual impairment from CI-DME.[8]

This study created a real-world scenario to investigate the cost burden for patients and insurance companies and demonstrated that switching from bevacizumab to aflibercept when needed is an economical option, while still seeing

SINCE 2002, THE DRCR RETINA NETWORK HAS MADE SUBSTANTIAL CONTRIBUTIONS TO THE WAY RETINA SPECIALISTS MANAGE DIABETIC EYE DISEASE, BOTH MEDICALLY AND SURGICALLY.

visual outcomes similar to those seen when starting aflibercept from the outset, in a population similar to patients enrolled in the study.[8]

Protocol AE was a phase 2 clinical trial that randomized patients to a home-based photobiomodulation (PBM) device versus placebo for CI-DME and good vision to see if this could be considered as a potential cost-effective treatment and whether a phase 3 trial would be warranted. The primary outcome was a change in CST on spectral-domain OCT at 4 months. The study concluded that, although photobiomodulation is safe and well-tolerated, it was not effective for reducing CST in eyes with CI-DME with good vision.[9]

ONGOING AND ENROLLING

Protocol AF is a randomized, double-masked, placebo-controlled trial that will evaluate the effect of fenofibrate compared with placebo for the prevention of worsening of DR over 4 years of follow-up in eyes with mild to moderately severe NPDR and no CI-DME at baseline. The study is currently enrolling participants.[10]

RETINAL PATHOLOGY BEYOND DR

In 2018, the DRCR Retina Network expanded its scope to all retinal pathologies in a collaborative research setting. The first two non-DR protocols included protocols AG and AH.

Protocol AG compared pneumatic vitreolysis (PVL) with clinic-based injection of C_3F_8 versus sham injection for vitreomacular traction (VMT) without macular hole.[11]

Protocol AH was a single-arm study that evaluated PVL with clinic-based injection of C_3F_8 for full-thickness macular hole associated with VMT.[11]

The main outcome was central VMT release at 24 weeks for Protocol AG and macular hole closure at 8 weeks for Protocol AH. Both of these studies were terminated early due to higher-than-expected rates of retinal tears and retinal detachments.[11]

Protocol AM is an ongoing trial that will compare visual acuity and OCT outcomes, changes in metamorphopsia, and complication rates at 36 months in eyes that undergo immediate versus deferred surgery for symptomatic epiretinal membranes.[12]

A LONG-STANDING TRADITION

Since 2002, the DRCR Retina Network has made substantial contributions to the way retina specialists manage diabetic eye disease, both medically and surgically. Now with an expanded scope of research to include all retinal pathologies, the DRCR Retina Network will continue to guide retina practices worldwide. ■

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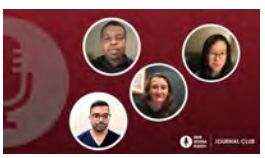

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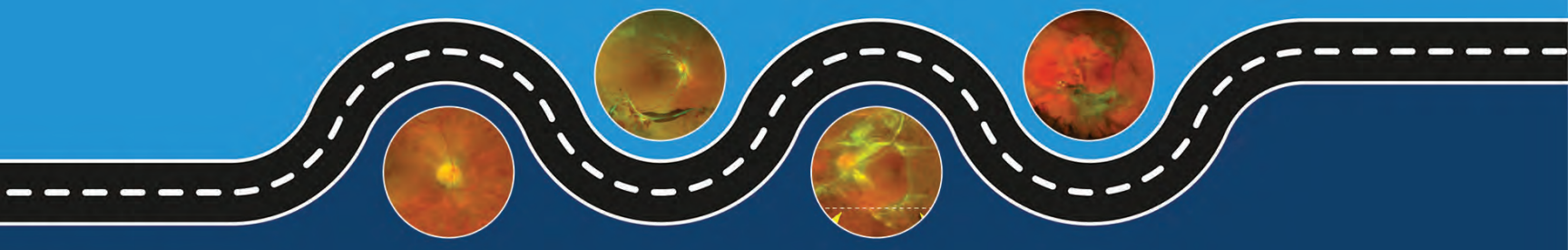

DIABETIC EYE DISEASE: WHEN TO INTERVENE

Knowing how to treat patients with diabetes remains a challenge. These tips can help.

BY DILSHER S. DHOOT, MD

The decision to treat diabetic retinopathy (DR) and diabetic macular edema (DME) is complex, and physicians must consider several factors beyond the underlying severity and presentation of the pathology. These factors include the likelihood that the patient will adhere to the treatment plan, socioeconomic factors, access to care, and patient preference. In addition, retina specialists have an ever-expanding toolkit to treat diabetic eye disease. Here I explore when and how to intervene for the treatment of DR and DME.

WHEN TO TREAT

Diabetic Macular Edema

Most retina specialists have a low threshold to treat center-involving or center-threatening DME, especially for patients with perceived vision loss (Figure). The Early Treatment Diabetic Retinopathy Study (ETDRS) group was one of the first to document decreased vision related to the duration and severity of DME. In patients with a VA of 20/40 or better at baseline, the proportion of 3-line losers over 3 years increased from 5% of patients who did not develop severe DME to between 15% and 25% of those who developed severe DME for a duration of 4 to 12 months. In patients who developed severe DME for 28 to 36 months, 61% had moderately severe vision loss at 3 years.[1]

A strong argument for earlier treatment is made based on data from the phase 3 RISE/RIDE trials, which included true sham control groups that were not eligible to cross over to the ranibizumab (Lucentis, Genentech/Roche) groups for 24 months from the time of enrollment. The baseline upper VA limit for inclusion was 20/40 in these trials. Once sham patients finally received anti-VEGF treatment, visual acuity gains were modest at 4.3 to 4.7 letters, despite improvements in anatomy that were similar to patients receiving ranibizumab treatment from the start of the trial.[2]

An argument for delaying treatment in select patients is made based on the results of the Diabetic Retinopathy Clinical Research (DRCR) Retina Network's Protocol V. This trial demonstrated that patients with center-involving DME and a VA of 20/25 or better did not benefit from early treatment with aflibercept (Eylea, Regeneron) in the 2-year follow-up period.[3] Post-hoc analysis identified risk factors associated with the need for rescue, including the need for DME treatment in the fellow eye, baseline central subfield thickness (CST) ≥ 300 µm, and baseline DR severity score (DRSS) ≥ 47.[4] Clinicians should consider these factors when deciding which patients with center-involving DME to treat.

Diabetic Retinopathy

The traditional treatment paradigm for patients with nonproliferative DR (NPDR) is observation and systemic risk factor control with reactive anti-VEGF agents and/or laser treatment if and when patients develop proliferative DR (PDR) or center-involving DME. The Diabetes Control and Complications Trial and the United Kingdom Prospective Diabetes Study demonstrated that intense glycemic control helped to reduce the risk of developing DR and slowed the progression of DR.[5,6]

AT A GLANCE

- Most retina specialists have a low threshold to treat center-involving or center-threatening diabetic macular edema, especially for patients with perceived vision loss.
- The traditional treatment paradigm for patients with nonproliferative diabetic retinopathy has been observation and systemic risk factor control.
- Improvements in durability for the treatment of diabetic eye disease are expected with emerging delivery methods.

Unfortunately, many patients progress even with good glycemic control, and the rate of conversion to PDR in eyes with level 53 severe NPDR is approximately 50% in 1 year. This number increases to more than 75% at 5 years.[7-10]

Moreover, the DRCR Retina Network's Protocols S and W and the PANORAMA trial demonstrated the benefits of treatment with anti-VEGF agents in DR patients.[11-14] With a large and expanding body of literature supporting the treatment of DR, there have been calls to shift the treatment paradigm for certain patients with higher-level NPDR to a more proactive treatment with intravitreal anti-VEGF agents. The ability to improve DRSS with VEGF suppression and ultimately reduce vision-threatening complications is significant.

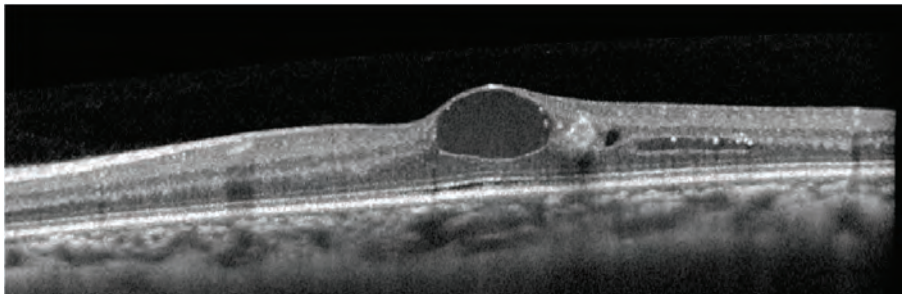

Figure. When a patient presents with clear signs of DME on OCT imaging, clinicians have a low threshold to consider treatment with anti-VEGF agents, laser therapy, steroids, or PPV.

However, a contentious debate continues regarding when and which patients to treat, especially in the absence of center-involving DME, and whether various approaches are cost-effective. Vision outcomes, quality-of-life improvements, and both short- and long-term dosing are all points to consider in this current debate.

HOW TO TREAT DME

Traditional treatment for DME with focal laser has been largely supplanted by intravitreal anti-VEGF therapy. While many patients respond well to anti-VEGF therapy, a subset of patients experience suboptimal or no response. Alternatives to anti-VEGF therapy include intravitreal corticosteroids and, to a lesser extent, pars plana vitrectomy (PPV).

Anti-VEGF Therapy

Most providers consider anti-VEGF agents as a first-line treatment for DME because they are effective for most patients and have a relatively favorable side effect profile.

As mentioned above, ranibizumab was shown to be an effective treatment for DME in the phase 3 RISE/RIDE trials.[2] Patients who were dosed with monthly intravitreal 0.3 mg ranibizumab gained an average of 10.9 and 12.5 letters compared with 2.3 and 2.6 letters in the sham groups in RIDE and RISE, respectively.[4]

Patients in the phase 3 VIVID and VISTA trials for aflibercept were randomized to receive 2 mg aflibercept every 4 or 8 weeks after five monthly loading doses or focal laser as controls. At week 148, visual acuity gains were significantly better in the aflibercept groups compared with the control group at 10.4 (4-week group), 10.5 (8-week group), and 1.4 (laser) letters.[15]

In the YOSEMITE and RHINE trials for faricimab (Vabysmo, Genentech/Roche), patients were randomized to 6.0 mg faricimab dosed every 8 weeks after six monthly loading doses, 6.0 mg faricimab dosed according to a personalized treatment interval after four monthly loading doses, or 2.0 mg aflibercept every 8 weeks after five monthly loading doses. At 1 year, faricimab was found to be noninferior to aflibercept with 11.8- and 10.8-letter gains in the 8-week and personalized treatment interval groups, respectively, compared with a 10.3-letter gain in the aflibercept group.[16]

In the KITE and KESTRAL trials for brolucizumab (Beovu, Novartis), patients were randomized to 6.0 mg brolucizumab with five loading doses every 6 weeks followed by every 12-week dosing, with the option to drop down to every 8 weeks if necessary, compared with 2.0 mg aflibercept with five loading doses every 4 weeks followed by fixed every 8-week dosing. At 52 weeks, brolucizumab was demonstrated to be noninferior to aflibercept in terms of mean change in BCVA. A lower proportion of patients in the brolucizumab arms had intraretinal and/or subretinal fluid at week 52 versus eyes treated with aflibercept (KITE, 54.2% vs 72.9%, and KESTREL, 60.3% vs 73.3%, in the brolucizumab vs aflibercept arms, respectively).[17]

Steroids

While most patients have good results with anti-VEGF therapy, those who do not may require adjunctive therapy with corticosteroids. These agents have found an ever-growing niche in the treatment of DME owing to a broader effect on the "other" cytokines implicated in DME.[18] The known side effects of increased rates of cataract and potential increases in IOP have kept corticosteroids as a second-line treatment for most providers. The most common corticosteroids used for DME include triamcinolone acetonide, the dexamethasone implant (Ozurdex, Allergan), and the 0.19 mg fluocinolone implant (Iluvien, Alimera Sciences).

Surgery

In cases of refractory nontractional DME, several authors have published on improvements in edema and anatomy following PPV.[19] While the mechanism of action is unclear, one theory focuses on the increased oxygenation to the retina following vitreous removal. Decreases in histamine, free radicals, and VEGF have also been proposed as possible

mechanisms for improvements in DME after PPV.[20] DME patients with subfoveal serous detachments have been shown to potentially have the greatest benefit in terms of vision and anatomy following PPV.[21]

HOW TO TREAT DR

As mentioned, the historical treatment of NPDR in the absence of DME has been observation with systemic risk factor control. This includes glycemic, hypertension, and hyperlipidemia control. Laser photocoagulation has been a mainstay of treatment for patients with proliferative disease, and the Diabetic Retinopathy Study also recommended laser treatment in one eye for patients with bilateral severe NPDR, eyes with severe retinal ischemia, and for patients with conditions that could accelerate DR, such as pregnancy or renal failure.[22] The ETDRS evaluated early versus deferred laser photocoagulation in patients with moderate to severe NPDR and early PDR and found that rates of vision loss were similar in patients with early and deferred photocoagulation, 2.6% and 3.7%, respectively.[7]

The ability of anti-VEGF agents to improve DRSS and reduce vision-threatening complications is a compelling argument in favor of considering early treatment for patients with NPDR without DME, especially for patients with DRSS levels 47 and 53.

The treatment regimen, including early and late dosing strategies and the duration of treatment, remains unclear. In the phase 3 DME registry trials, patients were treated for DME as frequently as monthly and did quite well in terms of DRSS secondary endpoints. However, monthly treatment, in often asymptomatic DR patients without DME, is generally considered untenable. The data from PANORAMA demonstrates that treatment as infrequently as every 16 weeks after initial loading doses improves DRSS and provides significant protection from DR complications.[14] Treatment with intravitreal aflibercept in the PANORAMA trial reduced vision-threatening complications by 77% when dosed every 16 weeks compared with sham at 100 weeks.[14]

The DRCR Retina Network's Protocol W also demonstrated similar results, showing a 16.3% risk of vision-threatening complications in diabetic patients treated with aflibercept compared with 43.5% of patients in the sham group.[13]

Ultimately, many other patient-specific factors play a role in the decision to treat with anti-VEGF agents, including cost considerations and quality-of-life improvements.

The therapeutic pipeline for diabetic eye disease is robust and centers on more durable treatments. Durability improvements are expected with emerging delivery methods, including devices such as the port delivery system with ranibizumab (Susvimo, Genentech/Roche) and, potentially, gene therapy. Interim data from the phase 2 Altitude trial demonstrated a 47% ≥ 2-step improvement in DRSS in patients dosed with a single suprachoroidal injection of RGX-314 (Regenxbio) at baseline.[23]

KEY TAKEAWAY

End-stage DME and DR can be devastating and often blinding conditions. Fortunately, retina specialists have a growing number of tools at our disposal to prevent and treat them. Thoughtful and timely treatment for our patients with diabetes using the tools we have is of utmost importance. ■

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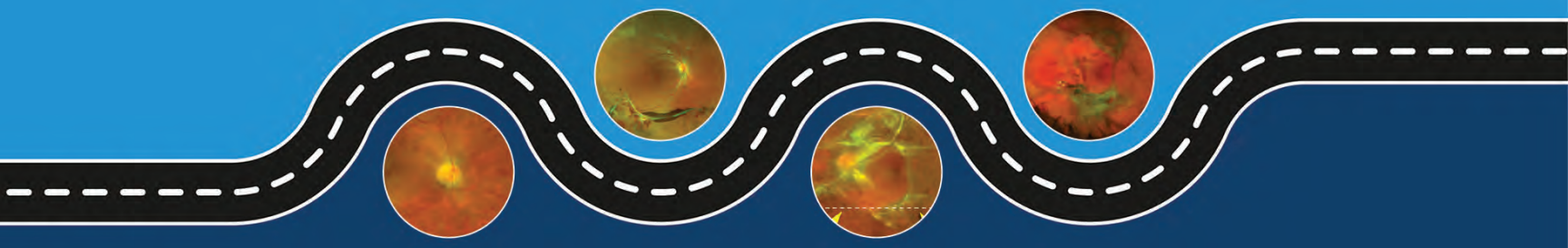

MANAGING DR ONE CASE AT A TIME

The best treatment for each case of diabetic retinopathy requires a close look at the whole picture.

BY MATTHEW R. STARR, MD

The management paradigm for diabetic retinopathy (DR) is very different than it is for other vitreoretinal disorders. For example, patients with rhegmatogenous retinal detachments (RRDs), macular holes, or epiretinal membranes typically require surgery if intervention is warranted. Patients with wet AMD are routinely treated with intravitreal anti-VEGF injections.

Each patient with DR, however, is unique and presents with an equally distinctive challenge in achieving optimal control of the retinopathy. Physicians treating DR have a multitude of treatment strategies to choose from, including intravitreal anti-VEGF injections, steroid injections, laser treatment, or even pars plana vitrectomy (PPV). The choice hinges on specific clinical and imaging parameters.

The management of DR, and diabetic macular edema (DME) in particular, was revolutionized with the advent of intravitreal anti-VEGF agents and steroid injections.[1,2] The Diabetic Retinopathy Clinical Research (DRCR) Retina Network's Protocol S popularized the use of anti-VEGF injections for the management of proliferative diabetic retinopathy (PDR).[3] PPV is often reserved for tractional retinal detachment (TRD) or non-clearing vitreous hemorrhages. However, early vitrectomy is an option for patients with advanced disease or burdening PDR who may be at risk for loss to follow-up and may even provide a lower socioeconomic cost over the life of the patient.[4,5]

In addition to the clinical presentation, many patient-centric factors guide the decision-making process, including socioeconomic status, systemic comorbidities, hemoglobin A1c levels, and type of diabetes, to name a few. The following cases help illustrate the decision-making process when treating patients with DR.

CASE NO. 1

A 56-year-old phakic man presented with moderate nonproliferative DR (NPDR) in each eye and center-involving DME in his left eye (Figure 1). He had been diagnosed with type 2 diabetes 10 years prior, and his most recent hemoglobin A1c was 10.4. He reported blurry vision in his left eye for approximately 6 months.

TREATMENT PEARL:
Given the results of the PANARAMA trial and DRCR Retina Network's Protocol W, it may not be of any visual benefit to treat patients with NPDR with prophylactic intravitreal anti-VEGF injections.[6,7] Of course, as longer data becomes available, that decision may change.

The patient's VA was 20/40 OS, and given the central location of the DME, I elected to treat with monthly injections of intravitreal bevacizumab (Avastin, Genentech/Roche). This may seem like a routine decision, but the patient's entire clinical picture must be evaluated before settling on this approach: his type of diabetes, duration of the disease, most recent hemoglobin A1c, lens status, IOP, duration of symptoms, and any systemic comorbidities.

AT A GLANCE

- Each patient with diabetic retinopathy is unique and presents an equally distinctive challenge in achieving optimal control of the retinopathy.
- Studies suggest that it may not be of any visual benefit to treat patients with nonproliferative diabetic retinopathy with prophylactic intravitreal anti-VEGF injections.
- Eyes with diabetic retinopathy that are lost to follow-up do better when treated with PRP compared with anti-VEGF injections alone.

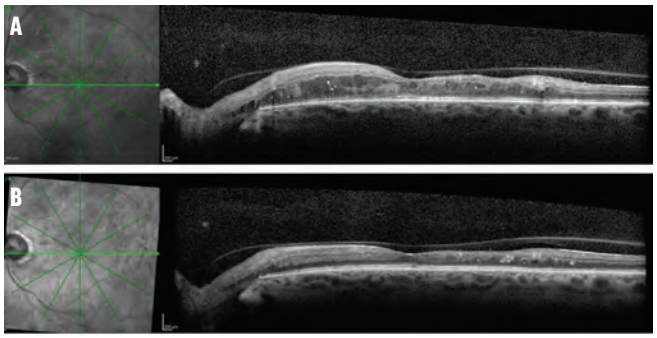

Figure 1. This 56-year-old man with moderate NPDR in each eye and center-involving DME in his left eye (A) did well with intravitreal anti-VEGF injections with resolution of the majority of the DME (B).

TREATMENT PEARLS:

DRCR Retina Network's Protocol V showed that patients with a VA of 20/25 or better had no difference in vision loss at 2 years whether they were initially observed, underwent focal laser therapy, or received prompt intravitreal anti-VEGF injections.[8] DRCR Retina Network's Protocol T found no difference between aflibercept (Eylea, Regeneron), ranibizumab (Lucentis, Genentech/Roche), or bevacizumab, unless the presenting VA was 20/50 or worse—those eyes had better visual acuity gains when initially managed with aflibercept compared with bevacizumab but showed no difference at 2 years when compared with ranibizumab.[9] Additionally, steroids may not be the best initial option for phakic patients with uncontrolled IOP. Lastly, patients with other systemic complications, such as renal disease, may have difficult-to-treat DME, and some diabetic medications such as thiazolidinediones may exacerbate DME.

After 6 months of monthly bevacizumab injections, the patient's VA improved to 20/25 OS, and he continues to receive intravitreal bevacizumab injections.

CASE NO. 2

A 73-year-old pseudophakic woman presented to the clinic with DME in each eye. Her VA was 20/60 OD and 20/50 OS, IOPs were normal, and cup-to-disc ratios were 0.3 OU. Her right eye had massive intraretinal fluid into the fovea that was not responding to monthly aflibercept injections, while the left eye had a small amount of temporal intraretinal fluid that was managed with aflibercept injections every 6 weeks (Figure 2).

Given that the right eye was not improving with anti-VEGF therapy, I trialed intravitreal dexamethasone (Ozurdex, Allergan/Abbvie). Although her IOP, cup-to-disc ratio, and lens status (with intact posterior capsule) made her an ideal steroid candidate, I still had an extensive discussion about the risks of ocular hypertension with intravitreal dexamethasone.

TREATMENT PEARL:

If intravitreal dexamethasone is not a viable option, an injection of shorter-acting triamcinolone is a good alternative.

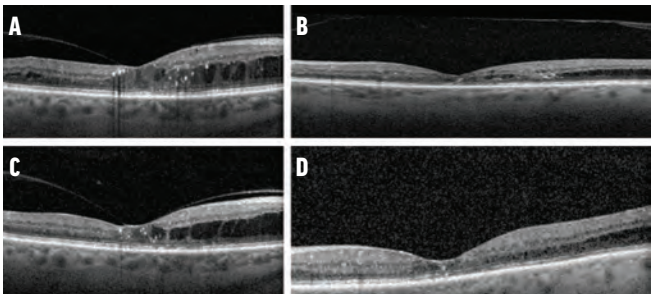

Figure 2. This 73-year-old patient presented with DME in each eye (A, B). The right eye had massive intraretinal fluid in the fovea and nasally (A) that was not responding to anti-VEGF injections; only after intravitreal steroid did she begin to see an improvement in the DME. The left eye had a small amount of temporal intraretinal fluid and underwent focal laser therapy (C) and has not received further treatment for 6 months (D).

If dexamethasone works well, patients also may be candidates for the fluocinolone acetonide intravitreal implant (Iluvien, Alimera Sciences), which can last up to 3 years with few rescue injections needed.

The patient's left eye was doing well and, given that she had a few temporal microaneurysms (MAs), I proceeded with focal laser therapy to the left eye and stopped anti-VEGF injections.

TREATMENT PEARL:

Focal laser therapy is a great choice for patients with parafoveal MAs; make sure to avoid targeting MAs within a disc diameter of the foveal center.

The patient had an excellent response to dexamethasone, and the stubborn intraretinal fluid was finally shrinking with no IOP spike. Further injections of a longer-acting steroid are planned in hopes of continued improvement. The patient's left eye has now gone 6 months without any further treatment following focal laser therapy.

CASE NO. 3

A 63-year-old woman was referred for a DR evaluation. Fluorescein angiography revealed several areas of neovascularization elsewhere (NVE) in each eye (Figure 3), and OCT imaging showed trace DME in each eye. VA was 20/20 OU, so I decided to treat both eyes with panretinal photocoagulation (PRP). This patient has done well for a year now while maintaining a VA of 20/20 with regression of the NVE in each eye.

TREATMENT PEARLS:

Counseling patients on the risks of each option—anti-VEGF or PRP—for PDR is important, as is taking into consideration the patient's systemic comorbidities and ability to follow up. Patients with PDR often miss appointments due to frequent medical appointments (eg, for dialysis) or hospitalization. Studies show that eyes that are lost to follow-up did better when treated with PRP compared with those treated with anti-VEGF injections alone.[10]

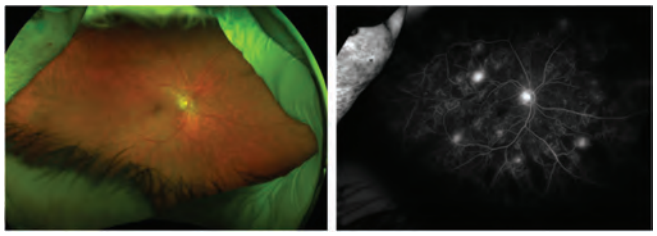

Figure 3. This 63-year-old woman with DR in each eye presented with NVE in each eye and subsequently underwent PRP in each eye, leading to the regression of the NVE.

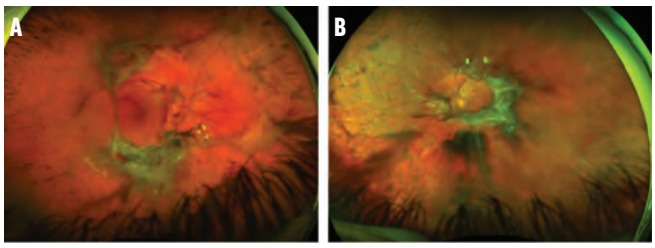

Figure 4. This 27-year-old woman with type 1 diabetes presented with a macula-on temporal and superior TRD with no previous PRP in the right eye (A). The left eye had a table-top macula-off TRD with scant peripheral PRP (B).

CASE NO. 4

A 27-year-old phakic woman with type 1 diabetes and a hemoglobin A1c of 9.4 presented, stating that she had lost vision in her left eye 3 months prior. VA was 20/20 OD and counting fingers OS. The fundus examination revealed a macula-on temporal and superior TRD with no previous PRP in the right eye; in the left eye, there was a table-top macula-off TRD with scant peripheral PRP (Figure 4). I elected to perform PPV in the left eye with intraoperative PRP in the right eye.

The patient received medical clearance from her primary care physician 1 week before surgery, and she received an intravitreal injection of bevacizumab in the left eye 4 days before surgery.

TREATMENT PEARL:

A patient must receive medical clearance before receiving any preoperative intravitreal injection because if the patient receives an injection but does not undergo surgery, they are at an increased risk of further contraction or "crunch" of the fibrovascular membranes, often leading to irreparable damage.

When performing PRP in the patient's right eye, I avoided the areas of detachment to reduce the risk of contracture of the membranes and propagation of a TRD. The left eye underwent careful internal limiting membrane peeling, 360° PRP, and silicone oil. One month after surgery, the subretinal fluid had progressed closer to, but not involving, the fovea in the right eye, and the left eye remained attached. Given that the fovea was still attached 1 month after surgery, I decided to observe the right eye. I did not recommend intravitreal medications due to the risk of crunch, and I needed more follow-up before committing the patient to surgery in the right eye.

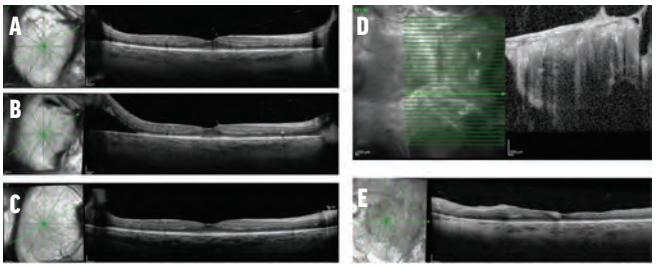

Figure 5. The initial OCT scan of the right eye of the patient in Figure 4 (A) showed minimal subretinal fluid that slightly progressed 1 month after PRP (B), but regressed over time. The subretinal fluid was out of the macula and the patient was stable 8 months after presentation (C). The OCT scan of the left eye at presentation (D) and 8 months later after surgical repair (E). VA in that eye improved from hand motion to 20/70 at the last visit.

One month later, there was no progression of the subretinal fluid in the right eye, and I continued to observe the patient. Eight months after PRP, I noted regression of the TRD in the right eye and a VA of 20/20 (Figure 5). The left eye underwent oil removal 5 months after the initial repair; 3 months after the oil removal, the retina was attached, and VA improved to 20/70 OS.

FINAL THOUGHTS

Each of these patients presented a unique scenario and required a tailored treatment plan. It is imperative that we treat patients with DR using a systematic approach and integrate their medical history into our decision-making process. We have many different tools at our disposal to help us manage patients with DR, and with further advances in retina, surely, new treatment paradigms will arise. ■

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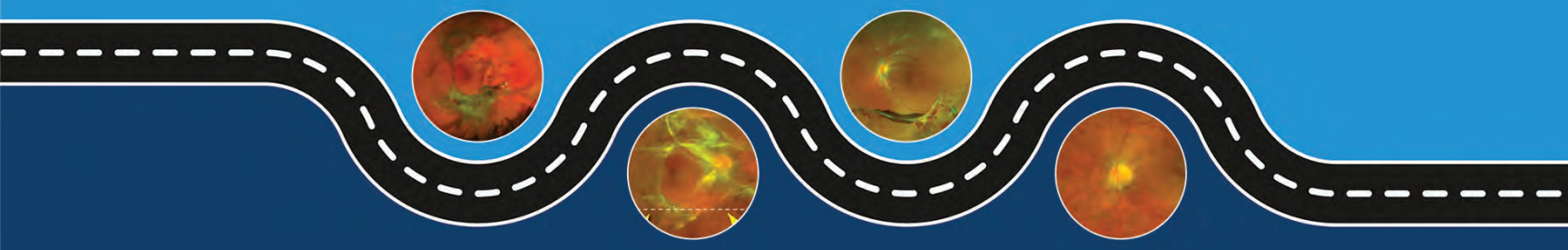

TIPS FOR A SUCCESSFUL DIABETIC TRD SURGERY

Preoperative care, surgical timing, and proper technique are all important considerations when faced with tractional detachments.

BY DAVID XU, MD

The original purpose of vitrectomy was to clear vitreous hemorrhage, most often due to proliferative diabetic retinopathy (PDR). Over the past few decades, improvements in the medical and surgical management of PDR have yielded vastly improved outcomes. Peripheral scatter photocoagulation and anti-VEGF therapy are disease-modifying therapies that alter the course of PDR and avert severe vision-threatening complications. Commensurate with medical management, there has been a dramatic evolution in our surgical instruments and techniques, allowing us to treat hemorrhage and tractional retinal detachment (TRD) more efficiently. After 5 decades of advances in vitreoretinal surgery, TRD remains one of the most significant surgical challenges in our field today.

Fortunately, most diabetic TRDs share phenotypic similarities in their presentation, anatomic relationships, and pathways toward progression. This has allowed us to develop certain approaches when tackling these cases. This article reviews preoperative care and shares the various intraoperative techniques that can help with diabetic TRD repair.

CARE BEFORE AND AFTER

Timing of Surgery

Before entering the OR, preoperative management of an impending TRD is critical. Aggressive prevention of recurrent vitreous hemorrhage is perhaps the most important prophylactic measure. This can be achieved through panretinal photocoagulation (PRP) and anti-VEGF treatment for neovascularization.

It's important to understand the pathogenesis. In the era of anti-VEGF therapy, our ability to regress vitreous hemorrhage has allowed eyes to advance to later stages of PDR without operation. Multiple episodes of recurring and resolving vitreous hemorrhage, a common phenotype in severe diabetic eyes, leads to incipient vitreoretinal traction that characteristically develops in the wake of regressed neovascularization and proliferates along the vascular arcades.

Loss to follow-up after anti-VEGF therapy without PRP can increase the risk of TRD.[1] Patients often have comorbid conditions and are of working age, making a trip to the OR less desirable. Early vitrectomy yielded faster visual recovery and less recurrent hemorrhage in the Diabetic Retinopathy Clinical Research Retina Network's Protocol AB,[2] but this new data may not yet reflect widespread practice. Surgery for TRD carries significant risk, and many surgeons choose surgery only as a last resort. Taken together, PDR/TRD patients may arrive in the OR with advanced and widespread tractional membranes that significantly complicate surgery.

Preoperative Therapies

The benefit of preoperative anti-VEGF therapy for diabetic TRD surgery is well understood.[3] It reduces the risk of

AT A GLANCE

- Aggressive prevention of recurrent vitreous hemorrhage is perhaps the most important prophylactic measure against diabetic tractional retinal detachment (TRD).
- The bulk of TRD surgery consists of removal of fibrosis along the arcades, which frees the macula of traction.
- Surgeons must remove vitreoschisis, as it serves as a nidus for proliferative vitreoretinopathy, leading to postoperative redetachment and epiretinal membrane.

CLINICIANS SHOULD BE CAREFUL TO REMOVE THE HYALOID IN ITS ENTIRETY BECAUSE ANY RESIDUAL HYALOID MAY LEAD TO PERSISTENT ANTERIOR TRACTION.

intraoperative hemorrhage and begins to regress neovascularization within the first 24 hours after injection. However, I prefer to give an injection approximately 1 to 2 weeks in advance of surgery, which allows more time for complete regression of neovascularization and improves vitreous/preretinal hemorrhage. In eyes with severe or impending TRD, many physicians opt to avoid anti-VEGF injections due to the concern for the contracture of membranes that leads to macular detachment, the so-called "crunch" effect. However, the overall risk of crunch is low, and eyes with advanced proliferative disease may benefit more from anti-VEGF therapy than without. In most eyes, the risk of progression of the traction is low and the benefit of injections is high.

PRP is also very helpful to ensure successful TRD surgery. Peripheral laser therapy limits the extent of posterior pole detachment and removes the periphery from the equation when operating on these eyes. When there is no PRP, TRD can extend far into the periphery, where dissection of the hyaloid membrane from a detached retina is at highest risk for iatrogenic breaks. Also, PRP helps tack the retina down and serves as counter traction when peeling membranes.

SURGICAL TECHNIQUES

Vitreoretinal surgeons generally agree on the overall approach when it comes to the intraoperative management of TRDs, although individual preferences and techniques vary. The primary pathologic entity in PDR is the hyaloid. Neovascular blood vessels grow into and along the posterior surface of the hyaloid membrane, eventually maturing into fibrotic tractional membranes. Thus, removal of the hyaloid and associated membranes is necessary for any diabetic case. Most tractional membranes exist along the vascular arcades and encircle the macula.

The goal of TRD surgery is twofold: 1) relieve the encircling traction from the arcades to the macula, and 2) relieve the traction from the arcades to the ora serrata. The latter is typically done first with peripheral segmentation of the posterior hyaloid membrane and removal of the cortical vitreous gel. This frees the membranes of their anterior attachment. Although some diabetic eyes already have peripheral hyaloid separation, eyes that do not have separation pose significant challenges for peripheral dissection. Clinicians should be careful to remove the hyaloid in its entirety because any residual hyaloid may lead to persistent anterior traction, which can cause recurrent hemorrhages and induce retinal breaks at the edge of fibrovascular pegs. Prior PRP increases the chance for hyaloid separation because it keeps the peripheral retina attached while gently regressing neovascularization, resulting in contracture and elevation of the peripheral hyaloid.

The bulk of TRD surgery consists of removing fibrosis along the arcades, which frees the macula of traction. I prefer to start dissection at the optic nerve and work using an inside-out approach. At the optic nerve, fibrotic tissue can be engaged with forceps and peeled without concern for retinal traction. This elevates membranes along the natural plane along the arcades, opening additional avenues for dissection.

The endpoint of membrane dissection is typically sufficient relief of the traction to flatten the macula. Dissection techniques fall into two broad categories: segmentation and delamination. Segmentation, or sharp dissection, can be accomplished with the vitreous cutter or intraocular scissors and works best on dense, encircling fibrous membranes. Delamination, or blunt dissection, involves peeling to separate membranes from the retina and can be accomplished with forceps, membrane scrapers, picks, and similar tools. Typically, surgeons use delamination for thinner membranes and to elevate the peripheral hyaloid.

SURGICAL TIPS AND TRICKS

In complex diabetic TRD cases, I typically use a hybrid 25-/27-gauge vitrectomy system, starting with the 25-gauge vitrector and light source for efficient removal of the cortical vitreous and hyaloid. The 25-gauge light source affords wider illumination than its 27-gauge counterpart. Additionally, 25-gauge forceps and accessory instruments are stiffer and easier to work with.

I switch to a 27-gauge vitrector for membrane dissection. Modern 27-gauge cutters with optimized mouth-to-tip distance have tangibly improved diabetic TRD dissection, allowing safe and efficient membrane segmentation. In fact, I find that unimanual dissection with the cutter alone is sufficient for most diabetic cases, although bimanual surgery and chandelier illumination is required in some cases.

The plane of dissection is always the preretinal and subfibrous membrane space. Respecting this plane and selecting instruments to best achieve safe dissection is paramount to avoid iatrogenic breaks. Fortunately, most diabetic membranes are not tightly and contiguously attached to the retina. Instead, they have strong focal attachments with

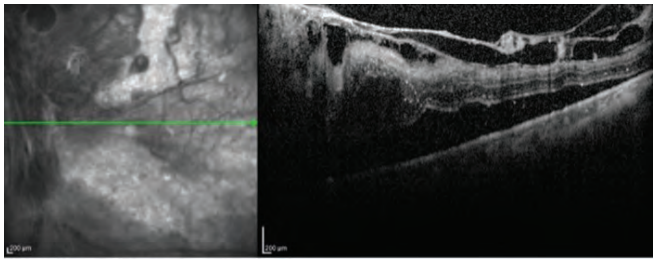

Figure 1. OCT reveals a preretinal fibrovascular membrane with focal attachments and intervening clear spaces. The clear spaces provide opportunities to propagate dissection.

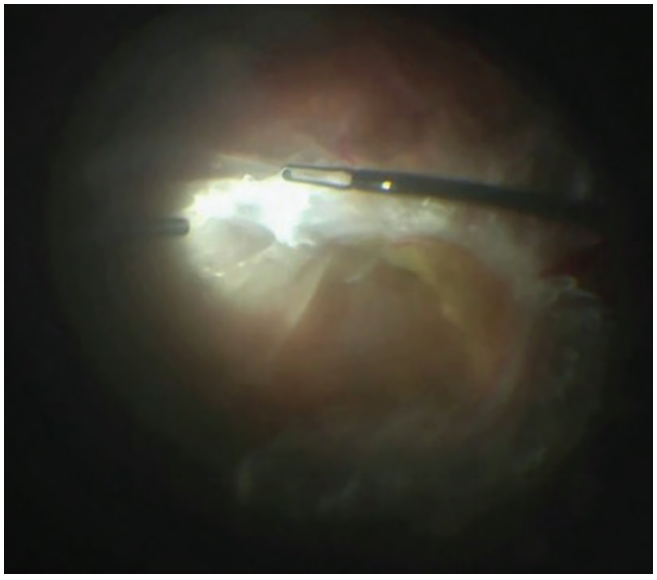

Figure 2. Preretinal membranes can be gently retracted to inspect for the open area. Dynamic manipulation of membranes can be very helpful to interrogate unique vitreoretinal relationships unique to the TRD and allow safer dissection.

intervening clear areas (Figure 1). These areas can be identified and exploited to efficiently segment and remove even broad areas of fibrosis. Before segmentation, I like to use forceps to dynamically examine the membranes. By gently lifting and reflecting over the edges, I can examine the underside of membranes and identify accessible areas to advance the dissection (Figure 2).

Research shows that internal limiting membrane (ILM) peeling in TRD repair can be an effective approach to prevent epiretinal membrane (ERM) and restore retinal elasticity to aid in resolution of persistent submacular fluid.[4,5] In rhegmatogenous retinal detachment (RRD) repair, ILM peeling yields better postoperative visual acuity due to the prevention of ERM.[6,7] Likewise, ILM peeling is an integral part of macular hole repair, where removal of this inelastic layer relieves tangential traction and adds retinal elasticity, allowing for mobilization of perifoveal retinal tissue. In TRDs, I perform ILM peeling for preexisting ERM and severe retinal folds, and when preexisting retinal breaks are present, such as with combined TRD/RRD. Breaks complicating TRD/RRD are usually found in the near periphery underneath tractional membranes and can be associated with particularly thick epiretinal fibrous proliferation. I peel ILM in these cases with special emphasis on extending the peel to encompass the hole. I find this allows the retina to better settle in these regions, improving retinal pigment epithelium adhesion and allowing laser treatment to effectively seal breaks.

Vitreoschisis is present in more than 80% of diabetic eyes and manifests as remnant layers of hyaloid adherent to the retinal surface after complete vitrectomy.[8] Often, surgeons mistake the presence of a posterior vitreous detachment with complete vitreous removal, but this is not true, as these eyes frequently harbor vitreoschisis. Surgeons must remove this layer, as it serves as a nidus for proliferative vitreoretinopathy, leading to postoperative redetachment and ERM. A distinguishing hallmark of vitreoschisis is its presence in both the macula and periphery. The layer can be visualized by triamcinolone staining. I assess for vitreoschisis in every diabetic case, generally instilling triamcinolone after membrane dissection. Vitreoschisis removal is generally straightforward. The membrane can be removed by elevating an edge using a Finesse Flex Loop (Alcon) and aspirating using the vitreous cutter.

FINAL THOUGHTS

Diabetic TRD surgery remains a significant challenge for vitreoretinal surgeons, but advances in techniques and instrumentation have turned the vast majority of cases into solvable problems. Surgical maneuvers should be driven by an understanding of the underlying pathophysiology of fibrovascular proliferation and its interaction with the posterior hyaloid. A wide array of techniques can help surgeons satisfactorily complete TRD repair based on their preference and the severity of the disease. Ultimately, it is up to the surgeon to decide how best to manage the unique nuances of each eye. ■

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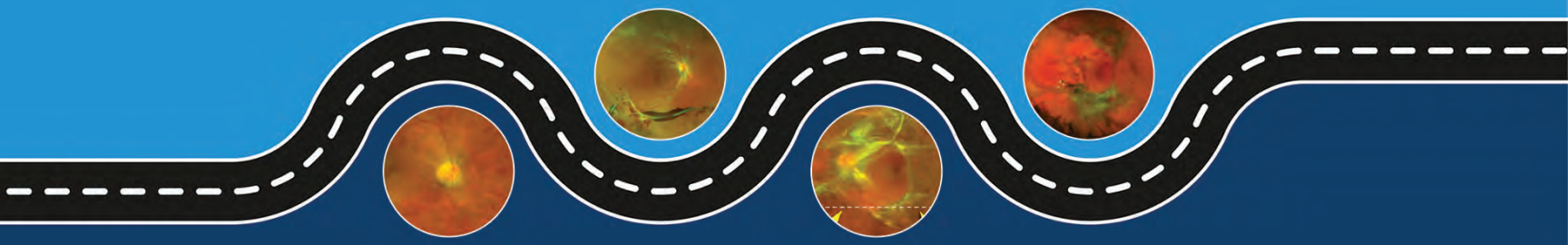
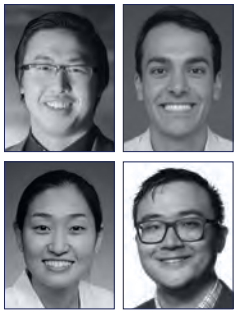


THE PATH TO VALIDATING AI SCREENING SYSTEMS

A close look at seven systems for diabetic retinopathy screening reveals significant performance differences.

BY RANDY Y. LU; ANAND RAJESH; CECILIA S. LEE, MD, MS; AND AARON Y. LEE, MD, MSCI



Artificial intelligence (AI) screening algorithms are a promising solution to the growing global diabetic retinopathy (DR) screening burden. Many AI algorithms have been shown to perform at or above the level of human experts on DR classification tasks when evaluated on their internal datasets.[1-4] However, these algorithms may underperform on larger, external validation datasets due to a lack of generalizability, overfitting, or underspecificity.[5-7]

Discrepancies between internal and external validation performance can be concerning, given that many of these algorithms are already commercially available; two algorithms (IDx-DR [Digital Diagnostics] and EyeArt [Eyenuk]) have FDA approval.[3,8]

Here, we share our findings after validating seven commercially available DR screening algorithms on a large-scale dataset collected from two Veterans Affairs (VA) hospitals.

HEAD-TO-HEAD VALIDATION

Our multicenter, noninterventional, head-to-head device validation study included seven commercially available AI-based DR screening algorithms from five participating companies.[9] The validation dataset consisted of 311,604 fundus photographs from 23,724 veterans from the Seattle VA Puget Sound Health Care System (HCS) and the Atlanta VA HCS. In addition, a randomly sampled subset of 7,379 images were regraded using double-masked arbitration.

Non-referable DR was defined as no DR (International Clinical Diabetic Retinopathy Severity Scale [ICDR] of 0), and referable DR was defined as the presence of any DR (ICDR 1-4) by the VA standard.[9]

The results showed substantial differences in overall performance between the algorithms. Using the original VA teleretinal grades as the reference standard, algorithm sensitivity ranged from 50.98% to 85.90%, specificity from 60.42% to 83.69%, negative predictive value from 82.72% to 93.69%, and positive predictive value from 36.46% to 50.80%. Overall, the algorithms achieved higher negative predictive values using the Atlanta data set (90.71% to 98.05%) compared with the Seattle data set (77.57% to 90.66%). In contrast, the positive predictive values ranged from 24.80% to 39.07% in the Atlanta data set, which was lower than the Seattle data set (42.04% to 62.92%).[9]

When the arbitrated grades from the 7,379 regraded images were used as the new reference standard, most algorithms performed worse in terms of both sensitivity and specificity compared with the VA teleretinal graders. While the VA teleretinal graders achieved an overall

AT A GLANCE

- Discrepancies between internal and external validation performance of diabetic retinopathy screening algorithms can be concerning.
- In the author's validation study of seven commercially available diabetic retinopathy screening algorithms, sensitivity ranged from 50.98% to 85.90% and specificity ranged from 60.42% to 83.69%.
- The goal of further study is to ensure that automated screening algorithms can maintain adequate performance standards regardless of variables such as race, image quality, and coexisting disease.

sensitivity of 82.22% and specificity of 84.36%, only one algorithm approached a similar level of performance in both sensitivity (80.47%) and specificity (81.28%). Two algorithms achieved higher sensitivities than the VA teleretinal graders (92.71% and 92.71%) but were also statistically less specific. Only one algorithm achieved higher specificity (90.00%), at the cost of a statistically lower sensitivity than the VA teleretinal graders.[9]

REFERRABLE THRESHOLDS

When we performed a sensitivity analysis for different thresholds of disease severity, we found that, although most algorithms had higher sensitivities when the threshold was raised to moderate DR or worse, none of the algorithms were better than human graders in identifying referable disease when analyzed by DR severity. When the referrable threshold was raised to severe DR or worse, the sensitivity of one algorithm only reached 74.42%. Thus, regional- and site-specific differences in the thresholds for referrable DR may be an important factor that can affect downstream model performance.[9]

OTHER VALIDATION WORKS

In a separate validation study, Tufail et al assessed the performance of three DR screening algorithms using 102,856 images from 20,258 patients.[6] The authors found that two algorithms achieved acceptable sensitivity for referable retinopathy (85% and 94%); however, both algorithms had low specificity, contributing to false positive rates of 47.7% and 80%, respectively. The third algorithm also classified all episodes as diseased or ungradable, resulting in a 100% sensitivity rate but also a 100% false positive rate.

Meanwhile, smaller studies validating individual DR screening algorithms have reported stronger results, with one study reporting a sensitivity of 100% and specificity of 82% when validated on 2,680 patients undergoing DR screening in Valencia, Spain.[10]

Another DR screening algorithm that was validated on 4,504 fundus images from five urban centers in Zambia showed clinically acceptable performance in detecting referable DR with sensitivity and specificity of 92.25% and 89.04%, respectively.[11] Still, single-algorithm studies are difficult to interpret, and multi-algorithm studies are better for direct head-to-head comparison of different algorithms.

CLINICAL IMPLICATIONS

The performance of many AI-based DR screening algorithms may differ significantly when being evaluated using large-scale external validation datasets. The discrepancy in performance highlights the issue of algorithm generalizability, or how well a model performs for all subsets of unseen data. Generalizability concerns often arise when the training and validation datasets are sufficiently different, which can be attributed to variations in image collection protocols, image quality, device manufacturers, or demographic factors.

Our study demonstrated site-specific differences in algorithm performance, and we hypothesized that differences in imaging protocols, disease prevalence, and patient demographics may be notable contributing factors.[9]

As more automated screening algorithms are introduced, they should be validated on datasets that are representative of the population in which they are deployed. While our study was strengthened by the head-to-head comparison and a large real-world dataset, the VA population may not reflect the general population.

Furthermore, a meta-analysis found that many AI-based DR screening algorithms often used the same datasets for training and external validation.[12-16] While these datasets are typically graded by trained ophthalmologists, many exclude ungradable images, are limited in size, lack extensive demographic information, and may not capture the full underlying distribution of disease.[5,12,17,18] This highlights the importance of conducting additional validation in diverse populations, as well as the need for prospective, interventional trials after clinical integration and regulatory approval. The goal is to ensure that automated screening algorithms can maintain adequate performance standards regardless of variables such as race, image quality, and coexisting disease.

HURDLES TO OVERCOME

Automated DR screening systems have shown potential in helping to alleviate the DR screening burden. However, many challenges still exist, and we must exercise caution when interpreting the performance of an algorithm that is trained and validated solely on internally curated datasets.

Large-scale external validation studies, although challenging to conduct, serve as the best indicators for an algorithm's true performance. Future work should aim to develop automated AI-based screening algorithms that are flexible, efficient, and able to demonstrate robust performance on the populations in which they are deployed. ■

CAN'T-MISS DISCLAIMER

Although automated diabetic retinopathy (DR) screening systems can greatly expand access, they do not replace routine eye examinations. Current commercial DR screening systems are approved only to diagnose referrable DR using specific devices and protocols. Sole reliance on automated screening systems may miss additional important features, such as undiagnosed glaucoma, macular degeneration, retinal detachments, or choroidal melanomas. DR screening systems should supplement traditional eye examinations to expand screening access, while also upholding a high standard of care.

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Less frequent treatments that still provide long-lasting benefit is the Holy Grail of attenuating the risk of LTFU.

Dr. Talcott: I'm excited about the new wave of diabetes medications that are easier for patients to use, and I've seen patients achieve better control of their diabetes, which then helps slow or prevent DR progression. In addition, I practice in an academic center with a plethora of resources, but I wonder if having social workers associated with our ophthalmology department could help with these issues as well.

Dr. Khurana: We know that diabetes is a challenging disease. These patients are under a lot of stress, and it's not easy to make all the visits. We are cognizant of that, but we must think about how to leverage technology and various tools to better educate and empower patients to follow-up. I also agree with Dr. Hsu that extended-duration therapies can minimize the treatment burden, which may help with LTFU.

Empowering our patients through better education of their disease process is crucial, and thinking outside the box on how to engage and motivate patients will help minimize LTFU in the future. Our field should look towards other specialties that manage chronic diseases with more providers to ensure our patients follow up for their sight-saving care. ■

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CYSTOID MACULAR EDEMA WITH AN ONCOLOGY TWIST

Watch out for this condition in patients taking certain types of chemotherapy agents.

BY REHAN M. HUSSAIN, MD, AND BILAL SHAUKAT, MD

A 61-year-old White man presented with complaints of blurry vision in both eyes with gradual onset over approximately 1 month. He was referred to the retina service after a cataract evaluation, during which his cataracts were deemed not visually significant. His medical history was notable for stage 4 pancreatic cancer, insulin-dependent diabetes, hypertension, and heart valve disease.

BCVA on initial presentation was 20/150 OD and 20/80 OS. Pupils, motility, confrontational fields, and IOP were within normal limits. Examination of the posterior segment revealed blunted foveal light reflex in each eye, but was otherwise unremarkable, without evidence of diabetic retinopathy (Figure 1). OCT showed severe cystoid macular edema (CME) in each eye (Figure 2). Fluorescein angiography did not reveal any evidence of leakage or neovascularization in either eye (Figure 3).

Differential Diagnosis

The differential diagnosis for CME without leakage includes nicotinic acid maculopathy, Goldmann-Favre syndrome, X-linked retinoschisis, retinitis pigmentosa, and toxicity from antimicrotubule (ie, taxane) chemotherapy agents. This patient was undergoing chemotherapy with paclitaxel (Abraxane, Bristol Myers Squibb), a microtubule inhibitor that is used to treat malignancies such as breast and pancreatic cancer, which was determined to be the cause of the CME.

Management and Clinical Course

After communicating with the patient's oncologist, paclitaxel was discontinued; he remained on his other chemotherapy agent, gemcitabine. The referring ophthalmologist had prescribed prednisolone acetate and ketorolac drops for several weeks prior to his appointment with the retina service. While OCT showed modest improvement after starting the drops, this change coincided with discontinuation of paclitaxel, so it is unclear how much each intervention affected the CME. Dorzolamide drops were also prescribed.

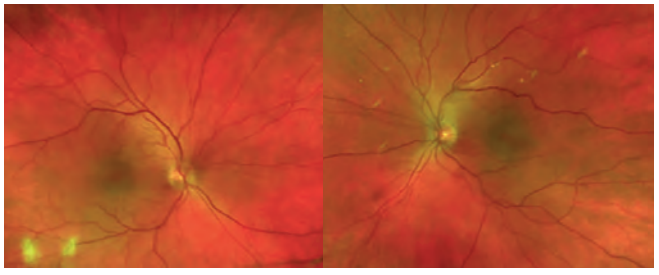

Figure 1. Fundus imaging did not demonstrate any evidence of diabetic retinopathy or other vascular abnormality. The white spots represent artifact from the camera.

One month later, the CME had nearly resolved in each eye. VA improved substantially to 20/80 OD and 20/60 OS (Figure 4). He was gradually tapered off all drops without any recurrence of CME for the next 5 months of follow-up. About 6 months after his initial presentation, the paclitaxel was restarted by his oncologist at half of the original dose due to poor control of his pancreatic cancer. Dorzolamide drops were resumed as prophylaxis, and there was no return of CME over the next 3 months of follow-up. On his final visit, VA was 20/40 OD and 20/30 OS. The patient passed away in September 2021.

PATHOPHYSIOLOGY

Ophthalmological side effects of taxane agents, such as paclitaxel, have been reported in 10% of patients using this medication; a decrease in visual acuity occurs in 4%.[1] Taxanes disrupt the microtubule network within cells that is essential for mitosis, ultimately resulting in cell death. While the pathophysiology of taxane-associated CME is not completely understood, it has been proposed that toxicity of Müller cells, which play a role in dehydrating the macula by metabolic pumps, leads to the accumulation of fluid.[2]

TREATMENT

There are no recommended treatment guidelines for this condition because of the unclear pathology; however, there is often resolution of CME and improvement in visual acuity after discontinuation of the causative agent.[3] The decision

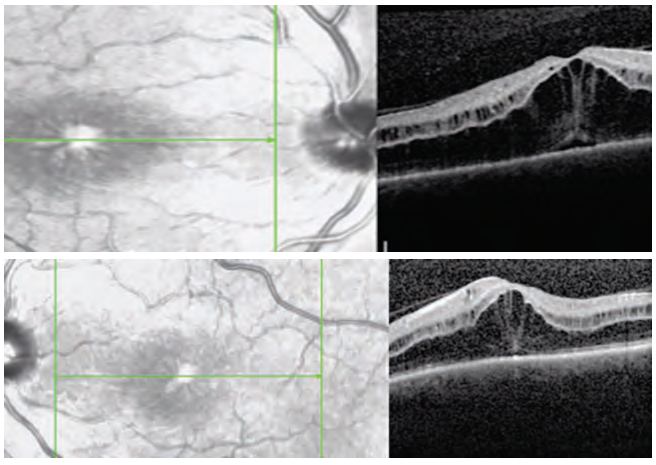

Figure 2. OCT shows severe bilateral CME with mild subretinal fluid.

to stop a chemotherapy agent must be weighed carefully in collaboration with the patient and their oncologist, including discussion of the potential effect on the patient's prognosis and quality of life.

Taxane-associated CME has not been shown to respond well to monthly bevacizumab (Avastin, Genentech/Roche) injections, suggesting that VEGF does not play a role in the pathogenesis.[2] Corticosteroids are a common approach to treating CME of various etiologies. In one case report, sub-Tenon triamcinolone injection had minimal effect on CME, while cessation of a taxane agent was required for complete resolution.[4] In another study, a dexamethasone intravitreal implant (Ozurdex, Allergan/AbbVie) resulted in improvement of CME after 1 month while the patient continued taking the taxane agent, but CME did not completely resolve until 2 months after cessation of the agent.[5] Thus, it is possible that ocular corticosteroids could have an adjuvant role in treating CME in these patients, especially if cessation of the taxane agent is not feasible; however, they are unlikely to result in complete resolution of taxane-associated CME.

Carbonic anhydrase inhibitors have been shown to be effective in treating CME associated with retinitis pigmentosa and have also been used for taxane-associated CME.[6,7] One case report showed that dorzolamide drops helped to resolve CME after inadequate response to cessation of paclitaxel alone.[8] Oral methazolamide was reported to prevent progression of CME and severe vision loss in the case of a Korean patient who continued paclitaxel therapy in spite of maculopathy, although the methazolamide did not completely resolve the CME.[9] In another case report, oral acetazolamide was shown to induce rapid improvement of visual acuity and complete regression of CME after 8 weeks, despite continued chemotherapy.[10]

In our case, the patient was treated with prednisolone, ketorolac, and dorzolamide drops, but because the improvement coincided with the cessation of the paclitaxel, we cannot determine whether there was any benefit from

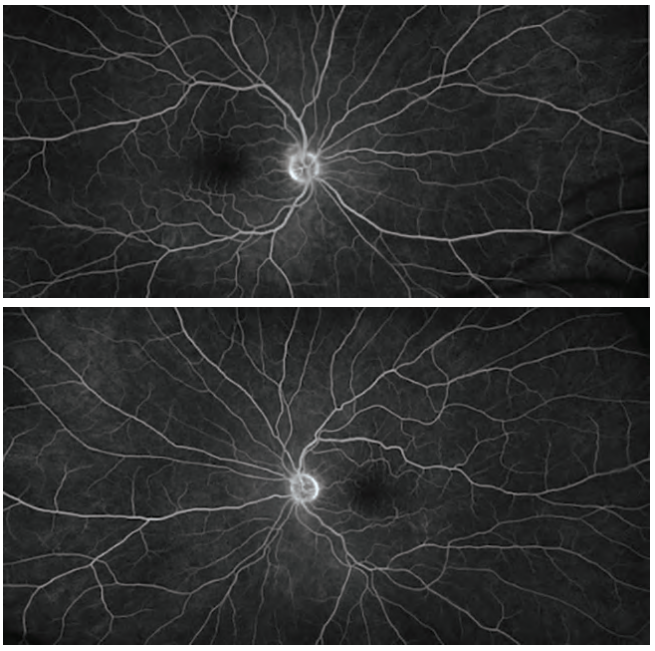

Figure 3. Fluorescein angiography did not show evidence of vascular leakage or neovascularization in either eye.

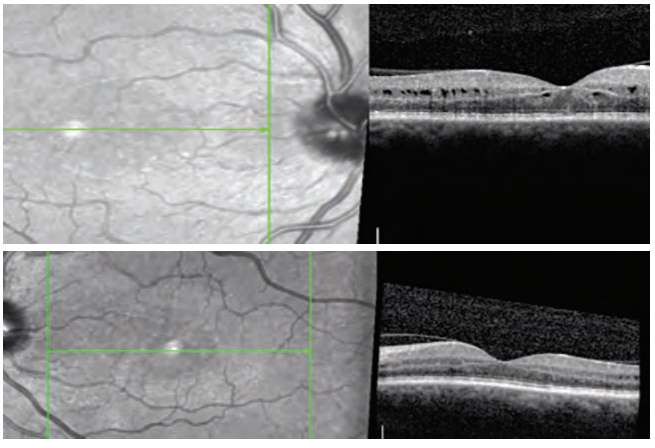

Figure 4. One month after cessation of paclitaxel, there was almost complete resolution of the CME.

these topical therapies. There is no clinical trial that compares cessation of the taxane alone versus cessation of the taxane combined with carbonic anhydrase inhibitors or antiinflammatory medication. It is also unclear whether prophylactic dorzolamide drops helped to prevent recurrence of CME in this patient when he resumed paclitaxel at half dose in the last few months of his life.

CLINCAL IMPLICATIONS

Patients receiving chemotherapy with microtubule-inhibiting taxane agents are susceptible to developing a form of angiographically silent CME. While the mechanism is not completely understood, Müller cell toxicity may play a role. CME typically resolves with cessation of the taxane agent, a

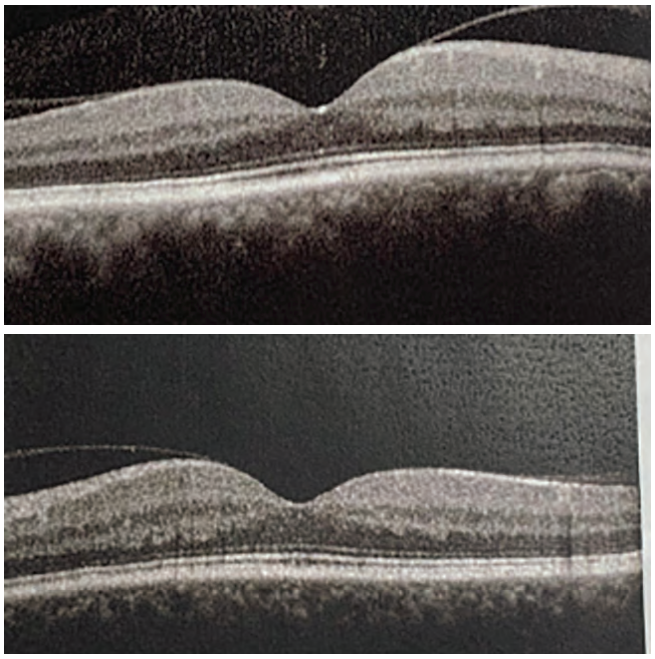

Figure 5. Two months after resuming paclitaxel, there was no return of CME in either eye while the patient used prophylactic dorzolamide drops TID.

decision that must be discussed with the patient and their oncologist. Several case reports support the use of oral or topical carbonic anhydrase inhibitors (and perhaps ocular corticosteroids to a lesser degree) as adjuvant treatment options if a patient must continue with taxane chemotherapy agents, but further research on these treatment approaches is warranted. ■

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congestion and macular edema for a few weeks after anti-VEGF injections to treat an exophytic JRCH, suggesting that more frequent or higher dosing of anti-VEGF agents may be adequate to control exudation.[5]

CLINICAL PEARLS

Because of its association with VHL, the diagnosis of a JRCH should prompt a careful fundus examination for additional RCHs, which would be consistent with VHL.

Ultra-widefield FA can sometimes identify ophthalmoscopically invisible RCHs elsewhere in the fundus. More than one RCH confirms a diagnosis of VHL. Patients with solitary RCH lesions may benefit from systemic evaluation, imaging for tumors in other organs, and genetic testing for the VHL gene. ■

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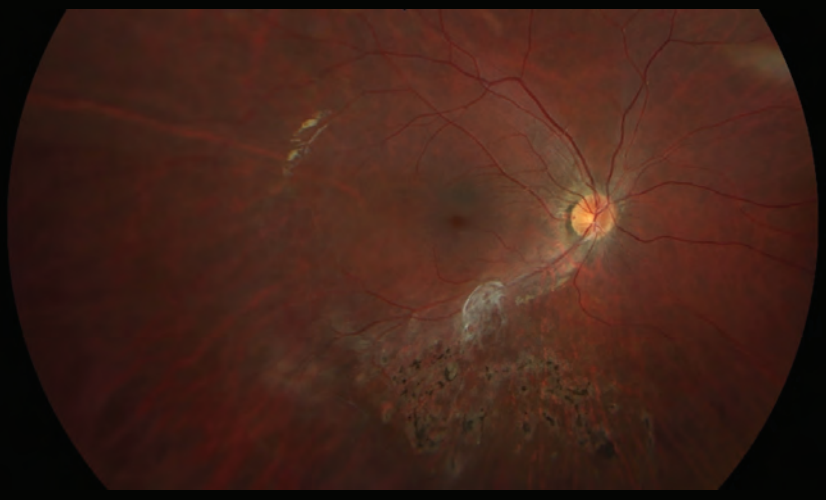
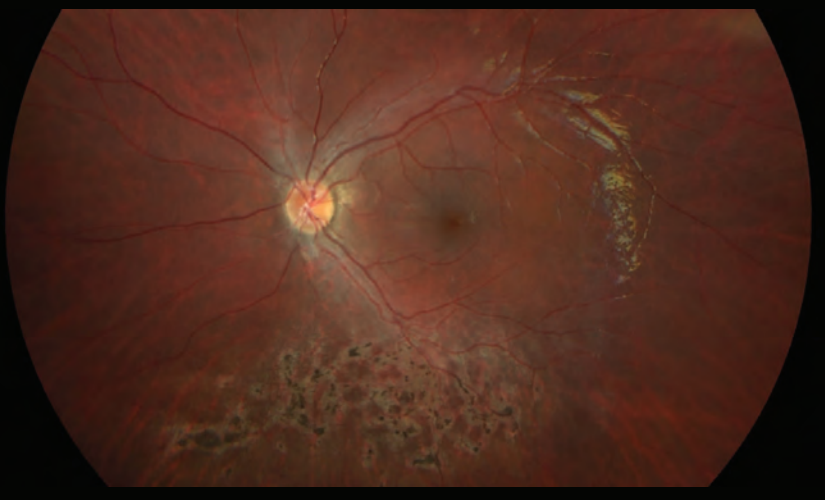




AN UNUSUAL CASE OF PIGMENTARY RETINOPATHY

A constellation of clinical findings, paired with genetic testing, reveals the true diagnosis.

BY MARIA PAULA FERNANDEZ, MD; CARLOS ERNESTO MENDOZA SANTIESTEBAN, MD; MUSTAFA TEKIN, MD; AND AUDINA M. BERROCAL, MD

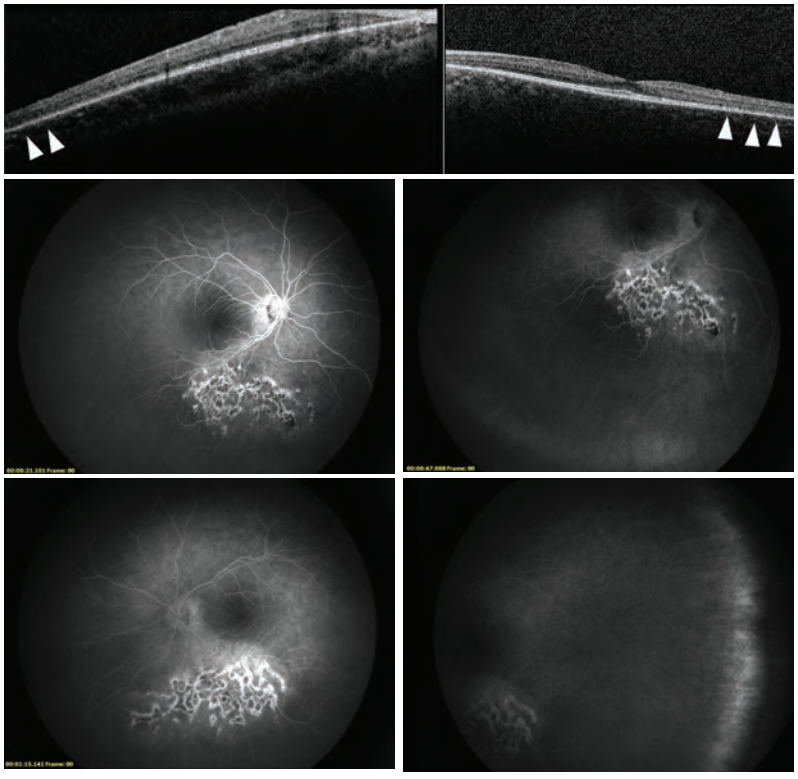
THE CASE

A 5-year-old boy was referred to a pediatric ophthalmologist for an evaluation after failing a vision screening test. The patient was noted to have bilateral pigmentary lesions in the retina, as well as hyperopia and astigmatism. The patient's mother reported that he had been complaining of problems with night vision and light sensitivity. The patient was born at 38 weeks with a birth weight of 6 lbs, 6 oz, and he had pedal and testicular edema that resolved at 6 months of age. He was diagnosed with microcephaly and mild cognitive delay. The patient had no significant family medical history, and his two biological sisters were healthy.

On initial examination, his BCVA was 20/30 OD and 20/40 OS. The anterior segment examination was unremarkable in each eye. The posterior segment was remarkable for an area of preretinal fibrosis along the inferior arcade in the right eye and symmetric extramacular pigmentary changes located at the inferior retina in each eye (Main Figure). During an examination under anesthesia, A- and B-scan demonstrated the axial length to be 23.9 mm in the right eye and 22.5 mm in the left eye.

OCT showed marked thinning of the retina, especially the outer layers, correlating with areas of abnormal pigmentation (Figure, next page). Fluorescein angiography showed staining of the chorioretinal lesions in each eye, as well as peripheral nonperfusion, mostly temporally (Figure, next page). An electroretinogram showed significant rod and cone dysfunction, which was suggestive of a recessive cone-rod dystrophy or retinitis pigmentosa (RP)–related retinopathy. Initial genetic testing obtained elsewhere was negative for RP, fragile X syndrome, and other genetic conditions.

At 7 years of age, the patient was referred for in-house genetic counseling. Given the presence of microbrachycephaly, upward-slanting palpebral fissures, upturned and rounded nasal tip, low hair line, hyperpigmented skin patches, past history of pedal edema, and the presence of pigmentary changes in the retina, the patient matched the phenotype for microcephaly with or without



chorioretinopathy, lymphedema, or intellectual disability (MCLID). Genetic testing was positive for the associated *KIF11* gene mutation, confirming the diagnosis. This mutation was not found in parental samples, confirming a de novo mutation. After 7 years of observation, the patient's retinal findings have remained stable.

DISCUSSION

MCLID was first described by Tenconi et al in 1991 as an autosomal dominant condition.[1] A mutation in the *KIF11* gene is causative in approximately 75% of MCLID cases. The *KIF11* gene encodes the EG5 homotetrameric protein, which participates in microtubule sliding, mitotic spindle assembly, and chromosome segregation.[2] More recently, this protein has been localized to the photoreceptors, which are considered modified cilia.[3] As such, these findings suggest *KIF11* mutations may be a part of the group of other ciliopathies, such as Bardet Biedl syndrome, Joubert syndrome, Alstrom syndrome, and other pigmentary retinopathies.

This condition is characterized by the presence of microcephaly, developmental delay with intellectual disability, lymphedema of the dorsa of the feet, and a characteristic facial phenotype with upward-slanting palpebral fissures, broad nose with rounded tip, long philtrum with thin upper lip, and prominent ears.[4,5] The associated chorioretinopathy occurs in approximately 60% of mutation-positive individuals and is characterized by chorioretinal atrophy with vessel attenuation and pigment clumping located outside of the arcades, sparing the macula.[6] Other ocular manifestations include hyperopia, astigmatism, and generalized rod and cone dysfunction on electroretinogram.[6] According to previous reports, the fundus lesions appear to be nonprogressive with variable expressivity and intrafamilial variability.

In addition, a phenotypic overlap has been found between MCLID and familial exudative vitreoretinopathy,[7-9] which may explain the peripheral nonperfusion of the retina found in this patient.

This case highlights the importance of considering *KIF11* mutations and MCLID in the screening of patients who present with retinal dystrophies and peripheral nonperfusion, because other syndromic manifestations, such as the presence of microcephaly, may be subtle. ■

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COATS DISEASE: WHAT'S NEW?

Recent findings may affect your treatment and management of this melanoma masquerader.

BY ORIANA D'ANNA MARDERO, MD; SANIKA UDYAVER, MD; AND CAROL L. SHIELDS, MD

Coats disease is an idiopathic, nonhereditary retinal vascular disorder manifesting with telangiectasia, exudation, retinal detachment (RD), and potential risk for neovascular glaucoma and phthisis bulbi. It typically presents in children (mean age of onset is 5 years), more often in boys (> 75% of cases), and can lead to blindness.[1-3] Although historically considered a unilateral disease, a 2019 report on 175 patients with Coats disease altered our understanding of the condition, revealing that asymptomatic retinal vascular abnormalities occurred in the fellow eyes of 19% of patients, including telangiectasia, aneurysms, segmental nonperfusion, leakage, and vascular tortuosity.[4] So, what else is new? Herein, we discuss a case of Coats disease and explore newly published findings on this condition.

CASE REPORT

A 14-year-old male patient noted blurred vision in his left eye for more than 3 weeks. He was found to have macular exudation and referred to our ocular oncology clinic for evaluation.

On examination, VA was 20/20 OD and 20/200 OS. The right eye was normal. The left eye had a normal anterior segment and IOP; fundus evaluation showed prominent macular and circumpapillary exudation and shallow subretinal fluid (SRF). Peripheral retinal evaluation disclosed a localized inferotemporal region of intense retinal telangiectasia and light-bulb micro- and macroaneurysms, surrounded by exudative RD. OCT documented macular detachment, intraretinal and subretinal exudation, and cystoid macular edema, further confirmed on ultrasonography demonstrating a shallow RD. Fluorescein angiography (FA) revealed extensive telangiectasia and aneurysms along the entire temporal periphery and concentrated inferotemporally, all with peripheral nonperfusion, consistent with Coats disease (Figure 1).

Treatment included laser photocoagulation for the less dense telangiectasia and cryotherapy for the denser macroaneurysms and retinal vascular abnormalities. Sub-Tenon corticosteroid injection of 10 mg (0.25 cc) was delivered to reduce inflammation. At 2 months, additional laser photocoagulation was provided to leaking telangiectasia. At 4 months, VA had improved to 20/40 OS, and the macular SRF, edema, and exudation had resolved, leaving a flat retina with minimal exudation (Figure 2).

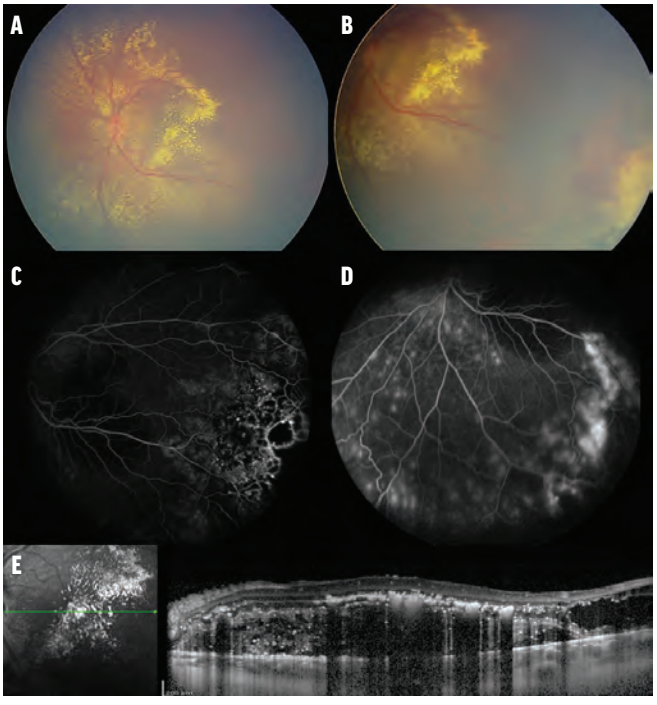

Figure 1. Coats disease at presentation (A). A 14-year old male patient with Coats disease in the left eye and VA of 20/200 presented with subretinal exudation in the posterior segment of the eye, including the macula (B). A region of intense retinal telangiectasia, light-bulb aneurysms, and nonperfusion was noted in the inferotemporal periphery (C), confirmed on FA (D) with leakage in later frames. OCT demonstrated subretinal and intraretinal fluid and exudation in the macula (E).

DISCUSSION

There have been several changes in the diagnostic and therapeutic approaches since Coats disease was first described in 1908.[5] In 2001, Shields et al classified Coats disease into five stages based on clinical features in 150 consecutive cases, ranging from asymptomatic retinal telangiectasia (stage 1), to telangiectasia with exudation (stage 2: 2A without macular involvement and 2B with macular involvement), exudative RD (stage 3: 3A1 with subtotal exudative RD sparing the fovea, 3A2 extending to the fovea, and 3B with total exudative RD), total RD with secondary glaucoma (stage 4), and end-stage disease with phthisis bulbi (stage 5).[2]

In that analysis, treatment options varied, with observation or laser photocoagulation for stage 1, laser

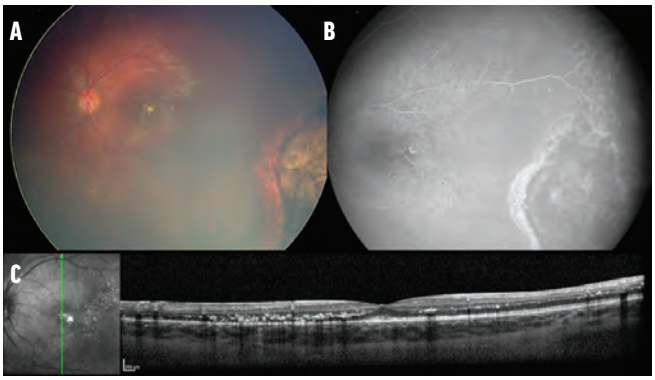

Figure 2. Coats disease after treatment (A). Six months after treatment with cryotherapy and argon laser photocoagulation, there was remarkable improvement of subretinal exudation, leaving a flat retina, minimal residual exudation, and a chorioretinal scar in the inferotemporal periphery (B). This was confirmed by FA and OCT (C), which documented resolution of macular edema and residual intraretinal exudation. VA returned to 20/40.

photocoagulation or cryotherapy for stages 2-3A, cryotherapy for stage 3B with shallow RD, and surgical repair for stage 3B with bullous RD.[2,3,5] Some cases of stage 4 disease with ocular pain required enucleation, and stage 5 cases usually required only observation.[2,3,5] Visual outcomes also varied, with poor VA (20/200 or worse) in 0% of eyes with stage 1, 30% with stage 2A, 86% with stage 2B, 70% with stage 3A1 or 3A2, 94% with stage 3B, and 100% with stage 4 or 5.[2]

What About the Fellow Eye?

Although Coats disease has been considered a unilateral disease, vascular changes with uncertain clinical significance have been documented by FA in the fellow eye. Jeng-Miller et al recently studied 350 eyes of 175 patients and found that 19% had peripheral fellow eye abnormalities, consisting of telangiectasias (42%), aneurysms (55%), segmental nonperfusion (18%), leakage (18%), and diffuse vessel tortuosity (6%).[4] These abnormalities were asymptomatic, remained unchanged during a mean follow-up of 25 months, and did not impact visual acuity. These authors questioned that Coats disease might represent a bilateral condition with asymmetric severity.[4]

What About Age of Onset?

Dalvin et al investigated the clinical features and outcomes of Coats disease by age and categorized patients as infant/toddler (≤ 3 years), child (> 3 to 10 years), or adolescent/adult (> 10 years). Comparison by age group revealed that the infant/toddler age group had worse presenting visual acuity; more anterior segment findings of xanthocoria, strabismus, and iris neovascularization (NVI); and more advanced disease stage.[6] The youngest patients also had worse final visual acuity, experienced less complete disease resolution, and were more likely to be treated with primary enucleation.[6]

Daruich et al studied 98 patients in 2018 and confirmed more severe disease with younger age of diagnosis, as well as more evident leukocoria and strabismus; greater clock hour extent of peripheral retinal nonperfusion and telangiectasia; more foveal involvement; greater requirement for enucleation; and poorer final visual acuity.[7]

ANY TRENDS OVER THE PAST 50 YEARS?

Shields et al evaluated 351 cases of Coats disease over 45 years and classified the disease per decade from the 1970s to the 2010s. They found significantly more advanced Coats disease in the 1980s, including greater mean clock hours of exudation, as well as greater prevalence of four quadrants of exudation, four quadrants of SRF, and total exudative RD.[5] They also found that treatment strategies have changed, with greater use of laser photocoagulation, sub-Tenon corticosteroid injection, and intravitreal anti-VEGF therapy in the 2010s, with less need for primary enucleation.[5]

Does the Amount of SRF Matter?

Failed resolution of SRF after treatment is considered to be a predictor of poor visual outcomes (< 20/200).[2] Khoo et al studied 177 patients with RD in Coats disease and found that factors predictive of SRF resolution included absence of NVI on FA and less SRF elevation by ultrasonography.[8] With each 1-mm decrease in SRF, the likelihood of SRF resolution increased by 16%.[8]

What's the Risk for Enucleation?

When conservative therapies fail, patients with Coats disease can develop secondary glaucoma or pthisis bulbi and may require enucleation of the affected eye. Udyaver et al studied 259 eyes with Coats disease and found that predictors of enucleation included presence of NVI, ultrasonographic RD, open funnel RD, closed funnel RD, increasing ultrasonographic elevation of SRF by millimeters, and increasing angiographic extent of light-bulb aneurysms.[9] Each 1-mm increase in SRF on ultrasonography increased the risk for enucleation by 20%, and each additional clock hour of light-bulb aneurysms by angiography increased the risk by 35%.[9]

Can We Predict Visual Outcomes?

In 2001, Shields et al found the most important predictive factors for poor visual outcome (< 20/200) included non-White race, diffuse disease, postequatorial and superior locations of telangiectasia and exudation, unresolved exudation after treatment, and the presence of retinal macrocysts.[2]

In 2019, Shields et al studied visual acuity outcomes in 160 patients with Coats disease who underwent Snellen visual acuity measurements before and after treatment. Using the stage at diagnosis, they found that advanced stage was associated with worse presenting VA (< 20/200; $P < .001$) and greater number of clock hours of telangiectasia, light-bulb aneurysms, exudation, and SRF.[10] Patients with more advanced disease stage at diagnosis were also more likely

to be treated with primary enucleation ($P < .001$) and had worse final VA (< 20/200; $P < .001$), typically from macular scar or persistent RD.[10]

CLINICAL TAKEAWAYS

The recent literature shows that Coats disease may be a bilateral condition with asymmetric involvement, and that younger age at presentation correlates with worse prognosis. Over the past 50 years, disease severity at presentation and diagnostic and therapeutic approaches have changed. Some presenting features can be predictive of SRF fluid resolution and risk for enucleation and can be used for prognosis. ■

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VABYSMO™
faricimab-svoa injection 6 mg

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

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

1 INDICATIONS AND USAGE

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

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

1.2 Diabetic Macular Edema (DME)

4 CONTRAINDICATIONS

4.1 Ocular or Periocular Infections

VABYSMO is contraindicated in patients with ocular or periocular infections.

4.2 Active Intraocular Inflammation

VABYSMO is contraindicated in patients with active intraocular inflammation.

4.3 Hypersensitivity

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

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis and Retinal Detachments

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

5.2 Increase in Intraocular Pressure

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

5.3 Thromboembolic Events

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

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

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

6 ADVERSE REACTIONS

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

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

6.1 Clinical Trial Experience

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

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

Table 1: Common Adverse Reactions (≥ 1%)

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

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

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

6.2 Immunogenicity

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

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

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

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

Data

Animal Data

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

8.2 Lactation

Risk Summary

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

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

8.3 Females and Males of Reproductive Potential

Contraception

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

Infertility

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

8.4 Pediatric Use

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

8.5 Geriatric Use

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

17 PATIENT COUNSELING INFORMATION

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

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

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INDICATIONS

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

IMPORTANT SAFETY INFORMATION

Contraindications

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

Warnings and Precautions

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

Adverse Reactions

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

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

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

*Dosing Information:

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

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

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

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

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

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