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eyetube

DIABETIC EYE DISEASE

Techniques, therapies, and tools to help you stop the clock on complications

TREATING DIABETIC RETINOPATHY: ANTI-VEGF VS PRP

PROTOCOL W: A SUMMARY OF 2-YEAR RESULTS

SUSTAINED-RELEASE STEROID OPTIONS FOR DME THERAPY

RETINA SPECIALISTS—

YOUR FIGHT AGAINST UVEITIS* DEMANDS OZURDEX®

(dexamethasone intravitreal implant)

*Noninfectious posterior segment uveitis.

HELP REDUCE VITREOUS HAZE

- **Achieved statistically significant reduction in vitreous haze vs sham at week 8 after a single injection**[1]
- **Suppresses inflammation by inhibiting multiple inflammatory cytokines**[1]

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.

IMPORTANT SAFETY INFORMATION (continued)
Contraindications (continued)
Glaucoma: OZURDEX® (dexamethasone intravitreal implant) 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.

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.

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.

Reference: 1. OZURDEX® Prescribing Information.

Ozurdex®
(dexamethasone intravitreal implant) 0.7 mg

Allergan
an AbbVie company

Ozurdex.com OZU148536 07/21 015041

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.

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 *[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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Apellis is exploring the role of complement in Geographic Atrophy[1]

C3 is the linchpin of complement overactivation in GA.[2-7]

All three complement pathways converge at C3 and it drives multiple downstream effects — inflammation, opsonization, and formation of the membrane attack complex — all of which can ultimately lead to retinal cell death. Increased levels of complement activity have been found not just in the lesion itself, but also in the area just outside the lesion, known as the pre-lesion.[2-9]

Scan the code to explore new territory with us at pre-lesion.com

Apellis

1. Katschke KJ Jr, et al. *Sci Rep*. 2018;8(1):13055. 2. Mastellos DC, et al. *Trends Immunol*. 2017;38(6):383-394. 3. Ricklin D, et al. *Immunol Rev*. 2016;274(1):33-58. 4. Heesterbeek TJ, et al. *Opthalmol Vis Sci*. 2020;61(3):18. 5. Seddon JM, et al. *Nat Genet*. 2013;45:1266-1370. 6. Yates JRW, et al. *N Engl J Med*. 2007;357(6):553-561. 7. Smailhodzic D, et al. *Ophthalmology*. 2012;119(2):339-346. 8. Boyer DS, et al. *Retina*. 2017;37:819-835. 9. Park DH, et al. *Front Immunol*. 2019;10:1007.

IF YOU'RE NOT EARLY, YOU'RE LATE


Diabetes has been labeled an epidemic for 15 years—*at least*—and its ocular complications are simply unavoidable in a retina practice. If left unchecked, diabetic retinopathy (DR) can cause catastrophic vision loss.[1] Despite a robust armamentarium of treatment options, DR remains the No. 1 cause of blindness in working-age adults in industrialized countries.[2]

Making matters worse, the demographics of this systemic disease are shifting. Historically, patients with type 2 diabetes were in their 40s; now, more and more of these patients are in their 20s and 30s.[3] Some are even in adolescence.[4] This poses a whole new set of problems because young eyes behave differently from aging eyes. For example, young eyes with signs of DR usually present with an attached hyaloid—and "the hyaloid is the enemy," as María H. Berrocal, MD, reminds us in this issue. In her experience, she tells us, the status of the hyaloid to some degree dictates a patient's risk for progression and complicates the treatment options.

Of course, diabetic eye disease is something we *should* be able to prevent with the therapies and surgical techniques at our disposal. Unfortunately, myriad factors interfere with a timely diagnosis, and even when they are diagnosed, patients with this chronic disease are notoriously lost to follow-up. Remember those young patients with diabetes? They are often reluctant to take time off from work and family to traipse into a specialist's office just to hear, "Everything looks good, see you next year!" That is, until we catch something, and by then it's often too late—the damage is done.

So researchers and clinicians continue to explore novel approaches to both the diagnosis and management of diabetic eye disease with a focus on early intervention and long-term stability.

In this issue of *Retina Today*, we look at some promising tools to help identify the first signs of retinopathy, including remote screening using deep-learning algorithms and ultra-widefield imaging to assess the retinal periphery.

When it comes to treatment, we have a lot to consider. Safer techniques and 27-gauge tools have made early vitrectomy an important consideration worth investigating in a randomized surgical trial. Intravitreal anti-VEGF injections have become a mainstay of treatment, and researchers are even exploring the potential impact of prophylactic anti-VEGF injections. The 2-year results of the DRCR Retina Network's Protocol W study suggest some benefit of preventive treatment, and we are all eager to see the 4-year results.

Regardless of how you choose to integrate these advances into your clinical care routines, one thing is certain: When it comes to caring for patients with diabetes, earlier is better. The sooner we identify changes, the sooner we can intervene—one way or another—and preserve vision. ■


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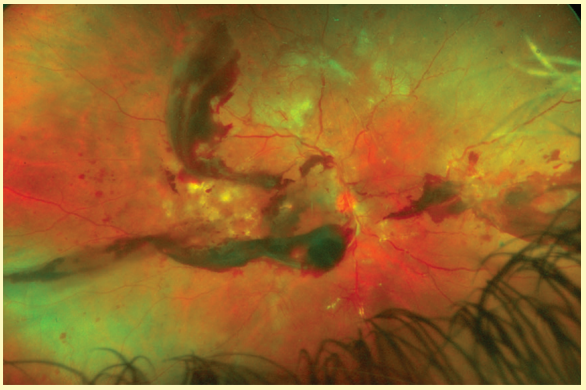
ON THE COVER:



María H. Berrocal, MD, author of "The Benefits of Early Surgical Intervention For Diabetic Retinopathy," saw this 37-year-old patient with type 1 diabetes who presented with vitreous hemorrhage. Although he was scheduled for vitrectomy, he missed his appointment due to the COVID-19 pandemic. Turn to page 25 to see what this eye looked like when he returned 8 weeks later.

1. Bassett MT. Diabetes is epidemic. *Am J Public Health*. 2005;95(9):1496.
2. Guariguata L, Whiting DR, Hambleton I, et al. Global estimates of diabetes prevalence for 2013 and projections for 2035. *Diabetes Res Clin Pract*. 2014;103(2):137-149.
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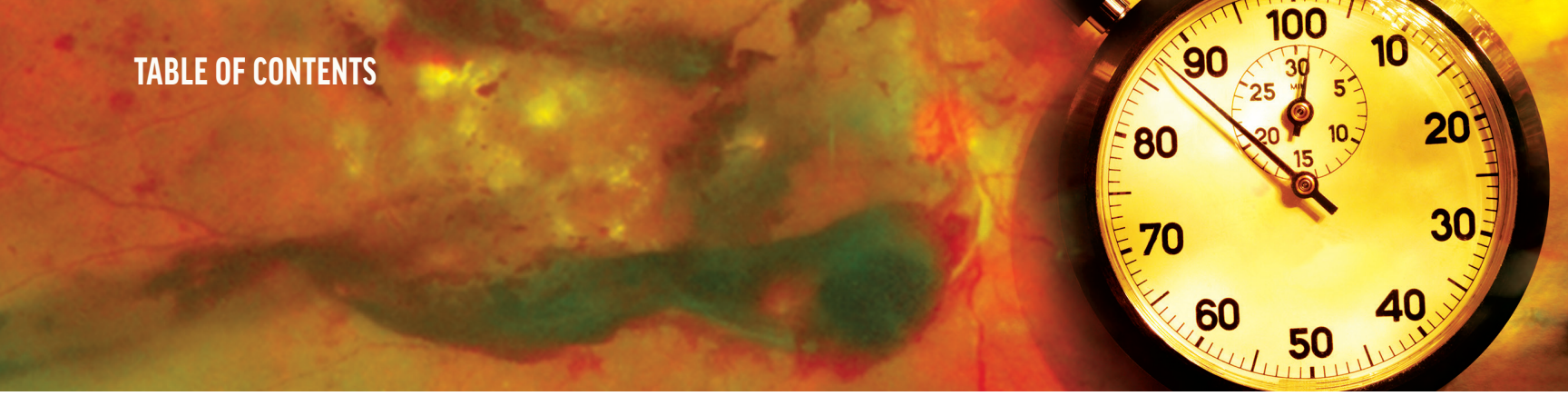

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DEPARTMENTS

RT NEWS

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LARGE STUDY EXPANDS CLINICAL SPECTRUM OF PENTOSAN POLYSULFATE MACULOPATHY

A large multicenter retrospective study documented novel imaging findings in patients prescribed pentosan polysulfate sodium (PPS; Elmiron, Janssen Pharmaceuticals), revealing the potential for uncommon presentations of PPS maculopathy.[1] In addition to confirming the characteristic findings of PPS maculopathy in most patients reviewed, the study also identified unusual presentations, including highly asymmetric disease and a vitelliform maculopathy.

Pigmentary maculopathy associated with long-term use of PPS, the only FDA-approved drug to treat bladder discomfort due to interstitial cystitis, was initially described in 2018 (Figure). The condition was listed as a potential adverse reaction in the drug's package insert as of 2020, but few studies have sought to characterize PPS maculopathy across a broad range of patients. In this study, members of the Macula Society submitted cases of apparent PPS maculopathy to be considered for inclusion, with a total of 18 US practices represented.

"We're still learning about the spectrum of manifestations of this newly described condition," David Zacks, MD, PhD, one of the study's authors, told *Retina Today*. "We felt this was a great opportunity to leverage the vast clinical expertise of the Macula Society to gain insight into this condition."

Of 105 submitted cases, 74 met inclusion criteria for the study. Median daily PPS dose was 300 mg, median cumulative PPS dose was 1.5 kg, and median cumulative exposure per unit body mass was 25.7 g/kg.

The median time of exposure to PPS was 14 years, but the study found that symptoms can appear earlier. "In most cases, patients present with characteristic fundus imaging findings after long-term use of PPS," Nieraj Jain, MD, the study's first author, explained in an email to *Retina Today*. "However, one patient in the series developed maculopathy after just 3 years on the drug."

RESULTS AND IMPACT

The most common symptom was blurry or decreased vision (66.2%), followed by prolonged dark adaption or nyctalopia (32.4%). Some patients experienced both decreased vision and nyctalopia (14.9%), and three patients (4.1%) reported no visual symptoms.

Findings on fundus imaging were consistent with prior PPS maculopathy studies for most study participants; however, unique findings were observed in a subset of patients. Asymmetry of disease was noted in two patients and prominent vitelliform maculopathy in two patients (three eyes total). Subtle alterations on near infrared reflectance imaging were observed in one patient, but without any observed abnormalities in fundus photography, fundus autofluorescence (FAF), or OCT imaging.

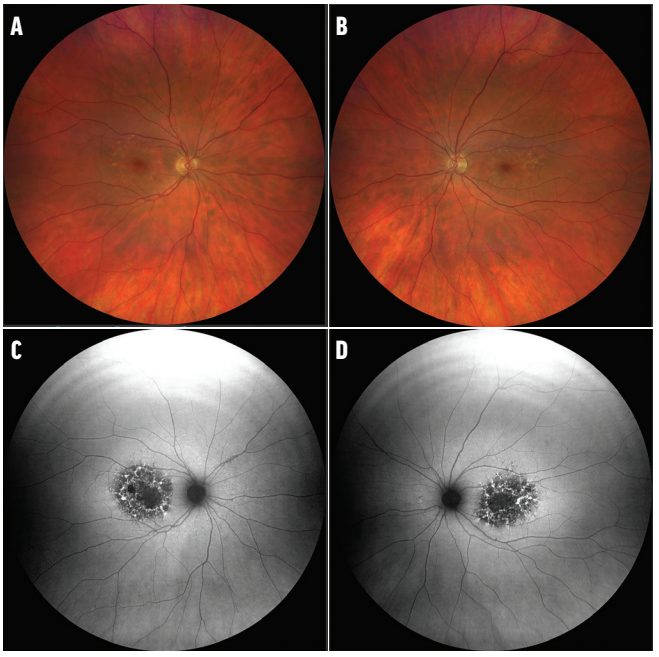

Photo courtesy of Ella H. Leung, MD

Figure. Fundus photos of the right (A) and left (B) eyes reveal maculopathy in a patient who had been taking PPS. FAF imaging shows damage to the right (C) and left (D) macula more clearly.

Annual screening of patients taking PPS may help with early disease detection, the study concluded. "We suggest considering yearly screening examinations with fundus autofluorescence, OCT, and near infrared reflectance imaging where available," Dr. Jain said. "To date, there is no consensus on screening guidelines, so our study helps start this conversation and provides a reference for what clinicians may expect to see in patients with PPS maculopathy."

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OPHTHALMIC BEVACIZUMAB MET KEY ENDPOINTS IN PHASE 3 TRIAL IN WET AMD

An ophthalmic formulation of bevacizumab (Lytenava, Outlook Therapeutics) met primary and secondary endpoints in the phase 3 NORSE TWO clinical trial in patients with wet AMD, according to an August press release from the manufacturer. Among patients who received bevacizumab-vikg, 41% gained 15 or more letters of BCVA at 11 months compared with 23% for the comparator drug. The formulation for intravitreal injection was well-tolerated, the company stated.

The data from this trial will be combined with safety and efficacy results from two other completed trials, NORSE ONE and NORSE THREE, also evaluating the ophthalmic formulation of bevacizumab, to support the company's biologics license application submission to the FDA, which Outlook anticipates filing in 2022. If bevacizumab-vikg is approved, the company expects to receive 12 years of marketing exclusivity for the only ophthalmic formulation of bevacizumab approved by the FDA to treat a retinal disease.

The NORSE TWO trial compared bevacizumab-vikg, dosed monthly, to ranibizumab (Lucentis, Genentech), which was dosed according to the PIER regimen listed in that drug's label (monthly doses for the first 3 months followed by less frequent dosing). For the secondary endpoint of mean change in BCVA through 11 months, bevacizumab-vikg also demonstrated a statistically significant benefit, with a mean change of 11.2 letters compared with 5.8 letters for ranibizumab.

NORSE ONE was a proof-of-concept trial in wet AMD patients. NORSE THREE was a supplemental safety trial in patients with AMD and other retinal diseases. All three trials are now complete, according to Outlook.

GENENTECH SUBMITS DATA ON FARICIMAB TO FDA

Based on data from four phase 3 clinical trials, the FDA accepted a biologics license application for faricimab (Genentech) for the treatment of wet AMD and diabetic macular edema (DME) in July, according to a press release from the company. Under its priority review program, the FDA is expected to act on the application within 6 months.

The TENAYA and LUCERNE trials evaluated faricimab in patients with wet AMD; the YOSEMITE and RHINE trials evaluated the drug in patients with DME. All four trials were randomized, multicenter, double-masked, and global with three treatment arms: faricimab 6.0 mg administered at personalized treatment intervals of up to 4 months; faricimab 6.0 mg administered at 2-month intervals; and aflibercept 2.0 mg (Eylea, Regeneron), the active comparator drug, administered at 2-month intervals. Sham injections were administered during study visits when treatment injections were not scheduled to mask participants and researchers. Each trial met its primary endpoint of visual acuity gains comparable to aflibercept.

If approved, faricimab would be the first bispecific antibody designed for the eye, according to the press release. Two additional trials are under way to evaluate the long-term safety and efficacy of faricimab: AVONELLE X (an extension of TENAYA and LUCERNE) and RHONE X (an extension of YOSEMITE and RHINE). The COMINO and BALATON trials, evaluating faricimab for macular edema secondary to central and branch retinal vein occlusion, are also ongoing.

RISUTEGANIB IMPROVED BCVA IN PHASE 2A TRIAL IN DRY AMD

Intravitreal injections of risuteganib (Luminate, Allegro Ophthalmics) resulted in significant improvement of BCVA in patients with dry AMD in a phase 2a clinical trial, according to a recent publication.[1]

For the trial's primary endpoint—the proportion of participants with ≥ 8 letters of BCVA gain from baseline—48% of patients in the risuteganib group met that goal compared with 7% of patients in the sham group. No drug-related serious adverse events were reported.

In the trial, participants were randomly assigned to intravitreal risuteganib 1.0 mg or sham injection. At week 16, those in the risuteganib group received a second dose, and the sham group was crossed over to receive one dose of risuteganib 1.0 mg. The primary endpoint was evaluated at week 12 for the sham group and week 28 for the risuteganib group. Observation was continued every 4 weeks until completion of the study at 32 weeks.

Among those receiving risuteganib, 20% gained 15 letters or more of BCVA at week 28, whereas no patients in the sham group achieved this gain at week 12.

"These clinical data suggest that risuteganib can reverse vision loss and restore functional vision in patients with intermediate dry AMD with treatment at a 12-week interval," the company said in an August press release describing the study results.

Risuteganib is a small peptide oxidative stress stabilizer that has been shown to protect human retinal pigment epithelium cells against oxidative stress–associated cellular dysfunction, according to the company.

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METHOTREXATE RECEIVED TWO ORPHAN DRUG DESIGNATIONS

Methotrexate for intravitreal injection (ADX-2191, Aldeyra Therapeutics) received orphan drug designation from the

FDA for the treatment of two ocular conditions, retinitis pigmentosa (RP) and primary vitreoretinal lymphoma (PVRL), according to separate press releases from the company. The drug had previously been granted both orphan and fast-track status from the FDA for the prevention of proliferative vitreoretinopathy. Fast-tracked drugs receive expedited review by the FDA and must have potential to fill a serious unmet medical need, among other requirements.

PVRL is a rare and aggressive intraocular cancer. RP is the most common inherited retinal disease. With the orphan drug designations, Aldeyra can receive financial incentives for supporting the development of methotrexate injection as a treatment for these rare diseases. Incentives may include tax credits, fee waivers, and marketing exclusivity up to 7 years with application approval.

Methotrexate is a chemotherapeutic and immunosuppressive agent used in the treatment of some cancers, rheumatoid arthritis, and other autoimmune conditions. Aldeyra is developing the drug for ophthalmic uses.

LIGHT THERAPY IMPROVED FUNCTIONAL VISION IN DRY AMD PILOT STUDY

Functional vision improvements were seen in patients with dry AMD in a pilot study of photobiomodulation (PBM) laser therapy using the Valeda Light Delivery System (LumiThera), according to a July press release from the company.

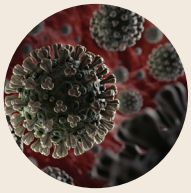
Fifteen patients (23 eyes total) were enrolled in the ELECTROLIGHT study and received PBM treatments three times a week for 3 weeks. They were tested for visual improvement at weekly intervals for 6 months after treatment using an electroretinogram (ERG). The mean age of participants was 75.1 years, and mean time since dry AMD diagnosis was 5 years.

Multiluminance ERG magnitude area under the curve indicated improvement by 14.1% after completion of treatment and by 9% after 6 months. Positive correlations between multiluminance ERG and BCVA were reported following treatment ($P < .05$). Fixed luminance (R = .870) and chromatic ERG outcomes (R = .676) were also positively correlated with multiluminance ERG at 1 month.

Compared with baseline scores, participants experienced a mean 2.8-letter improvement in BCVA and improvements in Mars contrast sensitivity scores at 40 cm, 80 cm, and 20 cm after 6 months.

The results of this pilot study validate findings from the LIGHTSITE I and II studies, the company stated in a press release. Those studies found that PBM therapy using the Valeda Light Delivery System was safe and led to sustained visual benefits in patients with dry AMD, who currently have limited treatment options. ■

CLICKWORTHY NEWS



COVID LONG-HAULERS MAY HAVE BLOOD CLOTTING ISSUES

Researchers at the RCSI University of Medicine and Health Sciences in Dublin are one step closer to understanding why some patients experience long-term effects of COVID. According to a new study, people with higher blood clotting markers were more likely to have long-lasting COVID symptoms than those with normal levels.

bit.ly/COVIDLONG

SCIENTISTS REVERSE MEMORY LOSS IN MICE

Using a viral vector, researchers at the University of Cambridge and University of Leeds manipulated the chondroitin sulphate composition of the perineuronal nets in mice to alleviate age-related memory deficits. The 20-month-old mice injected with 6-sulphate chondroitin sulphates experienced restored memory similar to the memory of 6-month-old mice.

bit.ly/MEMORYMICE

REMEMBER EBOLA? WE HAVE A VACCINE FOR THAT

COVID isn't the only viral threat out there, especially in Guinea and neighboring African countries. A 4-month outbreak of Ebola swept Guinea earlier this year, and the World Health Organization has been supporting neighboring countries to prepare for other outbreaks, including distribution of a vaccine to high-risk populations and health care workers.

bit.ly/EBOLANOW

30-MINUTE WORKOUT BOOSTS MOOD IN PATIENTS WITH DEPRESSION

Patients living with depression should consider a quick exercise routine in their afternoons, according to a small study. Researchers in Switzerland found that 30 minutes of moderate exercise late in the day was associated with improved mood without negatively impacting sleep.

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CLINICAL UTILITY OF OCT ANGIOGRAPHY FOR RETINAL AND CHOROIDAL VASCULAR DISEASES

In Part 2 of this two-part series, the authors continue to explore the pluses and minuses of OCTA.

BY KOOSHA RAMEZANI, MD; HAGAR KHALID, MD; LUÍSA S.M. MENDONÇA, MD; AND NADIA K. WAHEED, MD, MPH

In Part 1 of this two-part series, we summarized the clinical utility of OCT angiography (OCTA) in exudative and nonexudative AMD. In this report, we examine the usefulness of OCTA for other retinal and choroidal vascular diseases.

DIABETIC RETINOPATHY

OCTA can play a significant role in diagnosis and monitoring of diabetic retinopathy (DR; Figure 1). It can visualize microaneurysms and show reduced macular vessel density where detailed fundus examination fails to detect any signs of DR.[1] Nevertheless, only about half of the microaneurysms seen on fluorescein angiography (FA) are detected by OCTA, perhaps because of the limited ability of the latter modality to detect slow flow.[2]

FA, because of light scattering and limitations inherent to the technology, is unable to capture changes in the deep capillary plexus where some of the earliest changes of DR may occur.[3] The depth resolution of OCTA, however, enables visualization of the capillary plexus. Additionally, OCTA can detect nonperfused areas and enlargement of the foveal avascular zone (FAZ; Figure 2).[4]

OCTA may also be useful for precisely detecting retinal neovascularization (NV) without obscuring the margins by leakage, as occurs with FA. The area of NV can be monitored as it changes in size after laser treatment or anti-VEGF therapy.[3] However, the smaller field of view on OCTA compared with FA may limit its ability to investigate peripheral NV or nonperfusion in DR. To address this limitation, it is possible to create widefield images by montaging multiple images.[3] Some high-speed OCTA devices are capable of scanning larger areas. Although widefield OCTA offers a smaller field of view than that captured by ultra-widefield FA, OCTA provides more detailed visualization of vascular changes in a fast, noninvasive manner.[1,4,5]

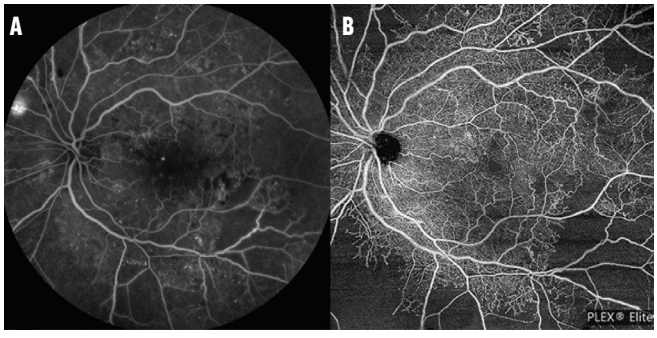

Figure 1. These are the FA (A) and the corresponding 6 x 6 mm OCTA en face images of the full retinal thickness slab (B) of an eye with proliferative diabetic retinopathy (PDR). Areas of nonperfusion can be seen with both technologies, but in greater detail on the OCTA image. FAZ margins are also better visualized with OCTA than with FA. The superonasal area of dye leakage captured on FA was not captured on the OCTA frame.

RETINAL VASCULAR OCCLUSION

Retinal vascular occlusions are common retinal disorders causing vision loss.[6] Traditionally, FA has been used for the evaluation of disease severity, degree of ischemia, and extent of NV.[7] Recently, widefield OCTA has been useful in evaluating the retinal vasculature with high sensitivity

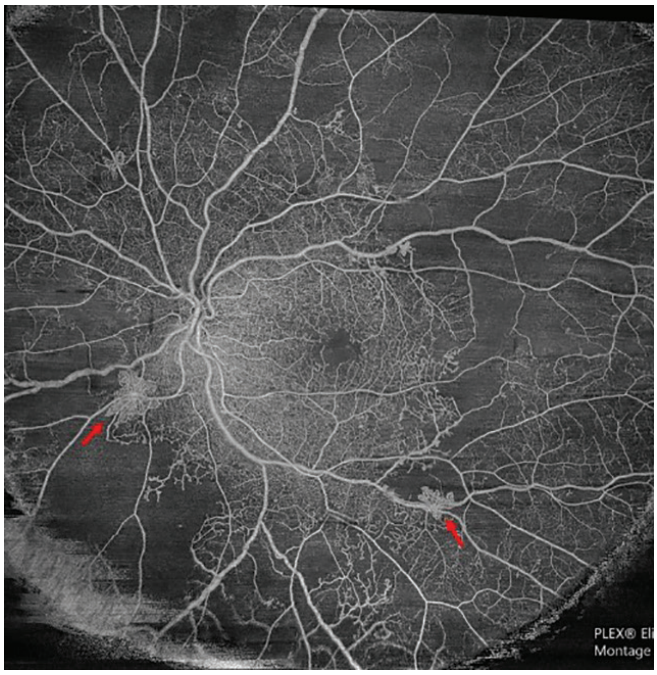

Figure 2. The widefield en face OCTA (12 x 12 mm montage) of the superficial capillary plexus in a patient with PDR shows extensive areas of nonperfusion, irregular FAZ, and multiple areas of NV elsewhere (red arrows).

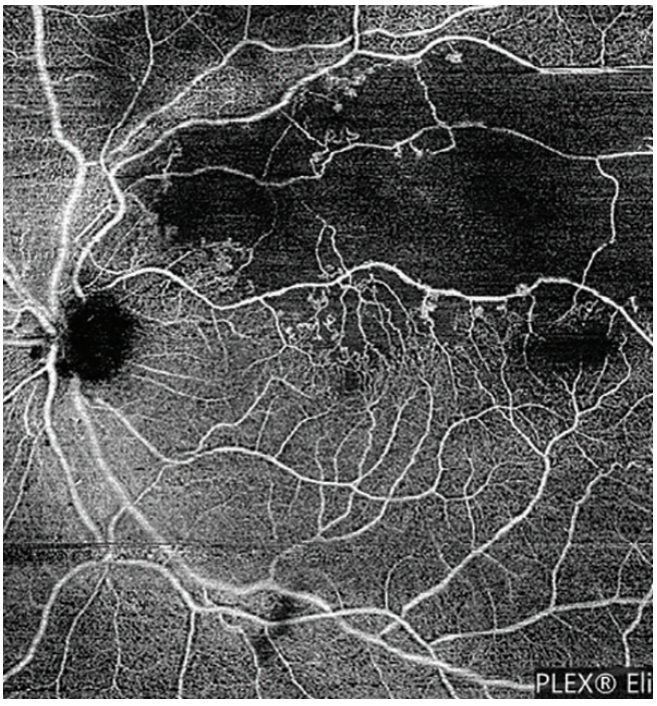

Figure 3. En face 12 x 12 mm OCTA scan of the superficial capillary plexus demonstrates an area of nonperfusion due to a left superotemporal ischemic branch retinal vein occlusion.

for early detection of nonperfusion and vasculature abnormalities (Figure 3).[8-11]

CENTRAL SEROUS CHORIORETINOPATHY

Choroidal NV is a known complication of central serous chorioretinopathy (CSCR) and can be a major cause of visual impairment.[12] Forming a definitive diagnosis of macular NV in this condition is often challenging using traditional imaging; late hyperfluorescence in FA is not easy to differentiate from window defects of the retinal pigment epithelium (RPE) and the ill-defined leaking points of CSCR.[13] Recent studies report that OCTA is more sensitive in the detection of macular NV secondary to CSCR and can enhance diagnosis compared with dye-based angiography (Figure 4).[14-16]

UVEITIS

OCTA findings in patients with uveitis may have significant implications, documenting potential biomarkers of retinal or choroidal inflammatory activity and response to treatment in a noninvasive manner.[17] If OCTA is unable to detect dye leakage in uveitis, however, it may still assist in evaluating vascular density changes in the superficial and/or deep retinal capillary plexus; these are significantly lower in eyes with vasculitis than in healthy eyes.

Recent advances in widefield OCTA imaging may enhance the detection of peripheral nonperfusion. Additionally, quantitative evaluation of the vasculature can be used to assess disease progression.[18,19]

OTHER APPLICATIONS

OCTA can be used to evaluate choroidal ischemia corresponding to areas of hypofluorescence on indocyanine green angiography in placoid lesions such as acute posterior multifocal placoid pigment epitheliopathy and serpiginous choroiditis.[20,21] In contrast, OCTA demonstrated normal choriocapillaris flow in the areas with corresponding hypofluorescence in patients with multiple evanescent white dot syndrome, suggesting shadowing rather than ischemia.[22]

In multifocal choroiditis or punctate inner choroidopathy, OCTA is useful in distinguishing inflammatory macular NV from avascular inflammatory lesions that are poorly identified using other imaging modalities (Figure 5).[23-25]

CONCLUSION

OCTA is a rapid, noninvasive imaging tool with clinical applications in a wide range of ophthalmic diseases. However, limitations such as artifacts and segmentation errors can challenge scan interpretation.[26]

The inability of OCTA to detect leakage is a shortcoming in comparison to FA, limiting its clinical utility. However, the higher resolution and the depth-resolved imaging capability of OCTA add to the clinical assessment of many conditions.[3]

Along with future technical improvements, more studies are needed to elucidate the clinical utility of OCTA in the diagnosis and monitoring of many common ophthalmic pathologies. ■

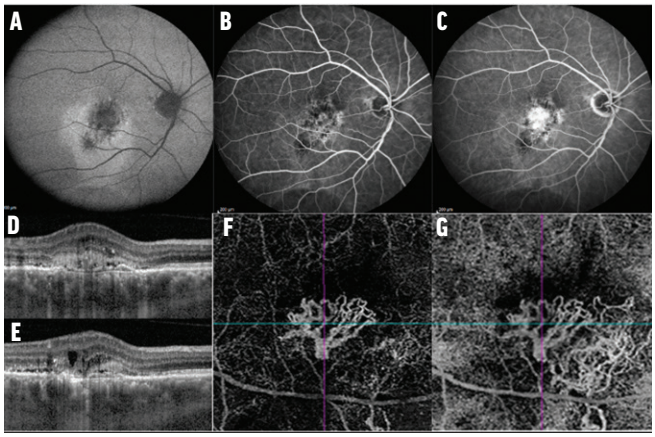

Figure 4. In this patient with choroidal NV secondary to CSCR, fundus autofluorescence shows RPE mottling and track sign of hyperautofluorescence (A). FA shows early hyperfluorescence (B) and late leakage (C). OCT B-scans (D, E) show a thickened choroid, subretinal fluid, intraretinal fluid, subretinal hyperreflective material, and a flat irregular pigment epithelial detachment. OCTA en face scans at the level of the outer retina (F) and choriocapillaris (G) show a choroidal neovascular membrane.

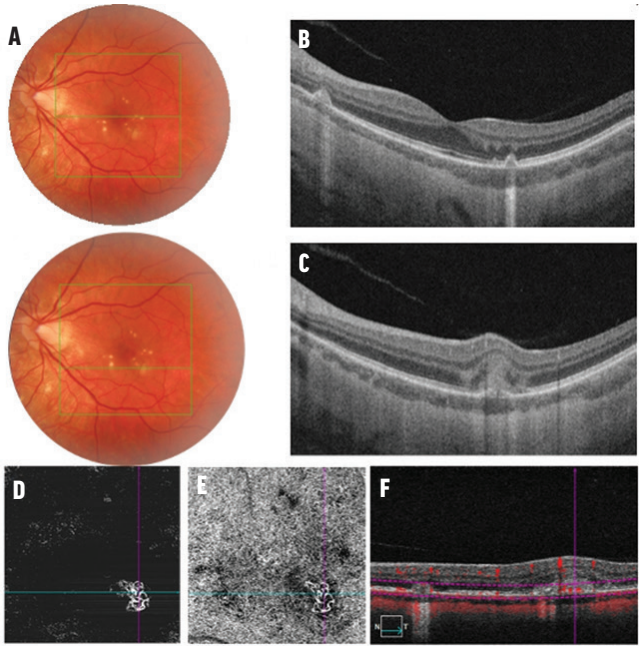

Figure 5. In this patient with uveitis and secondary macular NV, the color fundus photograph (A) and corresponding OCT B-scan (B) show punctate inner choroidopathy lesions. Lower OCT B-scan (C) shows a lesion that is suspicious for secondary type 2 macular NV. OCTA en face images at the level of the outer retina (D) and outer retina-choriocapillary complex (E) show an abnormal vascular network, and the corresponding OCTA B-scan (F) shows flow signals confirming the diagnosis of secondary type 2 macular NV.

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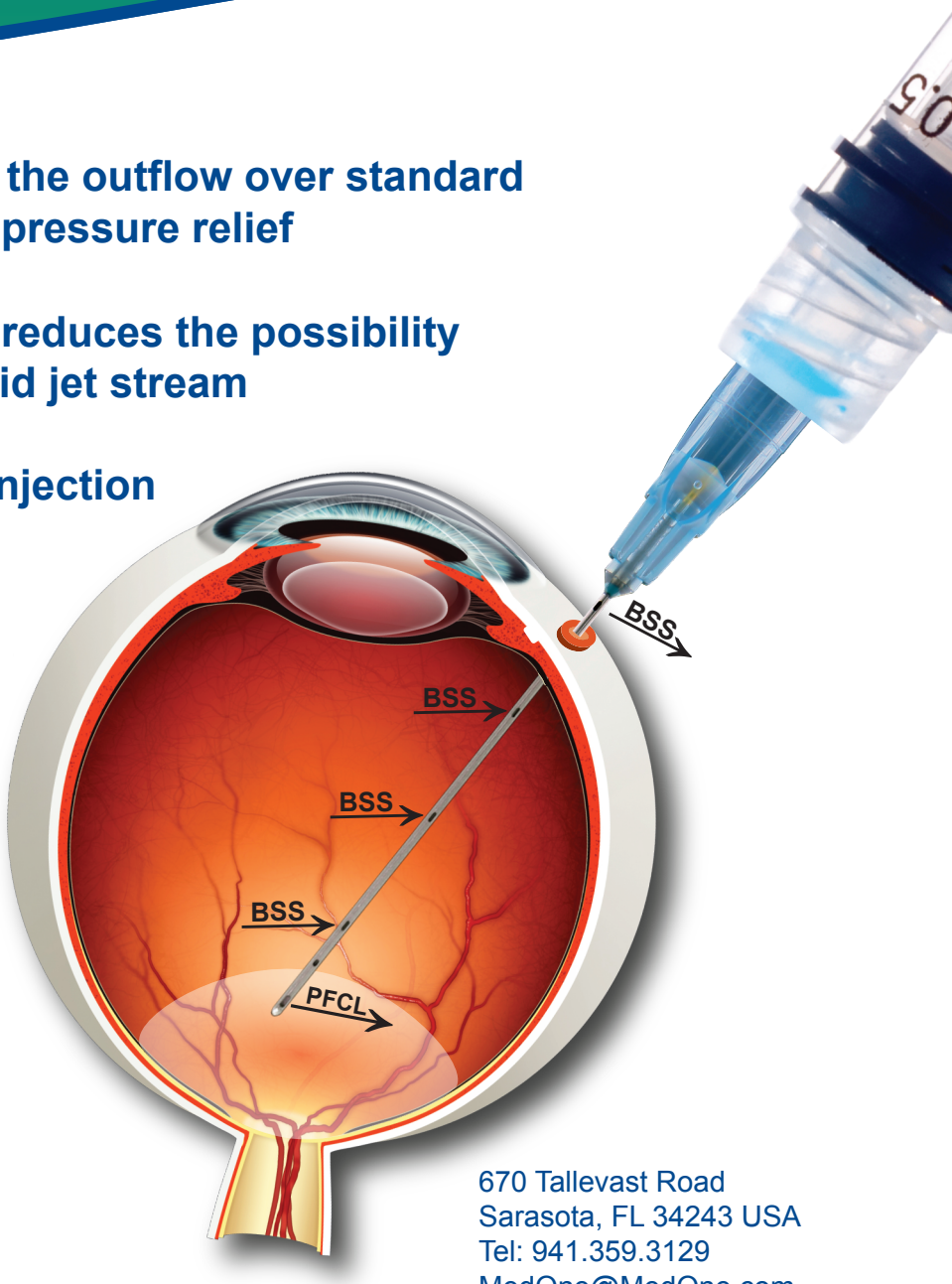

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HOW TO HANDLE EYE DROP ALLERGIES DURING SURGERY


This patient needed an urgent retinal detachment repair, leaving no time to order preservative-free medications. Here's what we did.

BY SAMANTHA SCHILLING, BA, OSC, AND BRIAN C. JOONDEPH, MD, MPS

Every Friday in the retina clinic is Friday the 13th, regardless of what the calendar says. A Friday last December was no exception, when a macula-on retinal detachment (RD) was added to the schedule. A 62-year-old woman presented with a complaint of seeing "a curtain" in her right eye vision for the past day. The kicker was that she also reported a severe allergy to all eye drops. Her allergy was more than itching and hives—she reported previous anaphylactic reactions to eye drops. A deeper dive into her medical history revealed that the preservative benzalkonium chloride was the likely culprit. Because Friday afternoon was already hectic, and we didn't want to test our resuscitation skills, we deferred use of any eye drops, including for IOP testing.

This presentation, a classic RD, usually prompts a cascade of surgical decisions. Who is available to operate? Should we handle it over the weekend or can it wait until Monday? Instead, we faced a far bigger problem with this patient: How could we diagnose, much less repair, an RD without dilating the patient?

In this article, we walk you through the myriad dilemmas and decision points we faced, hoping to provide a roadmap to help you successfully navigate similar cases you may encounter in the future.

DIAGNOSTIC CHALLENGE

Ultra-widefield fundus imaging (Optos), a controversial purchase within our practice due to cost, was a lifesaver, as it captured a superonasal RD through an undilated pupil (Figure 1). The detachment repair could wait up to 3 days (until the following Monday), but first we needed to decide where to perform the surgery.

TIMING ISSUES

We typically operate at one of several outpatient ambulatory surgery centers (ASCs). For this patient, however, we felt that a hospital setting, with the ICU down the hall, would be better in case she had a severe anaphylactic reaction requiring respiratory support.

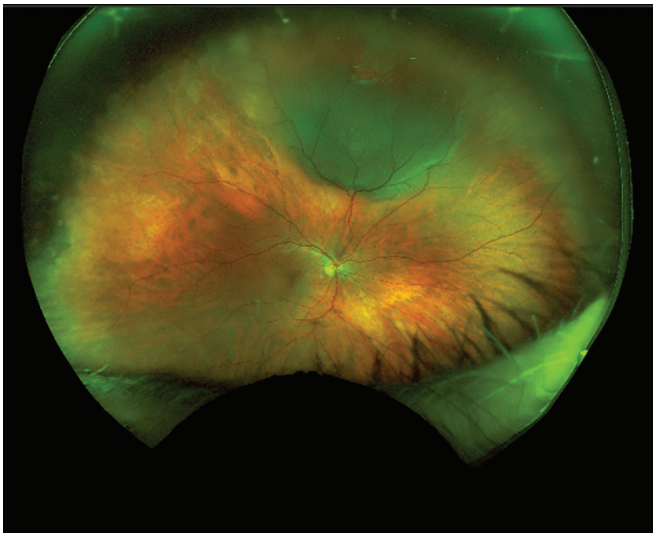

Figure 1. Widefield fundus imaging revealed the superonasal retinal detachment.

The patient was pseudophakic, and we knew she had been dilated 5 and 6 months prior for cataract surgery, with preservative-free drops ordered by her surgeon a few weeks before the elective surgery. This was not possible to achieve over the weekend for our urgent RD surgery. None of our local compounding pharmacies stocked preservative-free dilating drops, and we were referred to several out-of-state pharmacies that could provide the drops in 1 or 2 weeks, which was too long a delay for a macula-on RD.

Our first thought was to refer the patient to the local university eye department and let them sort it out. Their pharmacy might have preservative-free eye drops readily available, and they had the hospital backing them up for any allergy issues. However, we knew they would face the same issues we faced, possibly with no better solutions.

We decided to schedule the patient at the hospital for

early Sunday morning, when it was usually calm and the critical care team would be best equipped to handle any complications before, during, or after surgery. We spent our Saturday discussing the case with the nursing supervisor, pharmacist, hospitalist, and anesthesiologist.

One proposal was to admit the patient the day before to receive intravenous steroids, but she declined this due to a previous reaction to systemic steroids. The patient was insistent on outpatient surgery with no hospital admission.

SURGICAL STEPS

Pretreatment with diphenhydramine (Benadryl, Johnson & Johnson) was the next best option. We had no choice but to dilate her, for which we used two sets each of topical cyclopentolate 0.5% and phenylephrine 2.5%, with digital punctal occlusion and closed eyelids to minimize systemic absorption. Her eye dilated beautifully with no reaction.

Other options we considered using if the patient could not be dilated included iris hooks (the hospital never heard of and didn't stock), a Malyugin ring (Labtician Ophthalmics; we had no experience with), or intracameral preservative-free epinephrine in hope that this would dilate the pupil adequately. With modern wide-angle viewing systems, a large pupil, although nice, isn't essential for retina surgery.

The surgery was performed under local anesthesia with sedation. For the block, we used preservative-free bupivacaine 0.75%. The 25-gauge vitrectomy with endolaser and SF_6 gas injection was uneventful. The patient was able to receive the standard subconjunctival cefazolin and dexamethasone, both also preservative-free.

POSTOPERATIVE PICTURE

In the recovery room, the patient had no significant allergic reaction other than mild redness and itching. She was discharged to home with diphenhydramine for prophylaxis against any delayed reaction.

The next day in the office, we deferred an IOP check. Fortunately, she was still dilated from surgery. She had drops left over from her cataract surgery—preservative-free difluprednate and fortified gentamicin—both of which would suffice, given the urgency of her case and our inability to order new drops on such short notice, and we instructed her to used them four times a day for 2 weeks.

For subsequent postoperative dilation and IOP checks, we used a compounded preservative-free combination of cyclopentolate, ketorolac, phenylephrine, and tropicamide. This was likely excessive, but it was available from an out-of-state compounding pharmacy and was effective. We ordered the unit dose vials delivered to the patient for future visits with us or any other eye care provider.

Four months after surgery, the patient's VA was 20/20 OD, and subsequent monitoring was performed with ultra-widefield imaging (Figure 2).

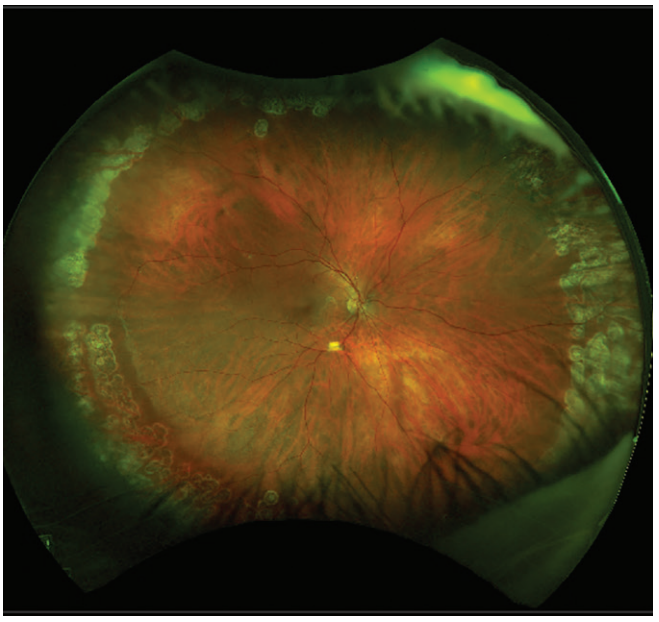

Figure 2. With careful planning, the patient had a successful outcome with no signs of allergic reaction to the medications used for her retinal detachment repair.

TAKE-HOME POINTS

The patient had a great result, and we were able to work around her severe eye drop allergy. If you encounter a similar case, keep the following pearls in mind.

- Preservative allergy is uncommon, but it can be severe.
- If surgery or other treatment is needed acutely, consider using commercially available preservative-free eye drops and medications. Compounding pharmacies may require 1 or 2 weeks of lead time, making them useful options for elective but not for urgent surgery.
- Although many retina specialists prefer the ASC setting for surgery, hospitals provide a valuable backup if medical conditions come into play that require a higher level of care. Make use of medical consultants who may also have suggestions or ideas.
- Nonmydriatic imaging, although not ideal, is a useful option when dilation isn't possible, for whatever reason.

Even in the heat of the moment, a few minutes of calm thoughtfulness can help you see the right path forward to achieve a positive experience for you and the patient. ■

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MEASUREMENT AND EVALUATION OF THE FOVEAL AVASCULAR ZONE IN A HEALTHY LATINO POPULATION

OCT angiography captured FAZ metrics in this multicenter international collaborative study.

BY CLAUDIA P. ACOSTA, MD; DANIEL GONZÁLEZ, MD; CAROLINA SARDI, MD, MS; NATALIA GONZÁLEZ, MD; ALEJANDRO LAVAQUE, MD; JUAN MANUEL JIMENEZ, MD; AND VANIA GARCIA, MD

Variation in the morphology of the foveal avascular zone (FAZ), the space located at the center of the macula that lacks capillary plexuses,[1,2] has been implicated in numerous pathologies such as diabetic retinopathy, albinism, sickle cell retinopathy, foveal hypoplasia, central serous chorioretinopathy, choroidal melanoma, and other systemic diseases, especially those involving microvasculature disorders.[3-5]

OCT angiography (OCTA) is a noninvasive modality that can be used to map the capillary network and the FAZ in high resolution without the need for dye injection.[6-8] It can rapidly capture 3D images of the choroidal and retinal vasculature.[9,10]

Furthermore, the OCTA algorithm known as *split spectrum amplitude decorrelation angiography* (SSADA) can be used to detect erythrocyte movement.[11] This novel technology allows study of the normal retinal vasculature in vivo with better depth resolution than was previously possible.[9]

The main objectives of the study we describe here were to measure FAZ metrics in healthy Latino volunteers using OCTA and to collate and analyze the data obtained to determine any correlation between FAZ metrics and age and sex among the studied population.

METHODS

This observational cross-sectional study included 365 eyes of 185 adult (> 20 years old) Latino volunteers who were recruited over a 3-month period at six Latin American eye centers.

When this study was performed, there were no reports in the literature regarding FAZ metrics in healthy Latino individuals; thus, the sample design was based on the mean superficial FAZ area reported by Coscas et al (0.28 mm^2).[2] Recently, single-center studies performed in Latin American countries have been published, although they do not encompass as many countries as the study described here.

The inclusion criteria for the present study were healthy adult volunteers older than 20 years who signed the informed consent form. The exclusion criteria were BCVA worse than 40 letters on the ETDRS chart and any refractive error greater than ±3.00 D; a history of ocular diseases

AT A GLANCE

- The authors describe their study aiming to measure foveal avascular zone (FAZ) metrics in healthy Latino volunteers using OCTA and to determine any correlations between FAZ metrics and age and sex among the population.
- The area and perimeter of the FAZ were both larger in the female study participants, indicating a dependent relationship between FAZ and sex.
- FAZ acircularity index demonstrated a direct positive correlation with age.

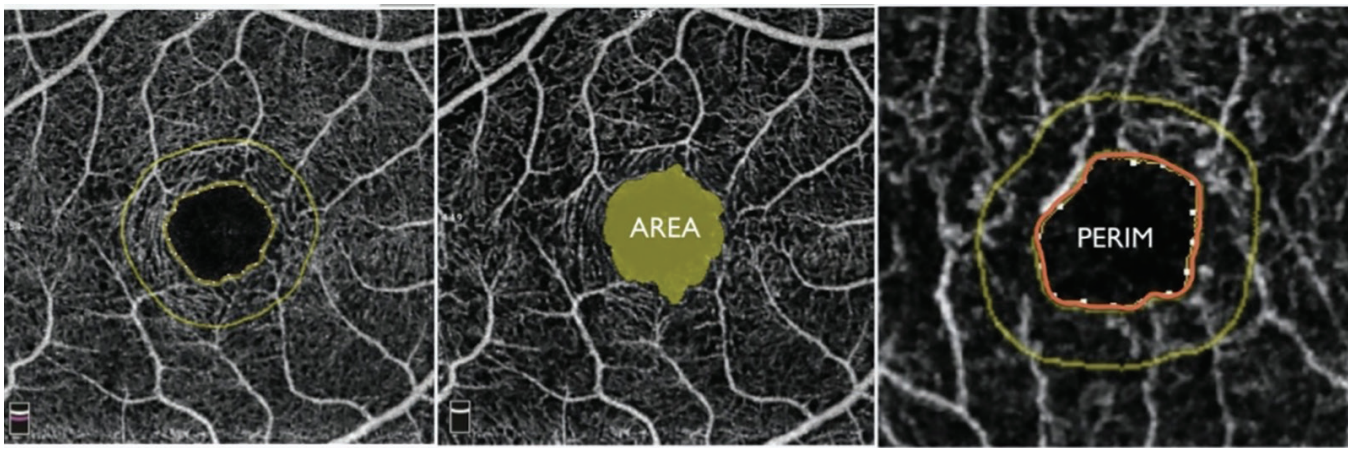

Figure 1. FAZ measurements were performed on a full retina slab based on full retinal vasculature.

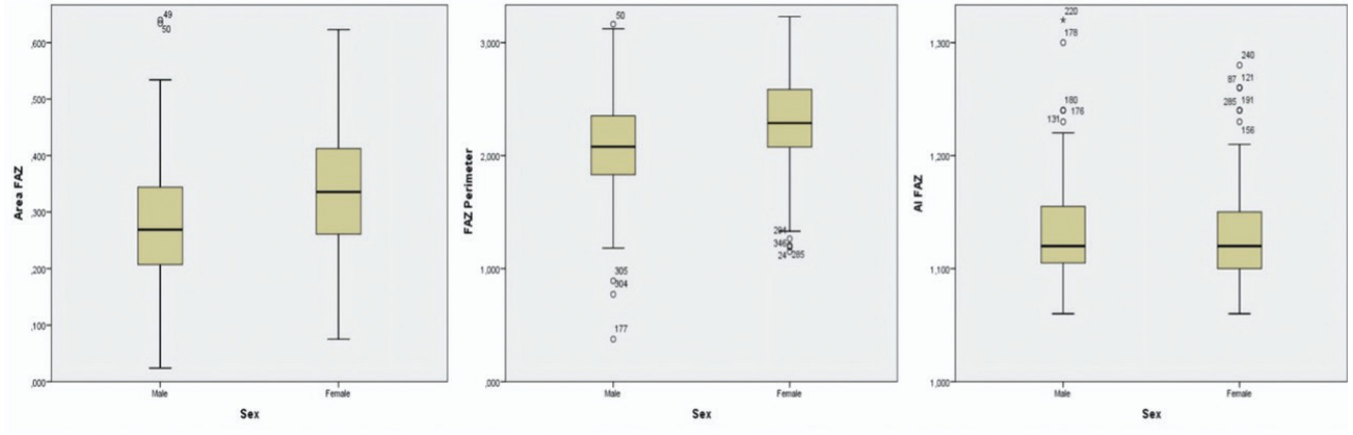

Figure 2. Area and perimeter of the FAZ were both larger in the female participants than in the males. No correlation was found between FAZ area or perimeter and age.

such as diabetic retinopathy, glaucoma (average retinal nerve fiber layer thickness outside normal limits), AMD, myopic degeneration, cataract, idiopathic macular hole, uveitis, or central serous chorioretinopathy; intraocular surgery in the past 6 months or laser eye surgery in the past 3 months; presence of systemic diseases or conditions such as pregnancy, diabetes mellitus, smoking, hypertension, carotid and/or cardiovascular disease; and the use of sildenafil, treatment with chloroquine, etc., that could affect OCTA results. The presence of any ocular condition (such as severe dry eye) that could prevent the acquisition of reliable OCTA images was also an exclusion criterion. Furthermore, images with a signal-to-noise ratio (signal strength index [SSI]) worse than 6/10 were excluded.

After it was verified that a volunteer met the inclusion criteria, both pupils were dilated for the OCTA procedure.

FAZ measurements were done on a full retina slab based on full retinal vasculature. The metric determinations obtained were area, perimeter, and acircularity index (AI; the ratio between the measured perimeter and the perimeter of a circular area of the same size) of the FAZ (Figure 1).

RESULTS

Among the 365 eyes evaluated, 230 (63%) were from female and 135 (37%) were from male volunteers. Mean age was 39 (range, 20–86) years. Demographic data are displayed in Table 1 and FAZ metric distribution is described in Table 2.

Mean FAZ area (± standard deviation [SD]) in the whole study population was 0.31 (0.11) mm^2; mean FAZ perimeter was 2.20 (0.43) mm; and median FAZ AI was 1.12 (1.10–1.15).

Among female participants, the mean FAZ area was 0.34 (0.11) mm^2; mean FAZ perimeter was 2.29 (0.41) mm, and median FAZ AI was 1.13 (0.38). Among males, FAZ area was 0.27 (0.11) mm^2; mean FAZ perimeter was 2.06 (0.42) mm; and median FAZ AI was 1.13 (0.05).

The area and perimeter of the FAZ were both larger in the female participants, indicating a dependent relationship between FAZ and sex (P = .00). No correlation was found between FAZ area or perimeter and age (Figure 2).

FAZ AI demonstrated a direct positive correlation with age (P = .00, r = .20); however, no correlation was found between FAZ AI and sex (Figure 3).

TABLE 1. DEMOGRAPHICS AND OTHER CHARACTERISTICS							
		Argentina	Bolivia	Chile	Colombia	Mexico	Peru
Sample Size (% of Total Eyes)	365	67 (18.4%)	54 (14.8%)	74 (20.3%)	78 (21.4%)	32 (8.8%)	60 (16.4%)
Female	230 (63%)	41	46	55	40	14	34
Male	135 (37%)	26	82	19	38	18	26
Age, 20–39	212 (58%)	33	42	43	42	12	40
Age, 40–59	106 (29%)	21	10	23	24	16	12
Age, 60 or older	47 (13%)	13	2	8	12	4	8

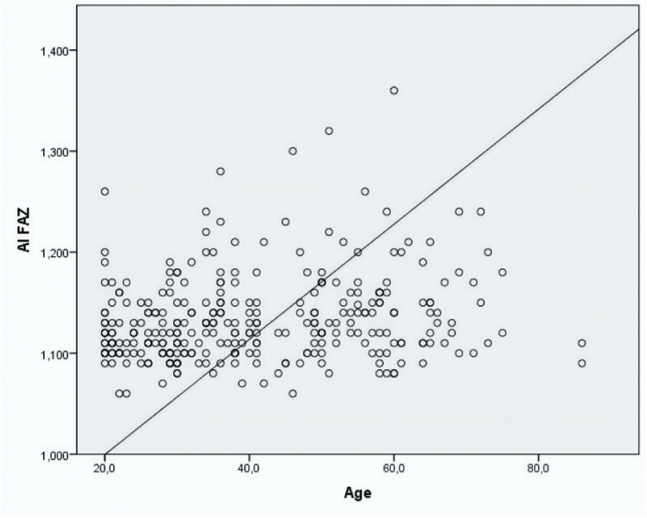

Figure 3. FAZ AI demonstrated a direct positive correlation with age; no correlation was found between FAZ AI and sex.

DISCUSSION

The main objective of our study was to describe the FAZ metrics of a healthy Latino population; however, other important findings were revealed after statistical analysis of the study data. Based on our results, we can conclude that both area and perimeter of the FAZ share a dependent relationship with sex. In our study population, the female group had larger mean FAZ area and perimeter values than the male group. In addition, there was a direct positive correlation between FAZ AI and age, but not between FAZ AI and sex. Interestingly, neither the area nor the perimeter of the FAZ had any statistically significant relationship with age.

We speculate that the variation in the FAZ AIs of the participants was due to loss of the terminal capillaries of the FAZ, which is expected to occur with aging. Furthermore, we theorize that the high natural variability of the FAZ area, due to statistical effects, may mask a possible relationship between area and age, as Morales et al found that FAZ area increases with age in normal individuals.[12]

Because bad quality images can alter FAZ metrics, images with an SSI value of less than 6 were excluded from our FAZ analysis. After adjusting the SSI, we found that both FAZ area and perimeter conserved their correlations with sex.

BASED ON OUR RESULTS, WE CAN CONCLUDE THAT BOTH AREA AND PERIMETER OF THE FAZ SHARE A DEPENDENT RELATIONSHIP WITH SEX.

Previous studies have demonstrated that FAZ measurements obtained via OCTA were comparable to those obtained using other techniques such as adaptive optics scanning and fluorescein angiography.[7,13] Coscas et al and Carpineto et al have already shown that measured FAZ metrics of healthy subjects have excellent reproducibility and repeatability; therefore, we did not deem it necessary to evaluate interobserver variability.[2,14]

Although our results are in line with those of some similar studies, they differ from those of others. Some studies have reported that the superficial FAZ and deep FAZ are larger in females.[15-17] Other authors, however, reached the conclusion that there is no correlation between superficial FAZ or deep FAZ and sex.[12,18]

In contrast to the results of our analysis, in which no correlation was seen between area and perimeter of the FAZ and age, Rommel et al reported that the size of the FAZ enlarges with increasing age.[16] Their findings cannot be fairly compared with those of our study because our data were taken using a full retina slab; hence, we could not differentiate between the superficial and deep plexuses.

Our study addresses a query posed in previous articles that hypothesized that the size of the FAZ may not be related to age.[13] Those authors could not confirm their results because

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1) References CryoTreQ Technical File STED 2.2.4 "Performance Specifications: In a water bath at a temperature of 37 °C, an ice ball will be formed with a layer thickness of 0.8 mm within 6 seconds".

TABLE 2. FAZ METRICS AND CORRESPONDING VALUES

FAZ Metrics	Area	Perimeter	AI
Mean (± SD)	0.31 (0.11)	2.20 (0.43)	1.13 (0.04)
Median	0.31	2.23	1.12
IQR (25–75)	0.23–0.38	1.93–2.48	1.10–1.15
Abbreviations: IQR, interquartile range.			

of their small sample sizes. Our results definitively showed that age was not correlated with the area or perimeter of the FAZ.

In all previously published articles, the deep and superficial plexuses were measured and reported separately because these measurements were done with experimental or manual software. However, the retina is a 3D structure with four plexuses that converge in the fovea to form the perifoveal capillary network; therefore, we concluded that FAZ measurements should be obtained by considering the structures as a single unit. Accordingly, we measured the FAZ in the present study using a single and complete slab of retina.

Another reason for using our method is that practicing physicians will use automated commercial software that is accessible and practical.

CONCLUSION

Given the fact that variability in FAZ measurements has been reported in many ocular pathologies, it is reasonable to conclude that our research will contribute to the establishment of a normative database that includes a healthy Latino population, which physicians can consult while assessing various pathologies.

The limitations identified in our study are recall bias and the fact that our sample size does not represent the total population of the cities or countries our volunteers came from. Equally important, there are multiple OCTA instruments on the market, including swept-source and spectral-domain devices. Our study was performed using spectral-domain OCT with a scanning rate of 70,000 scans per second, whereas swept-source devices may be capable of 100,000 scans per second. Because spectral-domain OCT can be limited in resolution when compared to swept-source OCT, it can yield different results. ■

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The Benefits of Early Surgical Intervention For Diabetic Retinopathy

Modern tools and techniques make vitrectomy an important early treatment option.

BY MARÍA H. BERROCAL, MD

Diabetes is an epidemic, and type 2 diabetes is increasing at an alarming rate in young patients in the United States. Historically, type 2 diabetes presented in patients older than 40 years; now we see 355,000 new cases yearly in patients between 18 and 44 years.[1] Even in children and adolescents, more than 6,000 cases of type 2 diabetes are diagnosed each year.[2]

This demographic shift creates a challenging management scenario for retina specialists because the eyes of these young patients with type 2 diabetes have an attached hyaloid, and the eyes behave similarly to those of patients with type 1 diabetes. Thus, we need to shift our treatment approach and consider early vitrectomy in these eyes.

DRVS PEARLS

The Diabetic Retinopathy Vitrectomy Study (DRVS) was done in the 1980s, but the important information that it provided remains clinically useful today.[3] First, the study included 4 years of follow-up, which is crucial when following a lifelong disease such as diabetes. If patients are managing their diabetes for decades, 1 to 2 years of follow-up isn't enough to truly understand the long-term implications of treatment for diabetic retinopathy (DR). Second, the DRVS showed that early vitrectomy can provide improved outcomes, particularly for patients with type 1 diabetes.

What's most remarkable about these findings from the '80s is that treatment at that time didn't include intraoperative laser; in fact, the instruments were rudimentary compared with what we use today. In the DRVS, 20% of the patients with DR, irrespective of the intervention, ended with no light perception, an outcome that has fortunately decreased with advances in vitrectomy.

Today, vitrectomy is significantly safer, making it an excellent choice for young patients with DR. Vitrectomy should no longer be a last resort; instead, we should see it as a long-term solution for this chronic disease.

THE REAL ENEMY

Often, patients with type 1 diabetes do poorly with surgical intervention because of their attached hyaloid. Older patients with type 2 diabetes have often already experienced a posterior vitreous detachment (PVD) or get a PVD before they progress to proliferative DR (PDR). However, this clinical picture is changing as younger people and children are increasingly diagnosed with type 2 diabetes.

The attached hyaloid is the enemy because eyes behave quite differently depending on whether they have a PVD,

AT A GLANCE

- Vitrectomy should no longer be a last resort; instead, we should see it as a long-term solution for diabetic retinopathy.
- Early vitrectomy can prevent the formation of tractional and rhegmatogenous RDs, DME, and vitreous hemorrhage over time.
- Often, patients with type 1 diabetes do poorly with surgical intervention because of their attached hyaloid.
- Although panretinal photocoagulation is an important treatment consideration for diabetic patients with an attached hyaloid, it isn't a long-term solution.

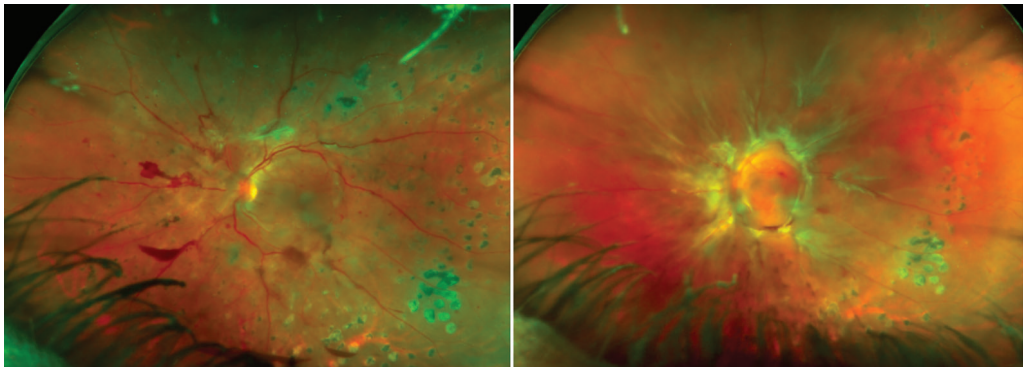

Figure 1. This 45-year-old man progressed in just 2 months from PDR to a combined tractional/rhegmatogenous RD. Had he undergone vitrectomy before the progression, the surgery would have taken maybe 30 minutes; the intervention for RD took significantly more time.

no PVD, or partial PVD. Ono et al[4] assessed DR progression at 3 years in more than 400 patients and found that 44% of patients with PDR progressed if they had no PVD. However, all patients who had a partial PVD with a thickened posterior hyaloid progressed during those 3 years. None of the patients with a complete PVD progressed. Not surprisingly, the data show that PVD can be protective and stabilize the diabetic eye in the long term.

In general, eyes that have had vitrectomy don't develop tractional retinal detachments (RD), and many don't develop diabetic macular edema (DME) either (Figure 1).

TREATMENT CONSIDERATIONS

Panretinal photocoagulation (PRP) is an important treatment consideration for diabetic patients with an attached hyaloid. However, it isn't a long-term solution. Based on the DRCR Retina Network (DRCR.net) Protocol S data, at 5 years 51% of patients (mean age, 51) needed more than a single full application of PRP.[5] From years 3 to 5, 11% required additional PRP. The mean number of ranibizumab (Lucentis, Genentech) injections needed in addition to the PRP was 5.4, and 46% developed vitreous hemorrhage. Even in this older population (compared with those 18 to 44 years of age), 12% developed tractional RD and 19% required vitrectomy. In the ranibizumab arm, 11% required a vitrectomy.[5]

Patients in Protocol S were followed perfectly, with monthly injections administered when needed, and 4% developed neovascular glaucoma.[5] However, study data and real-world outcomes differ, and compliance comes to the forefront, particularly for patients with diabetes. In the real world, among patients with PDR, 25% to 54% miss appointments because of illness, noncompliance, financial considerations, or age.[6] And PRP is not a panacea against noncompliance because more than 40% of eyes treated with PRP in Protocol S developed vitreous hemorrhage.

The DRCR.net Protocol AB has published 2-year follow-up of 205 eyes with DR and vitreous hemorrhage randomly assigned to receive either aflibercept (Eylea, Regeneron) or vitrectomy with PRP.[7] Again, the mean age in this study was 57, and only 17% of patients in the aflibercept group and 18% in the vitrectomy group had type 1 diabetes. The researchers noted worse visual acuity results at 1 month with aflibercept, which was expected because the blood doesn't clear that quickly.

The study reported similar visual acuity results at 2 years, although it was powered to detect only an 8-letter difference and underpowered to detect a benefit of vitrectomy. Also in this study, 42% of the patients in the aflibercept arm and 55% in the vitrectomy arm had had previous PRP. In addition, 22% of the eyes treated with aflibercept developed tractional RD versus 13% in the vitrectomy group. At 2 years, 49% of eyes treated with aflibercept developed recurrent vitreous hemorrhage and 29% had persistent neovascularization compared with 3% in the vitrectomy group.[7]

The Protocol AB researchers concluded that vitrectomy with PRP remains the standard of care for these patients—a crucial finding that should shape our care of patients with DR and vitreous hemorrhage.

Surgeons should also note that a meta-analysis of the VIVID, VISTA, RISE, and RIDE studies found that patients with diabetes have a threefold increased risk of death with monthly injections of ranibizumab or aflibercept compared with sham over 2 years.[8] Thus, anti-VEGF agents should be used with extreme caution as a singular treatment for PDR in patients without a complete PVD, because eyes lost

PDR TREATMENT COST ANALYSIS

Contrary to what some believe, early vitrectomy is quite cost-effective for the treatment of PDR. It reduces the treatment burden, there is no progression to tractional RD, and it reduces the incidence of DME. A cost-analysis study at Bascom Palmer Eye Institute comparing vitrectomy with PRP found that the cost for each treatment was similar over a span of 2 years;[1] however, the DRCR.net Protocol S data showed a significant treatment burden, with 50% of patients treated with PRP requiring supplemental treatment.[2] That extra treatment burden is rarely included in cost analyses focused only on the primary treatment.

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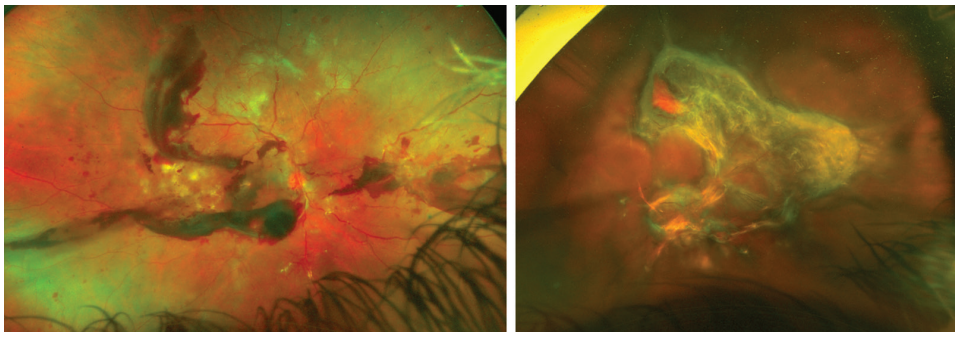

Figure 2. This 37-year-old with type 1 diabetes presented with vitreous hemorrhage and was scheduled for vitrectomy. However, due to the COVID-19 pandemic he missed his appointment and presented 8 weeks later with rapid progression of fibrovascular proliferation and tractional RD. This case underscores how quickly severe PDR can progress to tractional RD in eyes with an attached vitreous.

to follow-up do much worse when they are treated with anti-VEGF agents than with PRP. Obeid et al found that 33% of eyes treated with an anti-VEGF agent developed tractional RD versus 2% of PRP-treated eyes.[9]

CASES DRIVE HOME THE POINT

I recently analyzed results in 60 patients with diabetes followed for 8 years to track the visual outcomes in the worse eye, treated with vitrectomy, and the better-seeing eye, usually treated with PRP as needed.[10] In patients who were younger than 50 years, mean postoperative VA was 20/80 in eyes treated with vitrectomy. Eyes treated with PRP initially and then as needed had a mean postoperative VA of 20/400 at 8 years. In the vitrectomized eyes, only 8% had VA of hand motion or light perception compared with 36% in the better-seeing eyes of patients treated conventionally, in part because many were lost to follow-up or presented with complications. At 8 years, 20% of those better-seeing eyes ended with a VA of no light perception.

In addition, 16% of the vitrectomized eyes needed extra laser, 12% needed a reoperation, and 40% had cataract progression over the course of 8 years. Of the eyes treated with PRP, 72% needed extra laser, 60% required vitrectomy, and 72% developed RDs, 16% of which were inoperable.

In another series of 1,267 eyes treated with vitrectomy for vitreous hemorrhage, DME, tractional RDs, or neurovascular glaucoma, 72% had improved visual acuity and 28% stayed the same or decreased; 73% had VA better than 20/200.[11] In this series, 25% to 40% of the fellow eyes needed vitrectomy over time.

KEY TAKEAWAYS

With 27-gauge tools and high-tech visualization systems such as intraoperative 3D heads-up displays, we should start thinking of vitrectomy more as a preventive measure than as a last resort. Early vitrectomy can prevent the formation of tractional and rhegmatogenous RDs, DME, and vitreous hemorrhage over time (Figure 2). The eyes remain stable, reducing complications and lessening the treatment burden.

With today's advances, early vitrectomy may be a panacea for DR in eyes with an attached hyaloid. Although PRP and treatment with anti-VEGF agents can be effective in many eyes, young diabetic eyes will continue to progress when treated with these modalities. As we strive to choose the right treatment, the patient's age and the status of the hyaloid are crucial factors in our decision-making process. ■

WATCH IT NOW

Diabetic Retinopathy: Treat Them Early

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Treating Diabetic Retinopathy: Anti-VEGF vs PRP

The boom of intravitreal injections doesn't make laser obsolete—both serve essential roles in the management of diabetic retinopathy.

BY ARCHANA A. NAIR, MD, AND YASHA S. MODI, MD

The advent of anti-VEGF agents has revolutionized the way we address diabetic retinopathy (DR) and the severe complications associated with it. However, the role of these injections as primary treatment for DR remains controversial. Are we solving DR by reversing the disease staging, or are we simply covering up the problem? Should we abandon a 50-plus-year history of panretinal photocoagulation (PRP)?

In this article we discuss the significant research that has been done to answer these questions and provide evidence supporting and questioning the use of anti-VEGF agents as the primary treatment for DR.

NONPROLIFERATIVE DR WITHOUT DME

The rationale for treatment of patients with moderate to severe nonproliferative DR (NPDR) is simple: to prevent severe complications of the disease. The PANORAMA study and the DRCR Retina Network's Protocol W provide important data to help clinicians understand the efficacy, risks and benefits, and treatment duration of prophylactic therapy for patients with NPDR.

PANORAMA evaluated the efficacy of aflibercept (Eylea, Regeneron) injections in patients with moderate to severe NPDR without diabetic macular edema (DME).[1] Patients were randomly assigned into one of three treatment arms: three monthly injections followed by injections every 16 weeks, five monthly injections followed by injections every 8 weeks, or sham treatment. The results showed a statistically significant ≥ 2 step improvement in Diabetic Retinopathy Severity Score in treated patients compared with those in the sham group (65% and 80% vs 15%, respectively). Development of center-involved DME was also lower in the treatment arm compared with sham (7% and 8% vs 26%, respectively). This suggests that anti-VEGF injections can regress DR severity and lower the likelihood of DME.[1]

A criticism of the study's results, however, is that there

AT A GLANCE

- The PANORAMA results suggest that treatment with anti-VEGF injections can regress diabetic retinopathy (DR) severity and lower the likelihood of diabetic macular edema.
- Rates of anti-VEGF therapy use have increased since the publication of Protocol S, whereas rates of panretinal photocoagulation have decreased nationwide.
- Eyes treated with anti-VEGF agents that experienced regressed DR scoring to mild-to-moderate nonproliferative DR were prone to more rapid worsening with reduced anti-VEGF therapy compared with untreated eyes with mild-to-moderate nonproliferative DR.

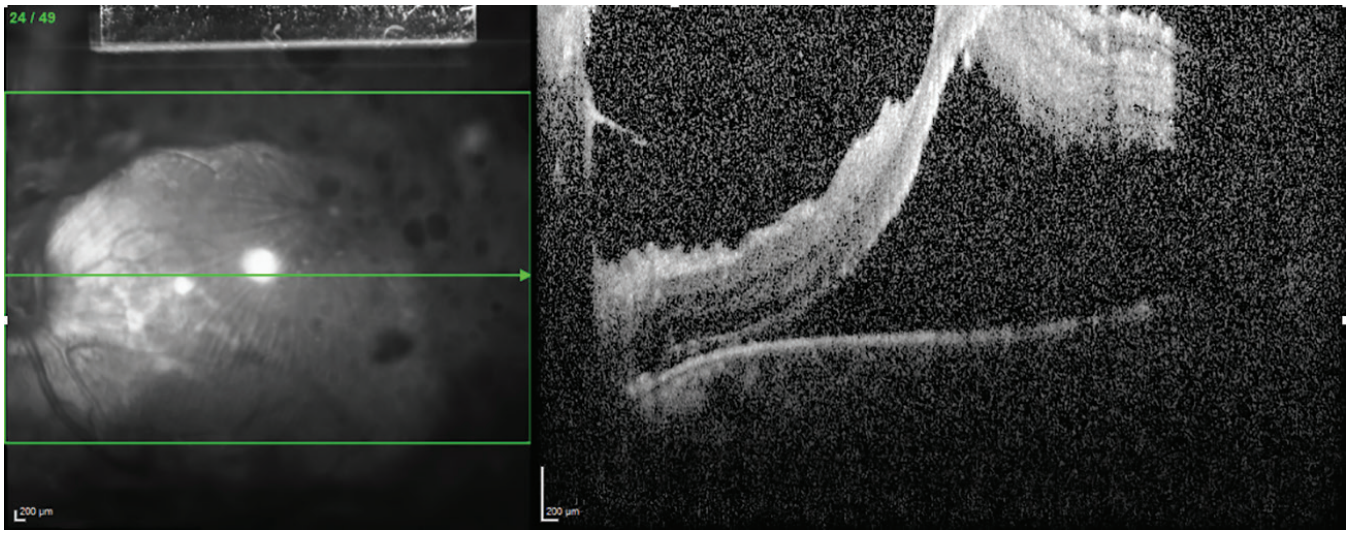

Figure. This 27-year-old woman with type 1 diabetes presented with recent onset vision loss in her left eye. She had noticed floaters for a couple of months but did not present to the clinic until her vision had decreased. On examination, VA was 20/400 with extensive tractional membranes inducing a fovea-off macular detachment. Ultimately, she required pars plana vitrectomy with extensive membrane segmentation and delamination to reattach her retina with 20/400 vision under silicone oil. The right eye received full PRP along with anti-VEGF therapy for treatment of PDR.

was no difference in mean visual acuity between groups at 2 years.[2] This raises the important question of whether we are treating the disease or the patient in front of us.

Protocol W also evaluated the efficacy of aflibercept treatment in moderate to severe NPDR without DME.[3] Patients were randomly assigned to treatment with aflibercept versus sham treatment at 1, 2, and 4 months and then every 4 months through 4 years. At 2 years, the cumulative probability of developing center-involved DME with vision loss or proliferative DR (PDR) was 16% in the aflibercept group versus 44% in the sham group.[3] This represents a threefold relative-risk reduction in preventing a severe complication. However, similar to the PANAROMA study, there were no differences in visual acuity between the groups at 2 years. Additionally, three patients in the aflibercept group developed endophthalmitis.

These results raise several questions, including these: What is the right number of injections to balance treatment efficacy with risks? Does the fact that visual acuity remains similar between arms affect the treatment decision? What if the patient already has PDR?

PROLIFERATIVE DR

PRP was established as the standard of care for the management of PDR in the Diabetic Retinopathy Study in the 1970s.[4,5] More than 3 decades later, Protocol S demonstrated that therapy with anti-VEGF agents was noninferior to PRP, thereby giving clinicians two treatment paradigms for the management of PDR.[6] An analysis of insurance claims data by Azad et al showed that rates of anti-VEGF therapy have increased since the publication of Protocol S, while at the same time the rates of PRP have decreased nationwide.[7]

Long-term successful outcomes of treatment with intravitreal anti-VEGF injections are predicated upon close follow-up. However, in a large study by Obeid et al, nearly 25% of all PDR patients were lost to follow-up (LTFU) after treatment initiation.[8] Obeid et al also sought to evaluate risk factors for LTFU. Over 4 years, the patients who received PRP had a 28% LTFU rate compared with 22.1% in the anti-VEGF group (P = .001). Increased rates of LTFU were seen in patients with lower adjusted gross income, patients of Black or Hispanic heritage, and younger patients.[8]

A delay in treatment for PDR can cause permanent visual impairment. Ohlhausen et al found that a delay in treating PDR with PRP by > 30 days can lead to decreased visual outcomes at 1 and 2 years after treatment compared with treatment on the day of diagnosis.[9]

Collectively, the results of PANORAMA, Protocol W, and Protocol S must be juxtaposed with the frequent scenario of a patient who is LTFU. Even in Protocol S, which maintained the highest standards to ensure that patients attended each visit, 39% did not comply at 5 years.[6]

PRP can be particularly valuable in conjunction with anti-VEGF therapy for patients with high-risk PDR (Figure). The PROTEUS study evaluated patients who were randomly assigned to treatment with intravitreal anti-VEGF injections plus PRP versus PRP alone.[10] At 1 year, 92.7% of patients who had combined therapy had regression of neovascularization of the disc or neovascularization elsewhere compared with 70.5% of patients who received PRP monotherapy (P = .009).[10]

HOW ANTI-VEGF AGENTS WORK

Therapy with anti-VEGF agents usually leads to the regression of clinically apparent DR. Hemorrhages and microaneurysms improve, and exudates slowly resolve. Less is

COLLECTIVELY, THE RESULTS OF PANORAMA, PROTOCOL W, AND PROTOCOL S MUST BE JUXTAPOSED WITH THE FREQUENT SCENARIO OF A PATIENT WHO IS LOST TO FOLLOW-UP.

known about the effects of anti-VEGF agents on retinal capillary nonperfusion, the primary driver of angiogenesis.

The PERMEATE study used ultra-widefield fluorescein angiography to evaluate panretinal leakage and ischemic indices in patients receiving intravitreal anti-VEGF injections for DME and retinal vein occlusion.[11] The study found that, although leakage improved with regular injections, the underlying ischemic index did not improve, and in fact worsened after 12 months of regular injections. Thus, ischemia, manifesting as peripheral nonperfusion, continues unabated in the setting of anti-VEGF monotherapy.

This is accompanied by functional loss of peripheral vision. Although visual field loss was greater in the PRP group than the anti-VEGF group after 1 and 2 years in Protocol S, the 5-year data demonstrated progressive field loss in the anti-VEGF arm. At 5 years, the mean standard deviation was -330 dB in the ranibizumab (Lucentis, Genentech) group versus -527 dB in the PRP group.[6]

SLOWING OR STOPPING ANTI-VEGF INJECTIONS

In a post-hoc analysis of the RISE and RIDE studies, Goldberg et al found that eyes treated with anti-VEGF agents that experienced regression of DR score to mild-to-moderate NPDR were prone to faster worsening when anti-VEGF therapy was reduced, in comparison with untreated eyes with mild-to-moderate NPDR.[12]

Additionally, the authors found that the rate of worsening DR in previously treated eyes occurred at a supraphysiologic level. This raises the question: Is anti-VEGF therapy truly improving DR, or is it instead masking the true DR grading? This analysis has fueled debate over whether anti-VEGF agents are, in fact, disease-modifying in this context.

HOPE FOR THE FUTURE

Every Friday at our center, we operate on patients who are bilaterally blind from traction retinal detachments. The surgeries are exhilarating, but we leave with an overwhelming sadness that we spend our Fridays like this. With the implementation of telescreening programs throughout the city, we hope to capture patients earlier and reduce the number of patients experiencing vision loss due to DR.

During educational meetings, experts in the field discuss anti-VEGF therapy versus PRP, presumably with the goal that the retina community will eventually migrate exclusively to anti-VEGF therapy. However, we hope to stop the binarization of the DR treatment paradigm. Anti-VEGF agents hold incredible merit for the management of DR and DME, and PRP continues to build upon a 50-year history of vision-saving outcomes.

The management of DR is complex and patient-specific. We must understand the entirety of the literature to support our decision-making, and we must also understand the needs of each unique patient and assess the likelihood of adherence to continuous therapy. To eradicate legal blindness due to DR in the United States—a lofty yet attainable goal—we will need a combination of therapies. Today, both laser and injection serve crucial roles, and both should be taught throughout residency and fellowship training programs. ■

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Protocol W: A Summary of 2-Year Results


New data highlight the role preventive anti-VEGF injections may play in reducing vision-threatening complications in eyes with diabetic retinopathy.

BY RAJ MATURI, MD, AND MOHAMED ASHRAF, MD, PHD

Multicenter studies have demonstrated that therapy with intravitreal anti-VEGF injections is effective in the management of both diabetic macular edema (DME) and proliferative diabetic retinopathy (PDR).[1,2] Until recently, it was unknown whether anti-VEGF therapy could be used to prevent these conditions and, if so, whether this strategy would result in long-term visual benefits.

Results from the PANORAMA study, which enrolled eyes with moderate-to-severe and severe nonproliferative diabetic retinopathy (NPDR) with or without DME showed that eyes treated with aflibercept (Eylea, Regeneron) had significantly greater improvement of 2 or more steps in DR severity compared with the sham group.[3] As a secondary outcome, the study demonstrated that the anti-VEGF treatment reduced the likelihood of developing vision-threatening complications such as center-involved DME (CI-DME) or PDR.

Protocol W is a prospective multicenter study by the DRCR Retina Network that included eyes with moderate-to-severe NPDR and without baseline CI-DME (Figure).[4] The study was designed as a long-term evaluation of intravitreal aflibercept's ability to prevent PDR and CI-DME in eyes with advanced DR.

STUDY DETAILS

The primary outcome of the study was either the development of CI-DME (> 10% increase in central subfoveal thickness [CST] from baseline) with vision loss (defined as a 10 letter or more decrease in VA on a single visit or a 5- to 9-letter decrease on two consecutive visits) or the development of PDR. PDR was defined as having neovascularization (NV) within the seven standard Early Treatment Diabetic Retinopathy Study (ETDRS) fields detected on fundus photography or fluorescein angiography (FA), vitreous hemorrhage (VH), preretinal hemorrhage, or neovascular glaucoma. The study also aimed to evaluate whether preventing these complications in patients receiving prophylactic anti-VEGF treatment resulted in visual benefits at 2 and 4 years compared with patients who were followed and treated only if they developed high-risk PDR or CI-DME with vision loss.[4]

The study included patients with type 1 or type 2 diabetes. Study eyes had NPDR (ranging from moderate to severe), no CI-DME on OCT, and no signs of NV within the seven standard ETDRS fields as detected by FA.

Patients were randomly assigned to either sham or aflibercept intravitreal injections. Eyes received injections at

AT A GLANCE

- In Protocol W, preventive treatment with anti-VEGF injections resulted in a threefold reduction in the development of center-involved diabetic macular edema with vision loss.
- At 2 years, there was no significant difference in mean change in visual acuity between the aflibercept (Eylea, Regeneron) group and the sham group.
- The longer-term outcomes remain unknown for patients receiving preventive aflibercept once they are switched to a prn regimen.

baseline and at months 1, 2, 4, 8, 16, and 20 during the first 2 years of the study. After the 2-year mark, patients were followed and given sham or aflibercept injections every 16 weeks. However, those in the aflibercept group had their injections deferred when DR severity was recorded as mild NPDR or better.

Regardless of the initial randomization group, aflibercept treatment was initiated in eyes with CI-DME if CST increased by 10% or more from baseline, associated with either a 10-letter decrease on a single visit or a 5- to 9-letter decrease on two or more consecutive visits. Aflibercept was also initiated if eyes developed high-risk PDR. DRCR Retina Network treatment algorithms were used after initiation of therapy for either DME or PDR.

INTERPRETING THE RESULTS

The study included 399 eyes of 328 participants, and approximately 80% of participants in each group completed the 2-year visit. Although the study initially aimed to include only eyes with moderate-to-severe (level 47 B-D) and severe (level 53) NPDR, after 9 months of recruitment eyes with moderate NPDR (level 43 and level 47 A) were included. At baseline, 17% of eyes in the study had moderate NPDR (level 43), 60% had moderate-to-severe NPDR (level 47 A-D) and 24% had severe NPDR.

Did preventive treatment reduce vision-threatening complications?

In Protocol W, preventive treatment with aflibercept resulted in a threefold reduction in the development of CI-DME with vision loss (14.8% in the sham group vs 4.1% in the aflibercept group). Treatment was also associated with a nearly twofold reduction in the development of new-onset PDR (33.2% in the sham group vs 13.5% in the aflibercept group).

Significantly more eyes in the aflibercept group had a 2-step or more improvement in DR severity compared with eyes in the sham group (44.8% vs 13.7%). In contrast, more eyes in the sham group had a 2-step worsening in DR severity (12.4%) compared with eyes in the aflibercept group (5.2%) at 2 years.

How many injections did each group require?

Participants in the aflibercept group who completed the 2-year visit received a mean total of eight injections. This included patients who required aflibercept for prevention as part of the protocol and those who required additional treatment for the development of vision-threatening complications (approximately 4.4% of eyes). In eyes that received only preventive treatment, the mean number of injections through 2 years was 7.7. In the sham group, 19.2% of eyes required aflibercept for treatment of PDR or CI-DME and, on average, received 5.7 injections through the 2 years.

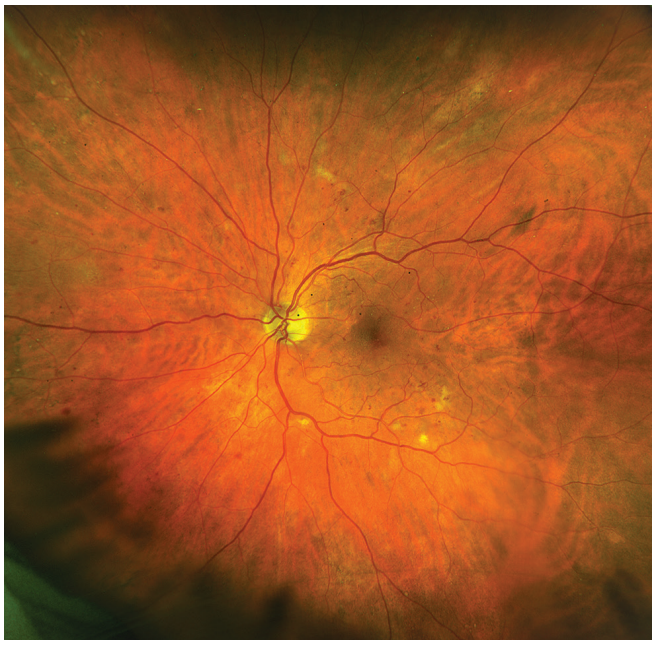

Figure. Moderately severe NPDR with cotton-wool spots and the absence of CI-DME.

Was preventive treatment associated with better vision?

At 2 years, there was no significant difference in the mean change in visual acuity between the aflibercept group and the sham group, with a mean difference of approximately 0.5 letters between the groups. The vast majority of eyes in both groups had a VA of 20/20 or better (75% in the aflibercept group vs 71.7% in the sham group), with few eyes losing 10 or more letters at 2 years (6.9% vs 8.4%). This suggests that initiating treatment after the development of complications achieves similar visual outcomes at 2 years compared with preventive use of anti-VEGF injections.

CLINICAL IMPLICATIONS

The results of this study suggest that early aflibercept treatment in eyes with NPDR results in a reduction in the development of both PDR and CI-DME with decreased vision at 2 years. However, this preventive therapy did not translate to better visual acuity compared with sham injection. It is important to highlight that the sham group was followed closely in a clinical trial setting, and patients received timely intervention as soon as their eyes developed any vision-threatening complications.

Thus, these data suggest that when patients are monitored closely (at least every 4 months) and receive adequate timely therapy at the onset of vision-threatening complications, vision loss can generally be prevented or recovered. However, long-term follow-up is necessary to determine whether visual outcomes will remain similar at 4 years or whether preventing PDR and CI-DME will result in better visual outcomes in eyes treated early with aflibercept.

(Continued on page 40)

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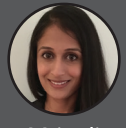
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Sustained-Release Steroid Options For DME Therapy

The promise of reduced treatment burden has researchers exploring new delivery methods.

BY SOBHA SIVAPRASAD, MBBS, MS, DM, FRCS, FRCOPHTH

Diabetic macular edema (DME) is the leading cause of vision loss in the working-age population in the developed world.[1-3] The average age at diagnosis is just over 50 years, and DME has a significant impact both individually and economically, with a high treatment burden.[1,4,5] Consequently, there is a strong rationale for developing treatments for DME that provide meaningful visual benefits while minimizing the monitoring and treatment burden.

INITIAL THERAPY OPTIONS

Anti-VEGF agents are the first-line treatment for visual impairment associated with DME, and they can help patients achieve clinically meaningful BCVA gains of up to 13 letters.[6-10] However, not every patient responds to therapy; as many as 40% of participants in pivotal trials do not reach a VA threshold of 20/40.[8]

A key challenge with current anti-VEGF agents is the treatment frequency required to achieve vision gains. Some phase 3 trials evaluating anti-VEGF agents in DME used continuous monthly dosing, and even the individualized dosing regimen used in the DRCR Retina Network's Protocol T study required a median of nine to 10 injections in the first year.[8,10]

Frequent injections may be difficult to maintain, and undertreatment leads to suboptimal outcomes. In a large observational study, DME patients receiving four or fewer injections in the first year of treatment with ranibizumab (Lucentis, Genentech) gained only 0.5 letters, while those receiving five or more injections gained a mean 6.9 letters from baseline.[11]

Investigational therapies with anti-VEGF activity—eg, faricimab (Roche), a bispecific anti-VEGF and anti-angiopoietin 2 antibody, and KSI-301 (Kodiak Sciences), an anti-VEGF antibody-biopolymer conjugate—aim to address undertreatment by achieving increased durability of action. This results in less frequent treatment in the maintenance phase (up to every 16 weeks with faricimab and every 24 weeks with KSI-301). However, pivotal trials investigating these agents still include three or four initial monthly treatments, resulting in up to six injections in the first year of treatment, even with the longest intervals.[12,13]

In patients who do not receive adequate benefits from anti-VEGF therapy, alternative treatments such as one or more preparations of corticosteroids may be an option.[6,7]

AT A GLANCE

- Diabetic macular edema (DME) comes with a high treatment burden, pushing researchers to develop new treatments that provide meaningful visual benefits while minimizing the monitoring and treatment burden.
- Sustained-release formulations of corticosteroids for DME offer a number of potential benefits, including less frequent administration and, potentially, reduced fluctuations in retinal thickness.
- A novel sustained-release steroid formulation of dexamethasone incorporated into biodegradable microspheres can be injected suprachoroidally.

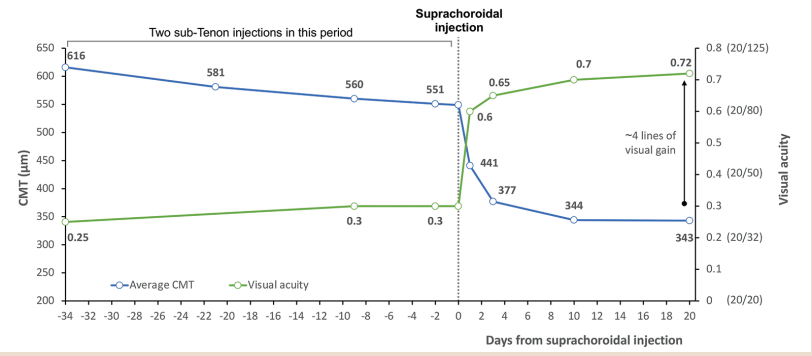
CASE STUDY

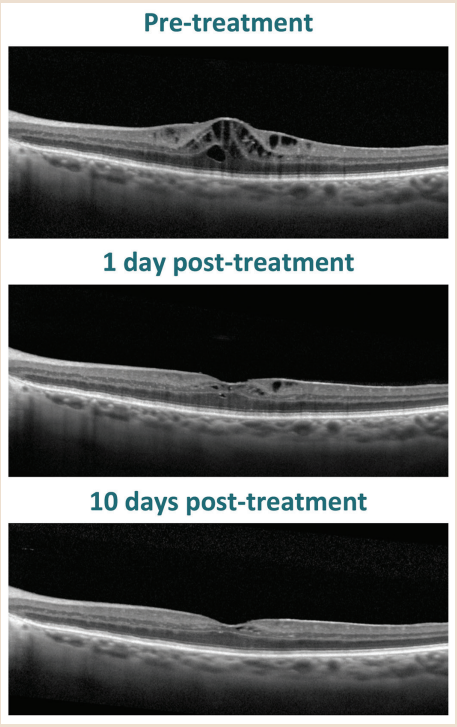
In this 78-year-old woman with chronic macular edema, a dexamethasone intravitreal implant was removed after its migration into the anterior chamber led to significant IOP increase and corneal edema.

Two subsequent monthly sub-Tenon injections of a triamcinolone 40 mg had little effect, and central macular thickness (CMT) remained at 551 µm.

A semiautomated ocular administration device was used to deliver triamcinolone 2.4 mg suspension to the suprachoroidal compartment.

The procedure was successful, with no hemorrhage or reflux, and CMT decreased to 344 µm after 10 days. At 20 days, CMT reductions were maintained, and the patient had gained around 4 lines of vision compared with baseline.





ADJUNCTIVE THERAPY

Corticosteroids have both antiinflammatory and antiedematous properties. They can help to address the pathogenesis of DME by limiting the permeability of the blood-retina barrier to reduce edema, downregulating VEGF expression, acting on inflammatory processes, and inhibiting prostaglandin and proinflammatory cytokine production.[14]

Sustained-release formulations of corticosteroids for DME offer a number of potential benefits. Less frequent administration reduces the patient's treatment burden, and consistent, gradual steroid release should reduce fluctuations in retinal thickness and maintain visual benefits.

Two sustained-release steroids are currently approved in the United States and Europe for use in patients with DME: the dexamethasone intravitreal implant 0.7 mg (Ozurdex, Allergan) and the fluocinolone acetonide intravitreal implant 0.19 mg (Iluvien, Alimera Sciences).

In phase 3 trials of the dexamethasone intravitreal implant, patients in the 0.7 mg treatment arm required a mean of 4.1 treatments during the 3-year study, and 22% achieved ≥ 15 letters in BCVA gains compared with 12% of patients treated with sham.[15] Patients receiving the implant also experienced a mean reduction in central retinal thickness of -111.6 µm from baseline compared with -41.9 µm in patients in the sham group.

However, rates of complications with the 0.7 mg implant were high: 68% of phakic patients had cataract-related adverse events versus 20% in the sham group, and more than 40% of treated patients required medication to control increases in IOP versus 9% in the sham group.[15] In addition, recurrence of edema has been reported 16 to 20 weeks after treatment in some patients.[16]

In clinical trials of the nonbiodegradable intravitreal fluocinolone acetonide implant, patients with persistent DME treated with a high-dose (0.5 µg/day) or low-dose (0.2 µg/day) implant were more likely to achieve a ≥ 15-letter BCVA improvement compared with those receiving sham treatment (29% and 28% versus 19%, respectively).[17] Approximately 70% to 75% of patients required only one treatment during the 3-year study.

However, among individuals who were phakic at baseline, 87% of high-dose patients required cataract surgery compared with 27% in the sham arm. Incisional glaucoma surgery was required in 4.8% of low-dose and 8.1% of high-dose patients.[17]

INNOVATIONS IN SUSTAINED RELEASE STEROIDS

The feasibility of using a suprachoroidal route of administration is currently being evaluated in trials of small molecules, biotherapeutics, and gene therapies for several ophthalmic indications (Figure).

With suprachoroidal delivery, studies show that the choroid, retinal pigment epithelium, and retina are targeted with high bioavailability while low levels of therapeutic agent are maintained elsewhere in the eye (eg, the vitreous or anterior chamber).[18,19]

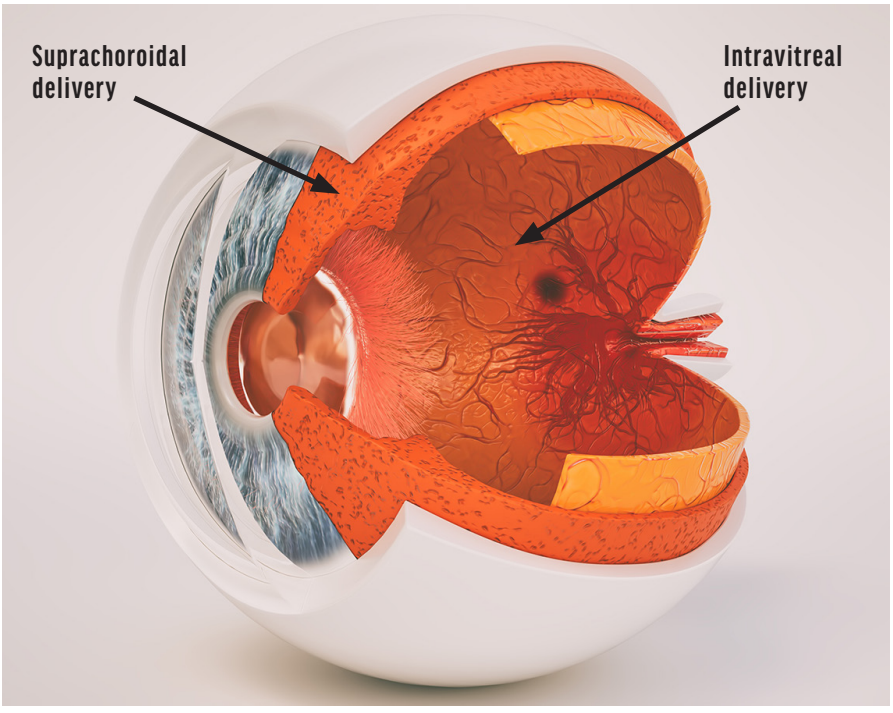


Figure. Suprachoroidal drug delivery may target the retina, choroid, and retinal pigment epithelium with high bioavailability.

OXU-001 (Oxular Limited) is a novel sustained-release steroid formulation of dexamethasone incorporated into biodegradable microspheres. Injected suprachoroidally, the microspheres are designed to deliver a precise daily amount of dexamethasone to retinal and choroidal tissues for up to 12 months.[20]

A preclinical study of suprachoroidal administration of OXU-001 in rabbits found that therapeutic levels of the drug were maintained for approximately 1 year.[20] Levels of steroid in the vitreous and lens throughout the study period were low, which the researchers suspect may translate into a favorable clinical safety profile.

In the clinic, OXU-001 is delivered using a semiautomated ocular administration device with a microcatheter to target the posterior suprachoroidal compartment. The catheter is injected at the pars plana and automatically deploys posteriorly upon reaching the suprachoroidal space. Illumination of the microcatheter provides transscleral visual confirmation of accurate location prior to drug delivery.

The developer is planning a phase 2 randomized clinical study of OXU-001 in patients with DME, to begin later this year. The study will compare suprachoroidally administered OXU-001 with the dexamethasone intravitreal implant.

CONCLUSION

Current anti-VEGF therapies for DME are effective but are associated with high treatment burdens for patients, caregivers, and retina specialists. Corticosteroids can provide benefit in DME due to their antiedematous and antiinflammatory effects, but current intravitreal steroids are limited by modest longevity and frequent adverse events. A novel suprachoroidal delivery option that permitted a yearly dosing regimen would be a welcome addition to our armamentarium for treatment of this growing patient population. ■

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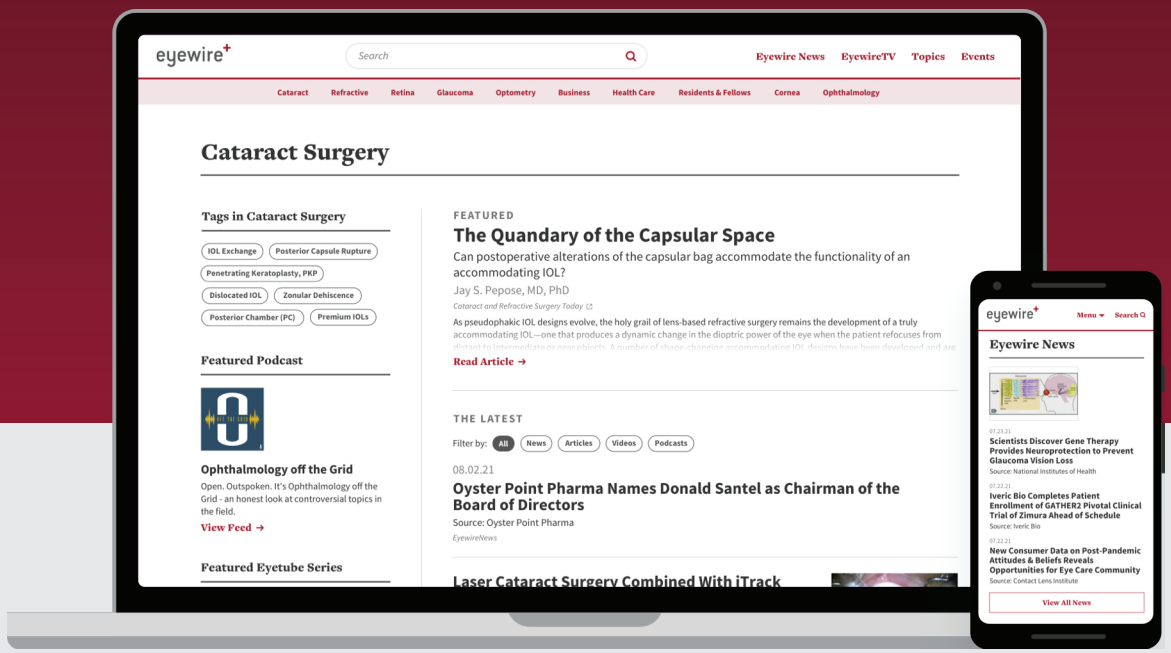

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The Role of Peripheral Imaging in Diabetic Retinopathy

Ultra-widefield technology is providing unprecedented views of the retina, allowing earlier diagnosis for patients with DR.

BY DAVID BOYER, MD

Imaging plays a critical role in the diagnosis and management of diabetic retinopathy (DR), and seven-standard-field (7SF) imaging, which captures 90° of the retina with a montage of seven 30° images, has long been the standard.[1] Advances in imaging have led to ultra-widefield (UWF) imaging technology, which can capture a high-resolution view of the posterior pole and peripheral retina in a single image. Depending on the platform used, up to 200° of the retina can be captured in a single image (Table).

UWF offers several advantages over 7SF: It allows clinicians to assess the retinal periphery for evidence of disease, and, in addition to color fundus photography, UWF platforms feature some combination of multimodal imaging, such as fluorescein angiography (FA), indocyanine green angiography, and fundus autofluorescence.

Because UWF technology collects data with a single capture and does not require dilation, patient discomfort is

AT A GLANCE

- Use of ultra-widefield (UWF) imaging in patients with diabetic retinopathy (DR) allows clinicians to detect intraretinal microvascular abnormalities and capillary nonperfusion, aiding early DR diagnosis.
- UWF imaging allows clinicians to image up to 200° of retinal anatomy in one capture.
- Recent studies have demonstrated a twofold increase in the rate of DR diagnosis with UWF and found that peripheral lesions were associated with a fourfold increase in risk of disease progression in patients with nonproliferative DR.

TABLE. ULTRA-WIDEFIELD IMAGING PLATFORMS AND FEATURES

Technology	Manufacturer	Field of View	Percentage of Retina**	Imaging Modalities
Optomap	Optos	200°	82%	Color, FAF, FA, ICGA
Spectralis	Heidelberg	150°*	63%	FA, ICGA
Clarus	Zeiss	133°	55%	Color, FAF, FA, ICGA
RetCam	Natus	130°	54%	Color, FA, ICGA

*Requires an optional add-on widefield angiography module.
**Based on total perfused retinal area of 1,200 mm².

Abbreviations: FAF, fundus autofluorescence; FA, fluorescein angiography; ICGA, indocyanine green angiography.
Adapted from: Patel SN, Shi A, Wibbelsman TD, Klufas MA. Ultra-widefield retinal imaging: an update on recent advances. *Ther Adv Ophthalmol*. 2020;12:2515841419899495.

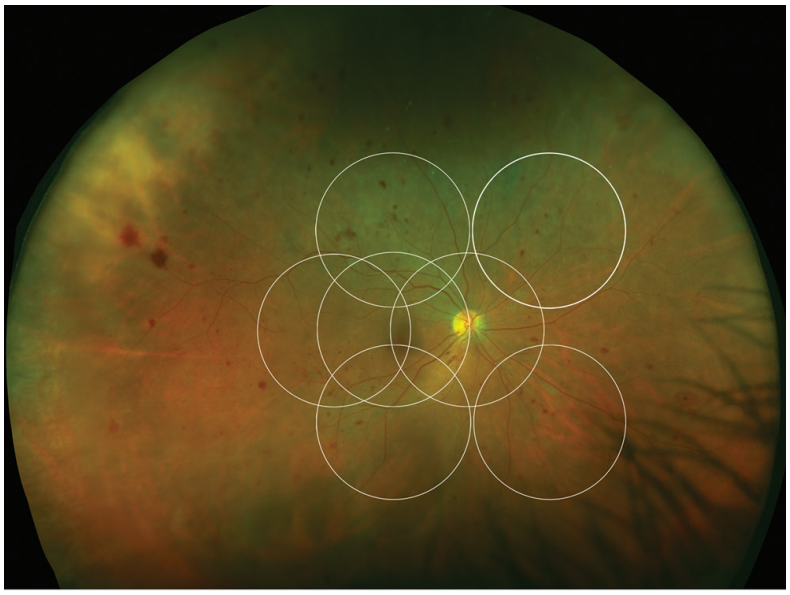

Figure 1. This UWF color fundus photograph of a patient with NPDR shows evidence of disease beyond the area seen in 7SF imaging. The white circles illustrate the area seen with 7SF imaging.

decreased and clinical efficiency is increased. In contrast, successful montage imaging of the 7SF (or a larger montage that results in a widefield image) requires patients to be compliant with multiple image captures and a skilled technician to edit the images into a single frame.

HOW UWF IMAGING AFFECTS DR DIAGNOSIS

Evidence of retinal capillary nonperfusion is a hallmark of DR. In some patients, atrophic retinal tissue falls within the area captured by the 7SF. In other patients, evidence of DR, including the presence of intraretinal microvascular abnormalities (IRMAs), is apparent only upon examination of the periphery (Figure 1). In these patients, UWF FA imaging can assist in early diagnosis of DR before the disease advances into the area captured by 7SF imaging.

Because it is difficult to predict which patients have peripheral ischemia, screening with UWF or UWF FA imaging is standard for most patients who present to my clinic with symptoms of DR or with long-standing diabetes, even if they have no visual complaints.

If I note IRMAs on UWF color imaging, I then consider performing UWF FA imaging (Figure 2), which helps me determine the severity of disease at diagnosis. The UWF FA is helpful in several ways: It establishes a baseline anatomy, it is useful as a teaching tool during patient education, and it helps me determine whether anti-VEGF therapy, laser photocoagulation, or observation may be the best course of treatment.

Given the invasive nature of angiography, I perform this test only when necessary and rarely more than once per patient. In some cases, however, capturing a second UWF FA image during the course of treatment is useful. For example, if a patient undergoing treatment for DR demonstrates evidence of continued leakage, UWF FA could reveal the source of that leakage, allowing me to adjust the treatment strategy.

Educating patients who do not have significant visual disruption is challenging but critical. When I show a UWF image with evidence of peripheral involvement and explain that the diseased area is likely to expand if the condition worsens, patients tend to understand their prognosis better and are more motivated to control their disease.

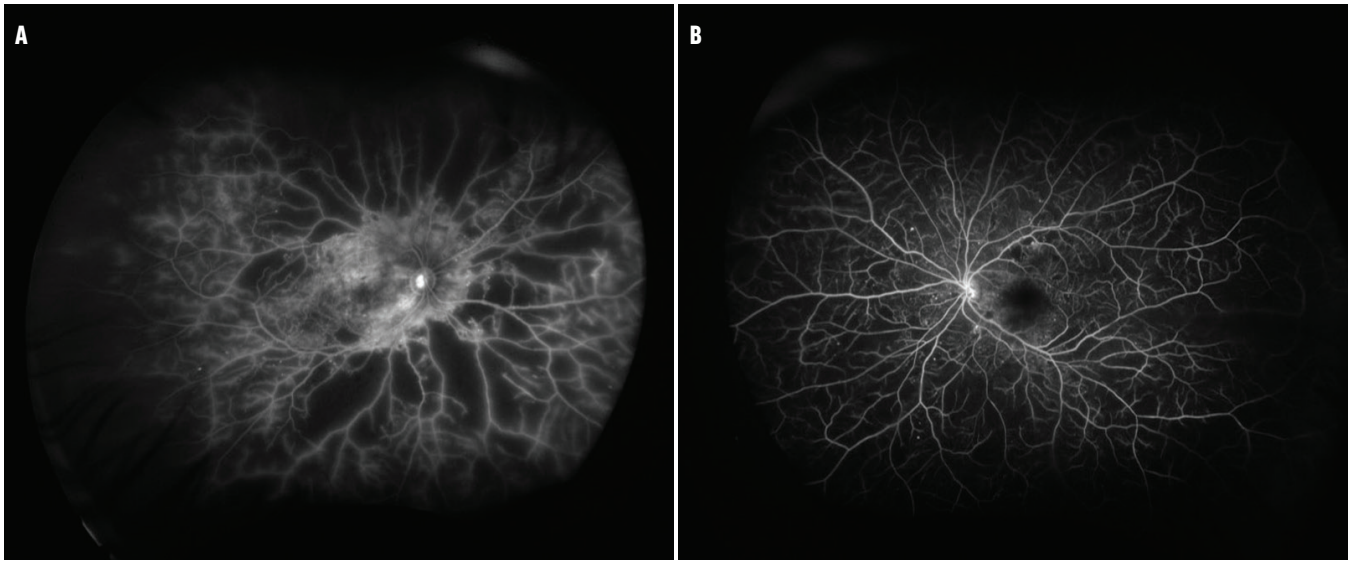

Figure 2. These UWF FA images of a patient with DR show evidence of peripheral activity in the right (A) and left eyes (B).

UPDATES FROM THE LITERATURE

Early diagnosis based on peripheral findings often allows more individualized treatment and monitoring, as just described. In addition, peripheral retinal findings can help to reveal risk of DR progression. Predominantly peripheral lesions in patients with DR have been linked with an increase in retinal nonperfusion area and worsening DR; they have also been associated with a more than fourfold increased risk of disease progression in 4 years in patients with nonproliferative DR (NPDR).[2,3]

Several peer-reviewed studies have documented substantial agreement between findings from 7SF and UWF color imaging.[2,4-6] These studies also found that 41% of imaged eyes had predominantly peripheral DR and that 11% were judged to have more severe disease when peripheral findings were considered.[2,5,6]

Additionally, a study comparing UWF FA and 7SF color fundus photography in patients with DR showed that UWF FA provided an extended view of the peripheral capillary network and that the area of peripheral capillary nonperfusion increased with DR severity.[7] This study also confirmed that use of UWF imaging resulted in a twofold increase in DR diagnosis.

THE FUTURE OF UWF IMAGING

UWF imaging allows doctors to identify disease before symptoms manifest. As artificial intelligence systems improve, developers may wish to leverage UWF images, as they offer the most data.

The more we learn about how peripheral findings impact disease progression in DR, the better we can equip ourselves to identify and treat the patients who are most at risk for vision loss. Clinicians who rely on UWF imaging today are using it to detect disease earlier, monitor at-risk patients more closely, and provide patient-specific care. ■

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(Continued from page 32)

Notably, 16.3% of eyes in the treatment group still developed either PDR or CI-DME with decreased vision. This suggests that, although preventive therapy works for most patients, some will still develop vision-threatening complications, reinforcing the need for regular visits and evaluation.

UNANSWERED QUESTIONS

Given the similar visual outcomes in the two Protocol W groups, many retina specialists may be unwilling to initiate prophylactic anti-VEGF injections in patients with no vision-threatening complications. In addition, longer-term outcomes remain unknown for patients receiving preventive aflibercept once they are switched to a prn regimen.

Studies using OCT angiography have demonstrated that anti-VEGF therapy does not appear to reverse nonperfusion or ischemia.[5] Patients enrolled in Protocol S required a mean of approximately three injections yearly even after 5 years of follow-up.[2] Therefore, although anti-VEGF injections can improve the clinical examination results in eyes with DR, the underlying pathology is likely to still exist, raising further questions: Will patients still require injections at 4 years? What percentage of patients will require continued injections? Will there be a rebound effect if preventive injections are stopped?

Protocol W's longer-term follow-up and 4-year results should help shed light on the answers to many of these questions. Stay tuned. ■

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Arshad M. Khanani, MD, MA, moderates a roundtable discussion with Christopher G. Fuller, MD; Nikolas J.S. London, MD, FACS; and Christina Y. Weng, MD, MBA, that addresses the modern challenges of wet AMD management. Dr. Khanani and the roundtable participants address questions of real-world safety, summarize late-phase and early-phase clinical trial data, and share cases of challenging patients.

Although vitreous opacities or floaters symptoms are minimal in most patients, they can cause significant impairment in vision-related quality of life in some patients. This panel discussion provides an overview of symptomatic vitreous opacities and their treatment options, discusses best practices in patient identification for surgical treatment, reviews surgical pearls for vitrectomies and the role of laser treatment, and provides clarity around the treatment approach to optimize outcomes.

Carl Regillo, MD, moderates a roundtable discussion with Caroline Baumal, MD; Usha Chakravarthy, MD, PhD, CBE; and Rishi Singh, MD; that addresses the modern challenges of treatment adherence in patients with neovascular AMD. Dr. Regillo and the roundtable participants address questions of real-world safety, summarize late-phase and early-phase clinical trial data, and share cases of challenging patients.

Detection of Diabetic Retinopathy Using Deep Learning Analysis

Telemedicine may be able to help catch this condition early and prevent progression.

BY MATIAS IGLICKI, MD, PHD; DINAH ZUR, MD; AND ANAT LOEWENSTEIN, MD, MHA

Diabetic retinopathy (DR) is the most frequent cause of blindness in working-age adults in industrialized countries, and its incidence continues to increase.[1] Diabetes affects at least 7% of the adult population, and researchers project that the prevalence will double in the coming decades.[2,3]

Prompt treatment of DR can prevent blindness in more than 90% of cases, but the right treatment depends on a timely diagnosis, and that continues to be a challenge worldwide.[4]

Researchers estimate that as many as half of all patients with diabetes remain undiagnosed.[5] In many cases the diagnosis is made only with the onset of complications.

Regular ophthalmic examinations for patients with diabetes are crucial to detect the earliest signs of DR and begin prompt treatment. However, a multitude of barriers keeps many of these patients from receiving the care they need to reduce the risk of blindness, including a lack of qualified ophthalmologists.

Thus, researchers and clinicians alike have been exploring tools that can facilitate ophthalmic examinations in underserved regions. The utility of telemedicine to screen for referrable and vision-threatening DR remains under investigation, mainly in developed countries. We wished to explore the feasibility of using a telemedicine screening platform to detect DR in patients in developing nations.

With advances in digital image processing and communications, we believe telemedicine can become a viable screening tool for patients at risk for developing DR, no matter their location.

EARLY SUCCESS

We recently participated in a study led by Fangyao Tang, PhD; Rajiv Raman, MS, FRCS; Carol Cheung, PhD; and Sobha Sivaprasad, MBBS, MS, DM, FRCOphth, FRCS. The team created a telemedicine platform that uses deep learning (DL) to detect referable and vision-threatening DR based on ultra-widefield scanning laser ophthalmoscope

AT A GLANCE

- With advances in digital image processing and communications, the authors believe telemedicine can become a viable screening tool for patients at risk for developing diabetic retinopathy (DR).
- A deep-learning telemedicine platform designed by the authors achieved statistically significant sensitivities, specificities, and positive predictive values for both referrable and vision-threatening DR.
- A follow-up study is planned to further assess the system's ability to automatically detect hard exudates and hemorrhages compared with traditional examination techniques.

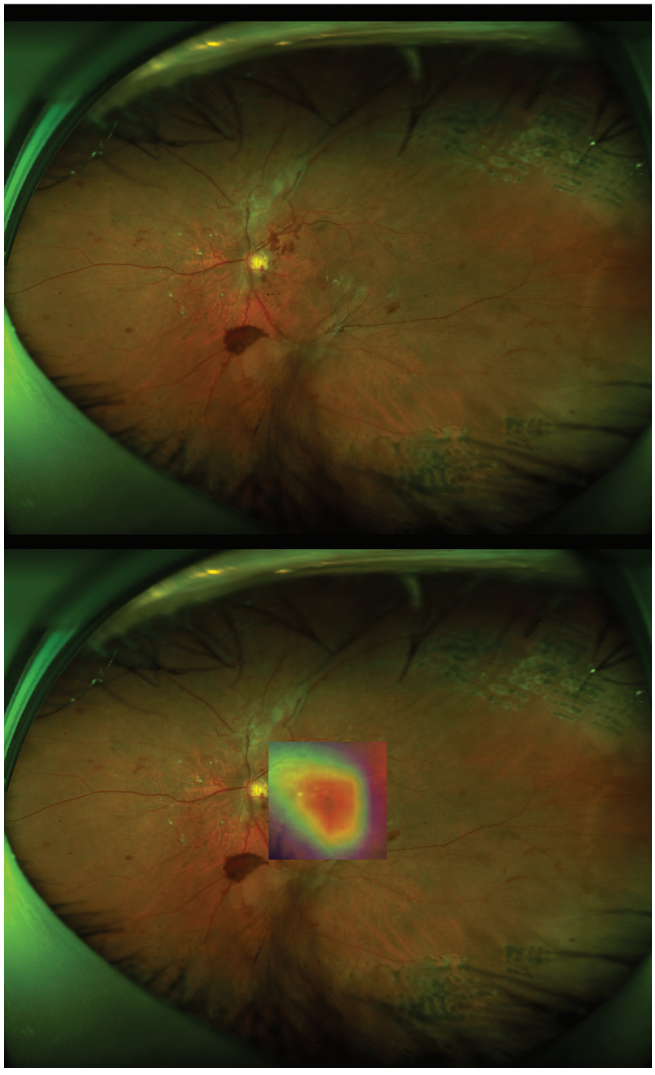

Figure. Using ultra-widefield scanning laser ophthalmoscope images, deep-learning tools can detect diabetic retinopathy. In the bottom image, orange-red indicates a relatively high discriminative power, whereas green-blue indicates a relatively low discriminative power.

(UWF-SLO) images.[6] In this study we collected 9,392 UWF-SLO images of 1,903 eyes of diabetic patients to assess the DL system's ability to grade images and detect referable and vision-threatening DR (Figure). Retina specialists determined the presence or absence of referrable or vision-threatening DR based on the International Clinical Diabetic Retinopathy Disease Severity Scale. The system was then trained to grade and detect signs of DR and then tested via external validation on four different datasets.

For gradeability, the system demonstrated a sensitivity of 86.5% and specificity of 82.1% for the primary validation dataset and > 79.6% sensitivity and > 70.4% specificity for the external validation datasets. As for DR detection in the primary validation dataset, the DL system achieved sensitivities of 94.9% and 87.2%, specificities of 95.1% and 95.8%, and positive predictive values of 98.0% and 91.1% for referrable and vision-threatening DR, respectively.[6]

We concluded that our DL system could be an efficient and effective tool to screen UWF-SLO images for signs of referrable and vision-threatening DR.

NEXT STEPS

Such positive findings led us to plan further studies within a private retina practice in Buenos Aires, Argentina, affiliated with the University of Buenos Aires, and Tel Aviv Sourasky Medical Center. These affiliates will serve as reading centers for images captured by general practitioners caring for patients in areas with no access to specialized ophthalmic care.

During a single visit, asymptomatic patients will undergo a multidisciplinary examination to confirm the diagnosis and clinical staging of diabetes. General practitioners will obtain widefield retinal images during visits and send these images to the reading centers to form the dataset. We plan to enroll approximately 200 patients with diabetes either with (study group) or without (control group) signs of retinal complications. For the study group, any patient with the presence of significant media opacities, with any signs of another eye disease (eg, glaucoma, cataracts), or with previous treatment for DR will be excluded. Those in the control group cannot have any signs of DR, as well as significant media opacities or another eye disease (eg, glaucoma, cataracts).

Using this dataset, we will assess our DL system's ability to automatically detect hard exudates and hemorrhages—the initial signs of DR—compared with traditional examination techniques.

We will analyze the images manually, then implement a DL algorithm to locate basic elements of the retina and the optic disc for the identification of false positives and for the classification of pathologies according to their severity and the measurement of lesions—often a time-consuming task for clinicians.[7-15] The system will further detect microaneurysms, hard exudates, and hemorrhages.[8,10,11,16-23]

To avoid discarding low-resolution images, we plan to develop techniques to improve contrast and reduce noise; this will help specialists better interpret the images and allow them to be included in the automated analysis. Contrast enhancement techniques and restoration algorithms have been used to improve poor quality images, usually due to cataracts.[24,25] We hope to implement this study at multiple sites around the world, similar to the study previously mentioned.[6]

FUTURE ASPIRATIONS

If this DL system proves to be as useful in this real-world setting as it was in our initial study, we hope to eventually use it to provide fully automated detection of DR for those most in need. ■

(Continued on page 46)

CHOROIDAL NEVUS: GROWTH WITHOUT TRANSFORMATION


One case illustrates how slow enlargement over time doesn't necessarily mean the patient has melanoma.

BY ANNIKA G. SAMUELSON, BS, AND CAROL L. SHIELDS, MD

In the United States, choroidal nevus—a stable, melanocytic tumor—is found in up to 6.5% of the White population, 0.6% of the Black population, and 2.7% of the Hispanic population.[1,2] Choroidal nevi can grow into melanoma, or they can enlarge slowly over a long period of time without melanoma transformation.[3]

Although choroidal nevi can affect vision, most are asymptomatic with little impact on visual function or refractive error. Shields et al evaluated a cohort of 3,422 consecutive eyes with choroidal nevi, categorized as either subfoveal or extrafoveal, and found that the median VA at presentation was 20/20 in both cohorts. However, at the 15-year follow-up, vision loss of ≥ 3 logMAR lines of vision was observed in 26% of eyes with subfoveal tumors compared with only 2% of eyes with extrafoveal tumors.[4] Vision loss due to a subfoveal choroidal nevus is most often related to tumor-induced retinal pigment epithelial (RPE) alterations (especially RPE detachment), lipofuscin pigment, and foveal edema.[4]

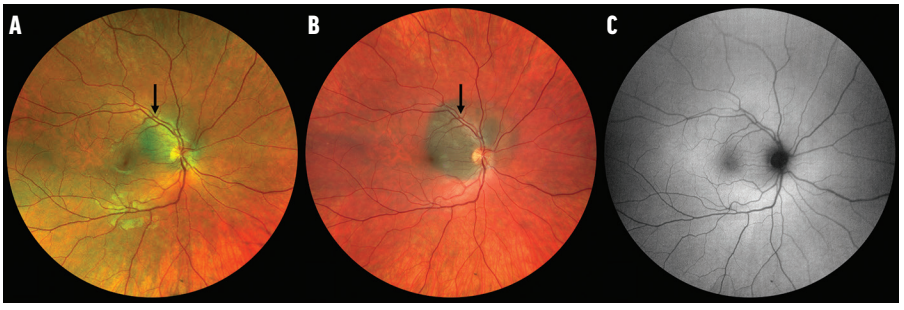

Figure 1. Wide-angle photography of the right eye shows a pigmented juxtapapillary choroidal nevus (arrow, A). Four years later, wide-angle photography reveals enlargement of the choroidal nevus (arrow denoting original margin, B) and fundus autofluorescence demonstrates absence of orange pigment or subretinal fluid (C).

Regarding progression to melanoma, Qiu and Shields used the US National Health and Nutrition Examination Survey to identify 5,575 participants 40 years or older and found no association between choroidal nevus and skin melanoma; however, there was a relationship with uveal melanoma.[2] Singh et al retrospectively estimated that one in 8,845 choroidal nevi demonstrated evolution into choroidal melanoma, presuming that all melanoma arises from a nevus.[5] Shields et al longitudinally studied the growth of choroidal nevi into melanoma and found that growth occurred in 2% at 1 year, 9% at 5 years, and 13% at 10 years.[6] Shields and colleagues subsequently identified objective criteria, based on multimodal imaging, to identify at-risk nevi for early treatment.[7]

Choroidal nevi that slowly enlarge without progressing to melanoma are poorly understood. Growth of a choroidal nevus has been considered a key determining feature suggestive of melanoma transformation.[8] However, recent literature shows that some choroidal nevi can enlarge slowly during a patient's younger years and thereafter remain stable.[9] Here we describe a case of slow enlargement of a benign choroidal nevus. Importantly, this case emphasizes that slow nevus growth in the absence of risk factors can represent benign enlargement, especially in young patients.

CASE REPORT

A 28-year-old White woman was diagnosed, using wide-angle imaging, with a choroidal nevus 4 years prior to presentation to our clinic (Figure 1A). The nevus was monitored annually and remained stable for 3 years, according to the referring physician. However, in year 4, enlargement was noted, and the patient was referred for our opinion. Medical and ocular history were noncontributory. Family history revealed cutaneous melanoma in a paternal grandparent.

On examination, BCVA was 20/20 OU. The pupils, IOP, and anterior segment findings were within normal limits in each eye. The left fundus was unremarkable. The right fundus revealed a juxtapapillary pigmented choroidal mass measuring 7 mm in basal diameter, appearing approximately 1 mm larger than was documented 4 years prior (Figure 1B). Fundus autofluorescence (FAF) showed no areas of orange

pigment or subretinal fluid (Figure 1C). Ultrasonography demonstrated a flat, dense choroidal mass with a thickness of 1.83 mm (Figure 2A). OCT showed an intact retina with no subretinal fluid (Figure 2B). Multimodal imaging revealed only one risk factor: diameter > 5 mm. A diagnosis of benign, slow enlargement of choroidal nevus was made, and observation was recommended.

DISCUSSION

Evaluation and imaging are important steps to determine if a choroidal nevus is at risk for progression into melanoma. There are six important risk factors related to the transformation of a choroidal nevus into melanoma, remembered by the mnemonic *to find small ocular melanoma doing imaging* (TFSOM-DIM), which represents **T**hickness > 2.0 mm on ultrasonography, **F**luid (subretinal) on OCT, **S**ymptoms (VA ≤ 20/50) on Snellen acuity, **O**range pigment on FAF, **M**elanoma acoustic hollowness on ultrasonography, and **DIaM**eter > 5.0 mm on fundus photography (Table 1).[7] Each of these risk factors is identified by imaging or visual acuity testing using objective criteria.

In this patient, all imaging risk factors were absent except for nevus diameter > 5.0 mm. Based on the mean 5-year estimates, patients with one risk factor have an overall 11% rate of growth into melanoma.[7] Furthermore, tumor diameter > 5.0 mm was found to be the weakest risk factor (P = .0275; hazard ratio, 1.84).[7] Thus, cautious observation was advised for our patient with the intent to treat if further growth or development of other factors was observed.

Choroidal nevus with growth into melanoma tends to occur with a mean 1.0 mm/year diameter growth rate and 0.5 mm/year increase in thickness, often with development of other features such as subretinal fluid (63%), orange pigment (40%), and acoustic hollowness (30%).[7] Benign choroidal nevus enlargement, however, is a relatively slow process with a mean diameter increase of only 0.06 mm/year.[9] In a study of 284 choroidal nevi, researchers observed 31% of the nevi with very slow enlargement on follow-up over a mean 15 years.[9] Enlargement was inversely related to age, with 54% of nevus growth observed in patients < 40 years, 34% in patients

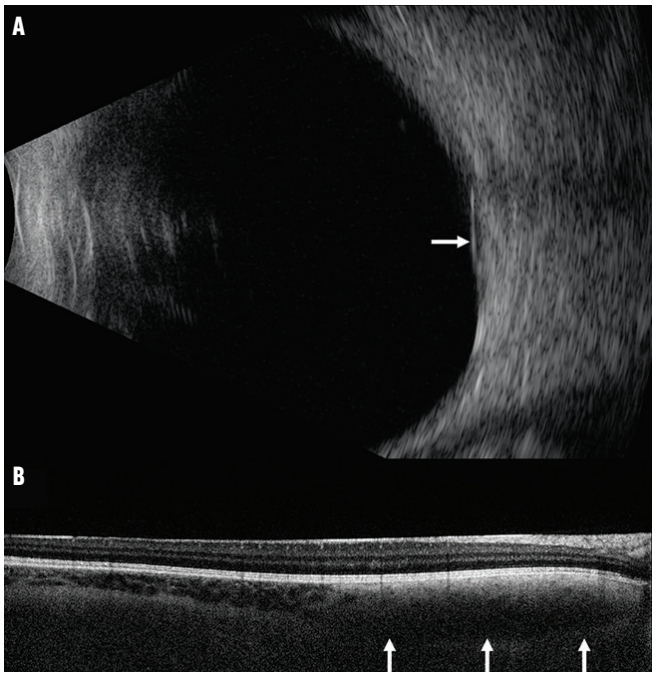

Figure 2. Ultrasonography of the right eye shows a flat, dense choroidal mass with thickness of 1.83 mm (arrow, A). OCT shows an intact retina with no subretinal fluid and the deep choroidal mass with loss of vascular markings (arrows, B).

TABLE. CHOROIDAL NEVUS TRANSFORMATION INTO MELANOMA IN 2,355 CASES

Variable	Letter(s)	Mnemonic	Representation	Hazard ratio (95% CI) by multivariable analysis	*P* value
Tumor thickness: > 2 mm vs ≤ 2 mm	T	**T**o	Thickness > 2 mm by ultrasonography	3.80 (2.22–6.51)	< .0001
Fluid subretinal: Cap vs none ≤ 3 mm from nevus vs none	F	**F**ind	Subretinal fluid by OCT	3.00 (1.77–5.09) 3.56 (1.78–7.12)	< .0001 .0003
Symptoms: visual acuity loss 20/50 or worse vs better	S	**S**mall	Symptoms, vision loss by Snellen	2.28 (1.28–4.04)	.0050
Orange pigment: present vs absent	O	**O**cular	Orange pigment by fundus autofluorescence	3.07 (1.65–5.74)	.0004
Melanoma acoustic density: hollow vs solid	M	**M**elanoma	Melanoma hollow by ultrasonography	2.10 (1.31–3.37)	.0020
Tumor diameter: > 5 mm vs ≤ 5 mm	DIM	**D**oing **IM**aging	Diameter by photography	1.84 (1.07–3.17)	.0275

Adapted from: Shields CL, Dalvin LA, Ancona-Lezama D, et al. Choroidal nevus imaging features in 3,806 cases and risk factors for transformation into melanoma in 2,355 cases: The 2020 Taylor R. Smith and Victor T. Curtin Lecture. *Retina*. 2019;39(10):1840-1851.

between 41 and 60 years, and 19% in patients > 60 years.[9]

We speculate that benign nevus enlargement may be more common in young adults. Most notably, patients with slow enlargement of choroidal nevus demonstrate further stability without the development of melanoma features over a mean follow-up of 15 years.[9]

In this case, the patient had only one risk factor, a basal diameter of 7 mm, with slow nevus enlargement of approximately 0.25 mm/year. Although this is faster than most nevi enlargement, it is slower than melanoma growth. Thus, we recommended cautious observation with long-term follow-up. This case highlights that slow growth of choroidal nevus, especially in young patients, is not a definitive sign of melanoma transformation.

Clinicians must assess all six risk factors of choroidal nevus when making a judgement regarding the potential for future growth, keeping in mind that a subset of patients might show slow enlargement of nevus without risk factors and without transformation into melanoma. For those patients, observation may be a suitable management option. ■

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(Continued from page 43)

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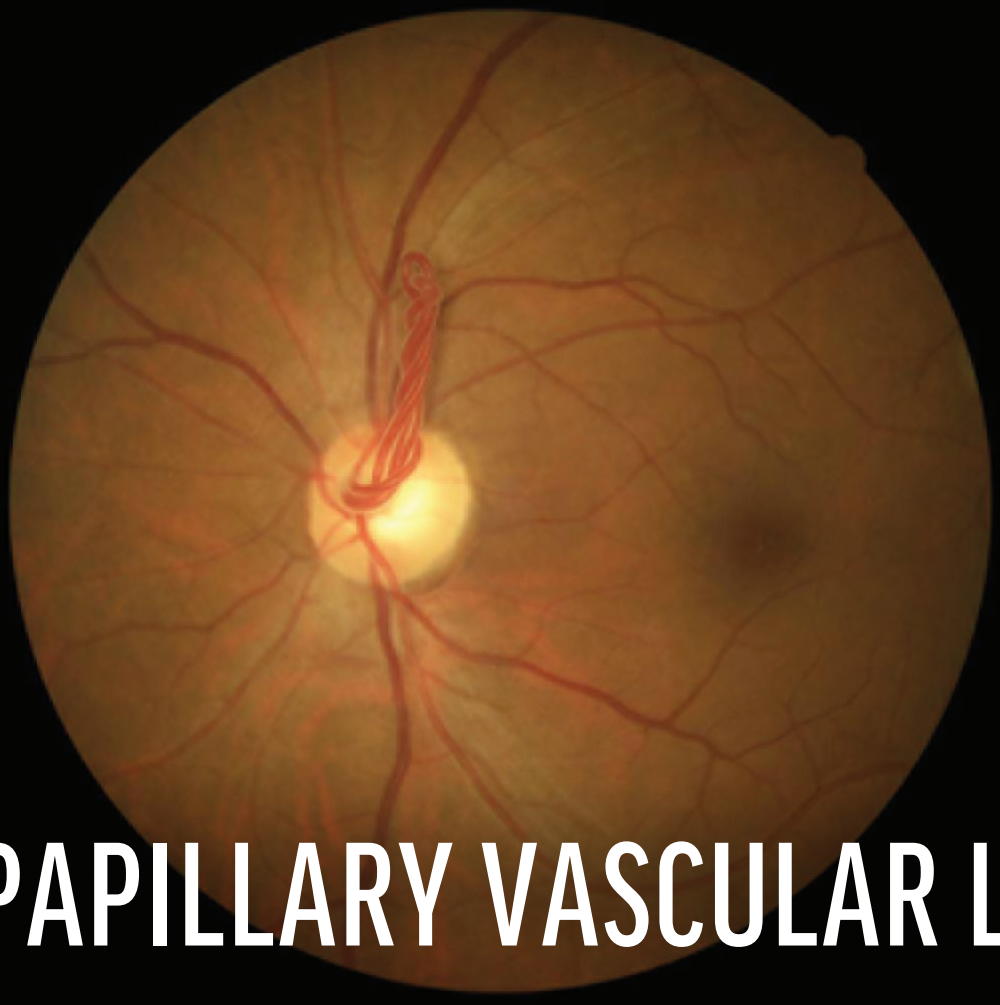

PREPAPILLARY VASCULAR LOOP

A rare congenital anomaly.

BY REHAN M. HUSSAIN, MD

A 70-year-old Black man with a history of hypertension and hyperlipidemia was referred for a vascular lesion on the optic nerve of the left eye. He was asymptomatic, with VA of 20/20 OD and 20/25 OS. The anterior segment was unremarkable in each eye. Fundus examination in the left eye revealed a prepapillary vascular loop without any abnormalities in the macula or peripheral retina (Main Figure). Fundus examination in the right eye was unremarkable.

DISCUSSION

Prepapillary vascular loop is a congenital anomaly of the optic disc that presents as an elevated and twisted bundle of vessels projecting into the vitreous cavity. It is rare, with estimated incidence ranging from one in 2,000 to one in 9,000 eyes, although those numbers may be underestimated given that it is asymptomatic in most cases and is usually detected on routine fundus examination.[1,2]

Prepapillary vascular loops have rare association with branch retinal artery occlusion, amaurosis fugax, retinal microaneurysm, recurrent vitreous hemorrhage, subretinal hemorrhage, and hyphema.[3] In asymptomatic cases such as this one, observation is recommended. ■

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If you have an image or images you would like to share, email Manish Nagpal, MBBS, MS, FRCS, Section Editor, at drmanishnagpal@yahoo.com.

THE 2021 VIT-BUCKLE SOCIETY: THE FORCE AWAKENS

Key takeaways from Episode I.

BY MATTHEW R. STARR, MD

The theme of this year's Vit-Buckle Society (VBS) Annual Meeting, The Force Awakens, was a play on the Star Wars movie series. Virtual Episode I of the meeting, held in April, comprised a lineup of intergalactic retina superstars. The speakers fully committed to the other-worldly theme, as the President of VBS, Charles C. Wykoff, MD, PhD, opened the meeting costumed as Chewbacca—and even let out a primitive yell periodically.

Joking aside, Episode I of this year's meeting was packed with great lectures and panels. New this year were watch parties held in New York and Miami, with participants offering comments and insights throughout the meeting.

MANAGEMENT OF SECONDARY IOLS

The meeting kicked off with a panel of experts that included María H. Berrocal, MD; Joseph M. Coney, MD; Ninel Z. Gregori, MD; and Katherine Talcott, MD. They discussed the pros and cons of different approaches to managing secondary IOLs including PTFE (Gore-Tex, W.L. Gore) suture fixation, modified Yamane techniques, iris fixation, and anterior chamber IOLs.

Dr. Gregori shared her expertise with iris-fixated IOLs. She described her technique that involves the placement of two polypropylene (Prolene, Ethicon) sutures around each IOL haptic and positioning the optic above the plane of the iris to facilitate visualization of the haptics. This then enables her to easily visualize the trajectory of the needle through the iris and around the haptic.

After sharing their various techniques and surgical tips, the speakers concluded that vitreoretinal surgeons should be familiar with each technique as they all may come in handy in the management of specific patients.

Dr. Gregori shared a final pearl of advice for the audience: Advise patients to avoid eye rubbing postoperatively, which can lead to iris chafing or IOL dislocation.

An audience poll showed that most of the attendees reported performing scleral-fixated secondary IOL placement, with scleral suturing a close second.

SURGICAL MANAGEMENT OF MEDICAL RETINA

Lejla Vajzovic, MD, delivered an excellent talk regarding the surgical management of medical retina, namely implantation of the Port Delivery System (PDS, Genentech) for delivery of anti-VEGF medication. As the PDS continues through clinical trials, compelling data is accumulating suggesting that this system will offer safe, sustained delivery of an anti-VEGF agent to the posterior segment. As with any new technology, the risks must be weighed, but the PDS may become an option for selected patients who wish to reduce their treatment burden.

SURGICAL VIDEOS

The meeting continued with surgical videos from Matthew A. Cunningham, MD; Kristen Harris-Nwanyanwu, MD, MBA; Marianeli Rodriguez, MD, PhD; and Yewlin E. Chee, MD. Keeping with the Star Wars theme, the videos focused on the membranous forces of the Dark Side, the enemy of all vitreoretinal surgeons.

The winner of the video competition was Dr. Chee with an incredible video of a sclopetaria-related tractional retinal detachment from preretinal and subretinal membranes. Her video showed the use of indocyanine green dye to stain the internal limiting membrane. She then used this as a plane to remove the preretinal membranes as they dove subretinally, treading carefully and segmenting the bands at these junctures. By relieving the preretinal forces while carefully leaving the intraretinal and subretinal fibrotic membranes undisturbed, she allowed the retina to settle and flatten quite nicely.

SURGICAL MANAGEMENT OF UVEITIS PATIENTS

Lisa J. Faia, MD, discussed the surgical management of patients with uveitis. Her most important take-home point was that the disease must be quiescent for a minimum of 3 months before surgery. These patients can still benefit from vitreoretinal surgery (epiretinal membrane removal, etc.), and the surgery can still be successful.

Once the inflammation has been under control for 3 months, the patient's baseline therapy should be increased perioperatively. This may be as simple as increasing the frequency of topical drops or adding oral or intravenous steroids depending on the level of preoperative immunosuppression. In performing retinal detachment repair in these patients, she said, peel, peel, and peel some more when handling membranes. An interesting pearl from Dr. Faia was the possibility of using a viscoelastic material in funnel retinal detachments. It works as well as perfluoro-n-octane to stabilize the retina, she said, and is perhaps even more stable for handling those tricky funnels.

DIVERSITY, EQUITY, AND INCLUSION

Perhaps the most important session of the meeting was one devoted to diversity, equity, and inclusion, led by Basil K. Williams, MD. Dr. Williams was joined by Jessica D. Randolph, MD, and Reginald J. Sanders, MD, and the panel was moderated by Aleksandra Rachitskaya, MD; Priya Sharma Vakharia, MD; and Dr. Williams.

At a time when the nation is undergoing critical dialogue on race and diversity outside of medicine, Dr. Williams led a discussion on this topic within ophthalmology and retina. He reported that underrepresented minorities represent only 7% of all ophthalmologists. Dr. Sanders offered remarkable insights on diversity, noting that increased diversity leads to innovation and improved care. Dr. Williams referenced the March 2021 *Retina Today* article "Managing Microaggressions in Practice," by Nathan L. Scott, MD, MPP, and Hasenin Al-khersan, MD, in which the authors describe challenges they have faced during their careers surrounding race and inclusion, as well as microaggressions they encountered during training. The article describes the inherent biases and challenges trainees from underrepresented minorities face and references the ongoing dialogue regarding how to improve diversity within ophthalmology.

The VBS panel members then discussed their own efforts to mitigate this racial inequality gap and to increase diversity within ophthalmology, with the message that the key to doing so is mentorship. Providing trainees with mentors who will advocate for and educate them will pave the way toward improving diversity and inclusion, participants said. Professional societies may be able to supply the framework to facilitate these relationships, and, through sessions such as this one, VBS is doing its part to change the landscape within retina and ophthalmology. ■

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MATIAS IGLICKI, MD, PHD

What led you to choose retina as a specialty?

My priority is my patients and how to improve their quality of life. My mission is to help solve unmet needs of the retinal diseases that lead to blindness around the world, such as macular edema, diabetic retinopathy, retinal vascular disorders, AMD, etc.

You were instrumental in the creation of the International Retina Group (IRG). Can you tell us about the goals of this organization?

I am flattered, delighted, and grateful to be part of the IRG, a program for young retina specialists with research interests. The IRG is a collaborative network of 25 members from 14 countries—12 retina surgeons and 13 medical retina specialists with expertise in uveitis, imaging, and epidemiology. Our aims are to deliver educational and scientific value to our delegates, to give them opportunities to develop their own personal skills, and to build an international collaborative research network with colleagues from other countries.

The IRG operates without private funding. Our focus is on improving patients' lives, not our own careers. If we could offer advice to other researchers hoping to do something similar, let it be this: Don't do research for research's sake, do it for a purpose. Believe that what you are doing matters, and have a mentor. I am more than grateful to have Anat Loewenstein, MD, MHA, as our mentor and Dinah Zur, MD, as a coauthor. Without them our achievements would not have been possible.

In 2019, you received the ICO-Allergan Advanced Research Fellowship Award for your work in early diagnosis of diabetic retinopathy lesions using telemedicine. What interested you in this topic?

Diabetic retinopathy is the most frequent cause of blindness in young adults in industrialized countries and one of the most serious complications of diabetes. The diabetic pandemic now affects 7% of the adult population, a prevalence that promises to double in the coming decades.

Because of the importance of timely diagnosis and follow-up in the prevention of blindness due to diabetic eye disease, it would be useful to develop tools that allow retinal examinations in individuals with diabetes in situations where examination by a qualified professional is not possible. There are few, if any, telemedicine programs in developing countries. Our project will be the first of its type, opening a huge potential market that has not yet been explored.

The objective of our project, led by myself and Dr. Zur with the academic and wisdom support from Dr. Loewenstein, is to offer our network telemedicine service to health insurance companies and governments in developing countries. Our pitch is that prevention of complications of diabetic retinopathy through early diagnosis using screening examinations can save costs and reduce the need for advanced treatments and surgeries.

Dr. Iglicki and the other members of the International Retina Group enjoying a nice time with mentors Anat Loewenstein, MD, MHA, and Jay Ambati, MD.

What advice would you give to young ophthalmologists interested in research in retina?

Focus on your research initiatives. Choose a mentor who can guide and support you. Get feedback on educational programs in your field. Put your skills into action by participating in workshops on presentations, speaker training, and media training. Find colleagues who are as enthusiastic as you are, whom you trust, and with whom you can share your ideas, concerns, and unanswered questions. Most important, do what you love and love what you do.

What is an interesting fact that most people might not know about you?

I love playing the violin and listening to classical music. I went to the Superior Conservatory of Music "Manuel de Falla," where I learned not only how to read music but also how to play the violin. That's where I completed my degree as a master of music with specialty in violin. ■

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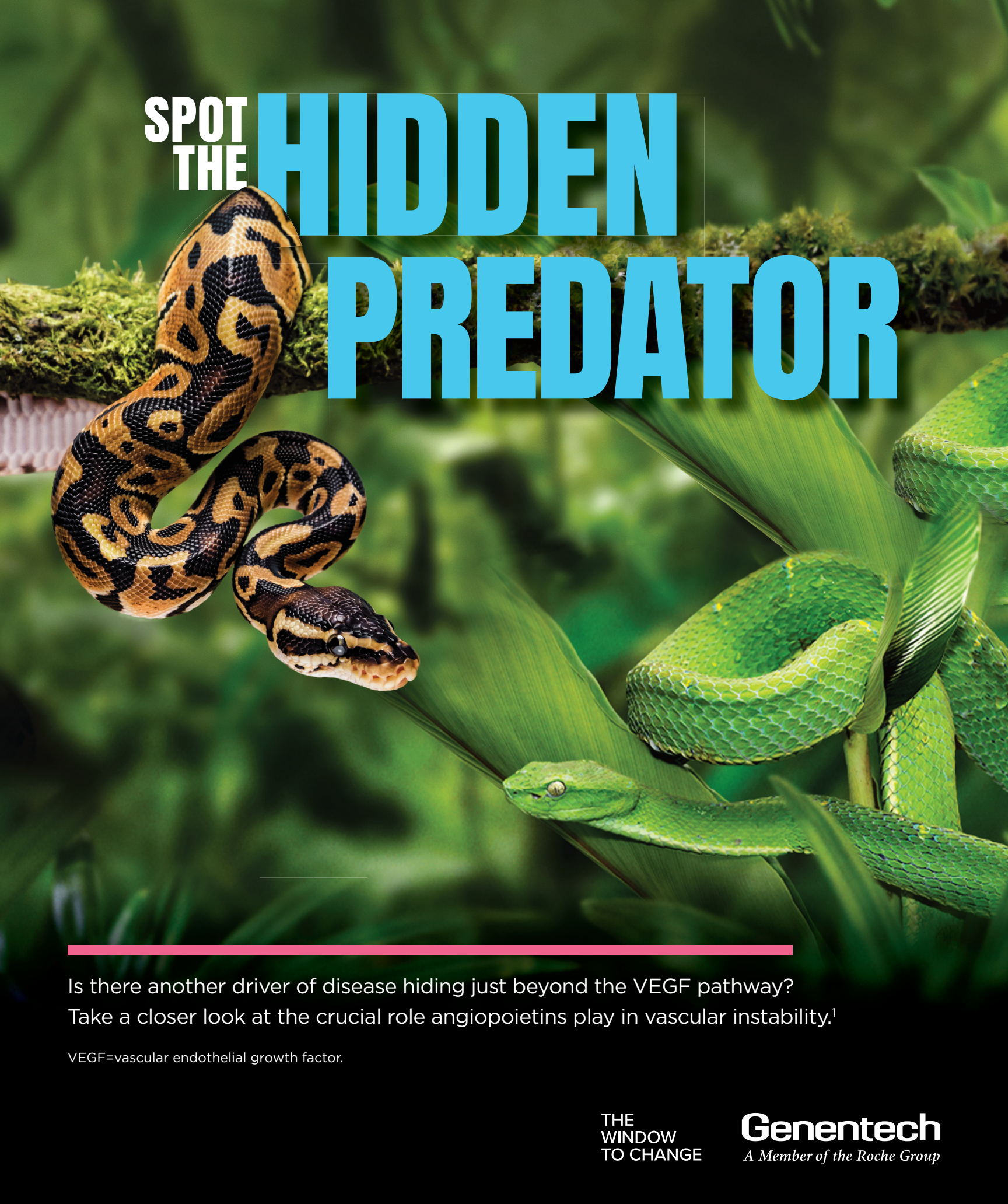

Is there another driver of disease hiding just beyond the VEGF pathway? Take a closer look at the crucial role angiopoietins play in vascular instability.[1]

VEGF=vascular endothelial growth factor.

THE WINDOW TO CHANGE

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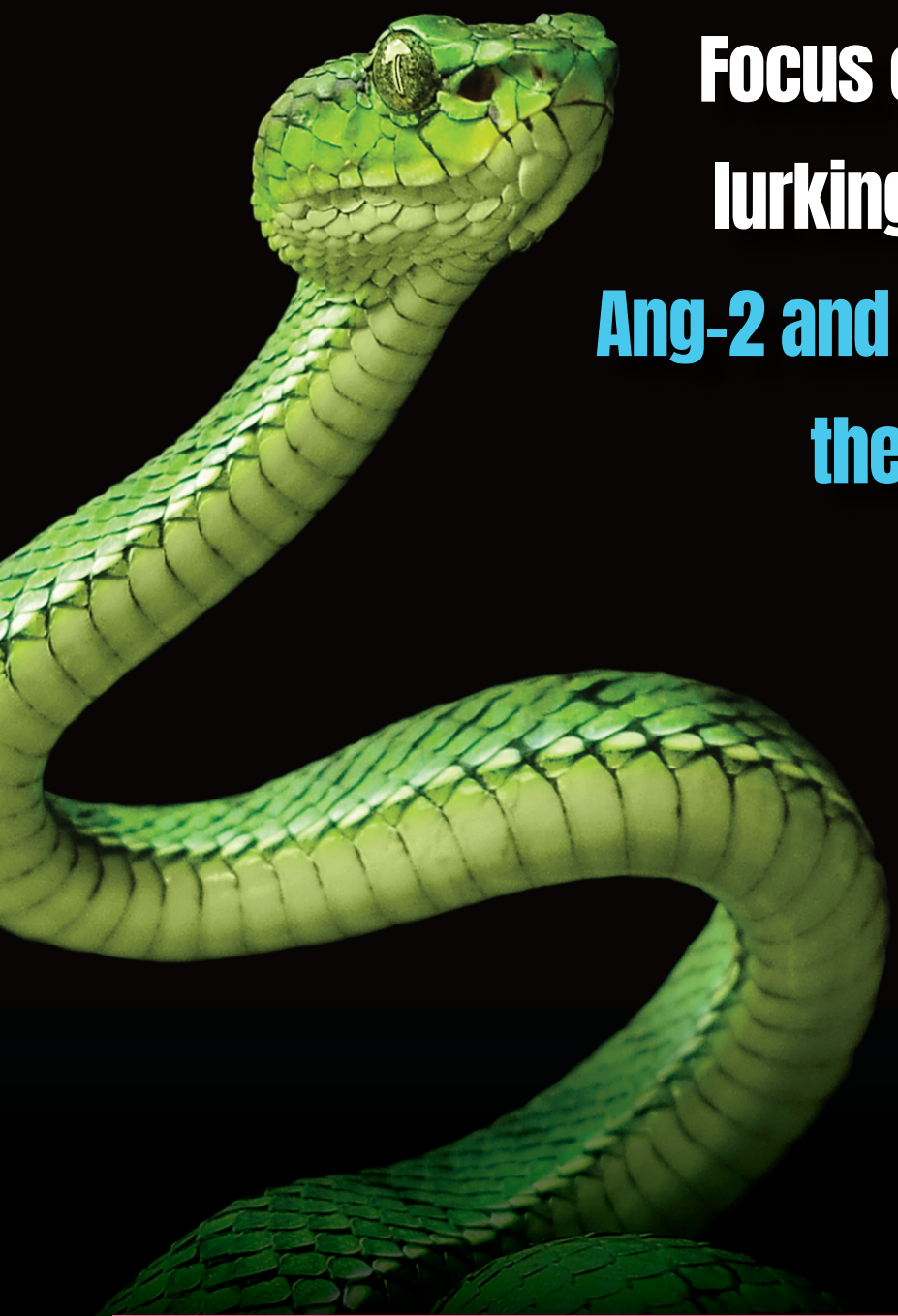

Focus on the threat that's lurking in nAMD and DME:

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Ang-2=angiopoietin-2; Ang-Tie=angiopoietin/Tie; DME=diabetic macular edema; nAMD=neovascular age-related macular degeneration.

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