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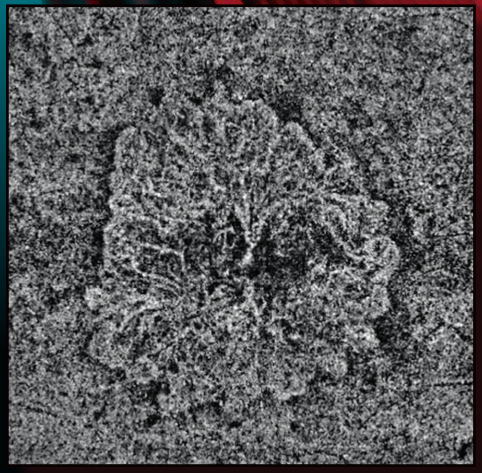
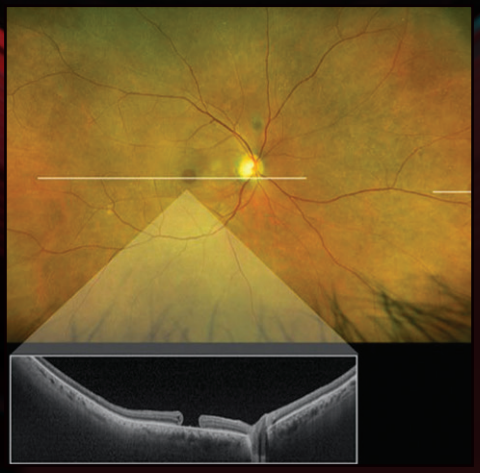
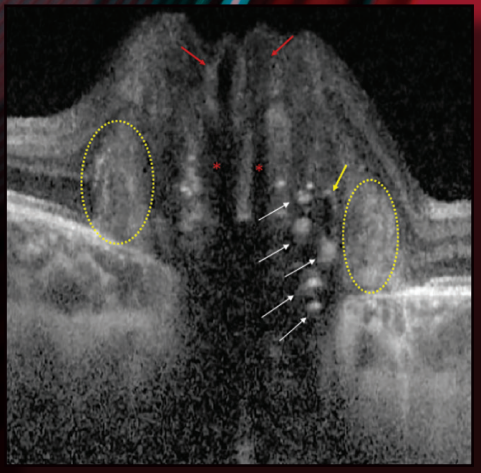
eyetube

IMAGING AND VISUALIZATION INNOVATION







THE INS AND OUTS OF INTRAOPERATIVE OCT

MAXIMIZING YOUR 3D VISUALIZATION SYSTEM

AI: THE MISSING LINK IN TELEMEDICINE

DON'T DELAY TREATMENT IN DME

HELP REDUCE INFLAMMATION IN DIABETIC MACULAR EDEMA (DME)

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

*BCVA = best-corrected visual acuity.

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

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

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

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

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

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

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

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

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

Corticosteroids are not recommended to be used in patients with a history of ocular herpes simplex because of the potential for reactivation of the viral infection.

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

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

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

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

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

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

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

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

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

Ozurdex®
(dexamethasone intravitreal implant) 0.7 mg

Allergan
an AbbVie company

Ozurdex.com OZU144337 02/21 008782

OZURDEX®

(dexamethasone intravitreal implant) 0.7 mg

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

INDICATIONS AND USAGE

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

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

Diabetic Macular Edema

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

CONTRAINDICATIONS

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

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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PICTURES WORTH 1,000 WORDS


When *Retina Today* launched in 2006, the technological talk of the town was the clinical utility of OCT.[1] The imaging modality was practically in its infancy, with only 10 years of commercial use under its belt.[1,2] At the time, only one device was well-known—the Stratus OCT from Carl Zeiss Meditec—and others were just becoming available.

The very first article *Retina Today* published on OCT touted a new ultrahigh-resolution version capable of acquisition rates of 16,000 axial scans per second with a resolution of 1 µm to 2 µm.[1] That, of course, was compared with the 10-µm resolution of the current (circa 2006) commercial OCT devices.[1] Even with that performance, researchers were discovering all sorts of new insights into the pathology and pathophysiology of Stargardt disease, retinitis pigmentosa, macular holes, lamellar holes, AMD, central serous chorioretinopathy, rhegmatogenous retinal detachment, and white dot syndrome, to name a few.

Today's OCT models are a far cry beyond those earlier iterations, boasting acquisition rates as high as 100,000 A-scans per second while maintaining similar resolution with digital imaging.[3] Added to that, we are using the technology in ways we never thought possible nearly 15 years ago.

In this issue, you will read about how surgeons are able to overlay OCT imaging during vitreoretinal surgery to aid in their clinical decision-making—affecting care more than 40% of the time. Another feature article highlights a new OCT model that can reach the far retinal periphery and integrates ultra-widefield fundus imaging, swept-source OCT, fundus autofluorescence, fluorescein angiography, and indocyanine green angiography. You will also find articles on the utility of enhanced depth imaging OCT for detecting buried drusen and of OCT angiography (OCTA), which provides extraordinary views of the retinal and choroidal vasculature.

But OCT isn't the only tool giving us unprecedented access to the eye today. That's why this April issue, in which we usually concentrate on imaging, now encompasses other technological advances in visualization and telemedicine. This issue's authors discuss how surgeons can get the most out of their 3D vitreoretinal surgery system and how an artificial intelligence–based telemedicine platform may one day revolutionize screening for referable AMD.

Beyond the feature articles, you will learn about the benefits of ocular endoscopy when there is a limited view of the posterior segment and how multimodal and OCTA imaging can help uncover paracentral acute middle maculopathy. And you can't talk about imaging without mentioning our Visually Speaking column, this month showcasing stunning images of a patient with Coats disease treated with core vitrectomy and endolaser photocoagulation.

When it comes to ocular imaging, the old adage, "a picture is worth a thousand words," rings truer every day, with new tools providing unparalleled views of the posterior segment, even down to the cellular level. ■

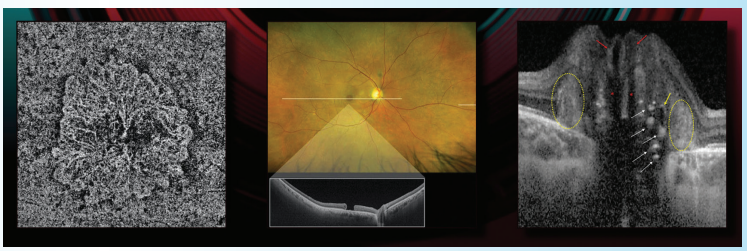
ALLEN C. HO, MD
CHIEF MEDICAL EDITOR

ROBERT L. AVERY, MD
ASSOCIATE MEDICAL EDITOR

1. Duker SJ. Advances in OCT improve understanding of disease states. *Retina Today*. 2006;1(1).
2. Sull AC, Vuong LN, Srinivasan VJ, et al. The evolution of spectral-domain optical coherence tomography. *Retina Today*. 2008;2(3):39-44.
3. Topcon. Topcon Triton. topconhealthcare.com/us/products/triton. Accessed March 4, 2021.

On the Cover

David Sarraf, MD, and colleagues used OCTA to track nonexudative MNV that remained fluid-free after 4 years of monitoring but grew larger in area (Left). With the use of peripheral OCT, Netan Choudhry, MD, FRCSC, discovered a retinal hole in the periphery, leading to prompt treatment before macular hole surgery (Middle). On enhanced depth imaging spectral-domain OCT of an optic disc, optic disc drusen usually have a hyporeflective core and hyperreflective margin, according to Meera S. Ramakrishnan, MD (Right).



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WET AMD EYE

ANTI-VEGF

Therapy yields better long-term VA results when wet AMD detected with good VA[1]

FELLOW EYE

20/79 VA

Mean VA of fellow eyes at wet AMD diagnosis according to real-world data[1]

Over 60% of wet AMD "fellow eyes" lose too much vision[1]– even with frequent treatment visits

Detect Early. Treat Early.

ForeseeHome is a **remote monitoring** program for at-risk wet AMD fellow eyes that helps **detect conversion** at 20/40 or better in 83% of patients.[2]

- FDA Cleared
- Medicare Covered

ForeseeHOME™
AMD Monitoring Program

Introduce your patients to ForeseeHome during an injection visit and offer them an extra level of protection.

Our Diagnostic Clinic works with your staff to easily implement an "inject and protect" protocol into your practice workflow that requires minimal effort or additional time.

The Key to Successful Home Monitoring

NOTAL VISION DIAGNOSTIC CLINIC

- Engagement & Education
- Benefits Verification & Authorization
- Continuous Monitoring
- Practice Workflow Implementation
- Remote Patient Management
- Vision Alert Management

NOTAL VISION™
Diagnostic Clinic

References: 1. Ho AC, Kleinman DM, Lum FC, et al. Baseline Visual Acuity at Wet AMD Diagnosis Predicts Long-Term Vision Outcomes: An Analysis of the IRIS Registry. *Ophthalmic Surg Lasers Imaging Retina*. 2020;51:633-639. **2.** Real-World Performance of a Self-Operated Home Monitoring System for Early Detection of Neovascular AMD (ForeseeHome device), presented by Allen Ho, American Society of Retina Specialist Meeting 2020.

See website for FDA Indication for Use.

SM-125.1

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APRIL 2021
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SAFETY, EFFICACY SEEN WITH SUPRACHOROIDAL TRIAMCINOLONE FOR NONINFECTIOUS UVEITIS

Suprachoroidal triamcinolone acetonide injectable suspension (CLS-TA, Clearside Biomedical) injections in patients with noninfectious uveitis were safe and prolonged the median time to rescue therapy by more than 200 days compared with untreated eyes in two recently published studies.[1]

The AZALEA trial included 38 patients with noninfectious uveitis, 20 of whom had macular edema (ME) at baseline, who were treated with two suprachoroidal injections of CLS-TA 4 mg, 12 weeks apart. The open-label safety trial found that 15.8% of treated eyes had an IOP rise > 10 mm Hg compared with baseline, and 5.3% had IOP > 30 mm Hg. Only one cataract formation adverse event was deemed treatment-related. The researchers concluded that suprachoroidally administered CLS-TA was safe and well tolerated over the 24-week study period.[1]

The phase 3 PEACHTREE trial enrolled 160 patients with noninfectious uveitis with ME, randomly assigned 3:2 to CLS-TA or sham; of those patients, 28 successfully completed the study and were enrolled in the MAGNOLIA extension study for an additional 24 weeks of follow-up to assess time to rescue therapy and safety.[2]

Over the total 48 weeks of follow-up in both PEACHTREE and MAGNOLIA, the researchers found that the median time to rescue therapy for those patients treated with CLS-TA was 257 days compared with 55.5 days for patients in the control group.[2]

In addition, 50% of treated patients in MAGNOLIA did not require rescue therapy for up to 9 months after the 12-week treatment, and they gained a mean of 12.1 letters and had a mean reduction in retinal central subfield thickness of 178.1 µm through week 48—all without any serious adverse events related to treatment.[2]

"Suprachoroidal administration is a potential alternative technique for delivering ocular therapies that may facilitate more targeted delivery and increased durability of therapeutic agents to the retina and choroid," said Christopher Ryan Henry, MD, of Retina Consultants of Texas, the primary investigator for AZALEA and contributor to PEACHTREE and MAGNOLIA, in a press release from Clearside Biomedical.

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OCT ANGIOGRAPHY HELPED PREDICT VITREOUS HEMORRHAGE IN PDR

The presence of extensive neovascularization (NV) and forward NV on widefield swept-source OCT angiography (SS-OCTA) may help physicians predict the development of vitreous hemorrhage in eyes with proliferative diabetic retinopathy (PDR), a recent study found.[1] Eyes with PDR that had NVs with total area greater than 4 disc diameters at baseline were more likely to develop vitreous hemorrhage on follow-up (odds ratio [OR] = 8.05) than those without extensive NVs.

The study included 55 eyes of 45 adults with PDR, none of whom had a history of vitreous hemorrhage. The patients were followed for a median of 363 days, and all were imaged with SS-OCTA. Two independent graders evaluated the images to identify parameters associated with the occurrence of vitreous hemorrhage.

The investigators found that 13 (24%) eyes developed vitreous hemorrhage during the follow-up period. They also noted a higher risk (OR = 5.42) for developing vitreous

hemorrhage in eyes with forward NVs that traversed the posterior hyaloid face into the vitreous. In addition, both extensive NVs and forward NVs on SS-OCTA were significantly associated with time to development of vitreous hemorrhage.

Another SS-OCTA parameter, the presence of flat NVs confined to the posterior hyaloid face, was associated with a lower risk of vitreous hemorrhage with borderline significance and an OR of 0.25.

The study authors concluded that widefield SS-OCTA is a useful tool for evaluating NVs in eyes with PDR, but larger samples and longer follow-up are needed to verify the imaging biomarkers identified here.

1. Cui Y, Zhu Y, Lu ES, et al. Widefield swept-source OCT angiography metrics associated with the development of diabetic vitreous hemorrhage a prospective study [published online ahead of print 25 Feb 2021]. *Ophthalmology*.

SAFETY, EFFICACY OF GB-102 FOR AMD SEEN IN PHASE 2B STUDY

A microparticle depot formulation of 1 mg sunitinib malate (GB-102, Graybug Vision) injected intravitreally every 6 months showed good initial results in the phase 2b ALTISSIMO study, according to a press release from the company. The primary endpoint of median time to first supportive therapy (anti-VEGF) in the trial was 5 months, and 48% of patients did not require supportive therapy for at least 6 months; additionally, 62% of patients did not require anti-VEGF for at least 4 months, at least once during the trial.

The masked, controlled phase 2b dose-ranging study evaluated two doses of GB-102 (1 mg and 2 mg) with a control arm of patients receiving aflibercept (Eylea, Regeneron). Interim safety analysis led to the discontinuation of the 2 mg dose, and all patients were switched to the 1 mg dose.

Secondary endpoints included central subfield thickness (CST) and BCVA; for the former, treatment was consistent with the control arm, for the latter, mean change from baseline in the GB-102 arm was approximately 9 letters lower than in the control arm.

No drug-related serious adverse events were seen, and the majority of adverse events were mild to moderate. No adverse event required surgical intervention.

A participant survey found that more than 80% of respondents who had been treated with GB-102 said they were equally or more satisfied with their treatment, similar to the respondents treated with aflibercept.

The trial will continue with a 6-month extension with 28 of the 50 patients who completed the 12-month visit and agreed to masked clinical monitoring. Patients will be followed for a maximum of 6 months to document the need for supportive therapy.

PEGCETACOPLAN SLOWED GEOGRAPHIC ATROPHY PROGRESSION, INCREASED EXUDATION IN PHASE 2 TRIAL

Monthly intravitreal injections of 15 mg pegcetacoplan (Apellis Pharmaceutical) significantly controlled geographic atrophy (GA) progression in a phase 2 trial, even in the presence of newly identified risk factors.[1] Researchers in the FILLY trial found that extrafoveal lesions ($P = .001$) and larger low luminance deficit ($P = .023$) were significantly associated with GA progression.

The phase 2 multicenter, randomized, single-masked, sham-controlled trial included 192 patients with 12-month follow-up. For the primary efficacy endpoint of change in GA lesion size from baseline, the researchers noted a change of 0.26 mm ($P < .01$), 0.27 mm ($P < .05$), and 0.36 mm in those receiving monthly pegcetacoplan, every-other-month pegcetacoplan, and sham treatment, respectively. Extrafoveal lesions ($P < .001$), BCVA ≥ 20/60 ($P = .001$), and larger low-luminance deficit ($P = .002$) were associated with greater mean changes in lesion size.

Monthly and every-other-month treatment with pegcetacoplan also significantly reduced progression ($P < .05$) when controlling for these risk factors.

However, the FILLY trial also showed a higher incidence of investigator-determined new-onset exudative AMD among trial participants. At 12 months, the researchers observed an incidence of exudative AMD of 16.3% in the monthly treatment group, 6.3% in the every-other-month group, and 1.2% in the sham group.[2]

A post-hoc analysis showed that risk factors for the development of exudative AMD with pegcetacoplan treatment included a history of exudation in the fellow eye and the presence of the double layer sign in the study eye at baseline. Three independent masked graders evaluated baseline structural OCT images to evaluate for the presence of the double layer sign, defined as an irregular low-lying retinal pigment epithelial detachment with low internal reflectivity > 250 µm in the greatest horizontal linear dimension.[2]

Among the eyes that developed exudation, 69% had a history of fellow-eye exudative AMD, and 73.1% presented with the double layer sign on baseline OCT imaging; of eyes that did not develop exudative AMD, 33% had fellow-eye exudation and 32.5% had the double layer sign at baseline.[2]

Based on the data, the investigators concluded that pegcetacoplan's safety profile was sufficiently benign to allow proceeding to phase 3 trials without adjusting enrollment criteria.[2] ■

1. Steinle NC, Pearce I, Monés J, et al. Impact of baseline characteristics on geographic atrophy progression in the FILLY trial evaluating the complement c3 inhibitor pegcetacoplan [published online ahead of print 02 March 2021]. *Am J Ophthalmol*.
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PPV WITH PKP AFTER TRAUMA REPAIR

Even when the insult is limited to the anterior segment, this surgical approach may offer benefits.

BY RADHIKA NATARAJAN, DO, DNB, FRCS

Trauma to the anterior segment may or may not be associated with posterior segment injury or complication. Patients who have had trauma limited to the anterior segment undergo initial wound repair (group A). If the resultant corneal scar is dense, full thickness, and precluding vision, penetrating keratoplasty (PKP) is done with or without lensectomy and limited anterior vitrectomy, depending on the extent of the injury. However, patients with associated posterior segment injury or complication (group B)—such as retinal detachment, nonresolving vitreous hemorrhage, intraocular foreign body, or endophthalmitis—will require a combination procedure including pars plana vitrectomy (PPV) and PKP.[1]

The question of whether or not to perform PPV arises only for patients in group A who do not have posterior segment pathology. Patients in group B—who have both corneal and retinal damage requiring combined surgery—would be expected to have a poorer prognosis than those in group A due to the involvement of both segments.

However, in a series of cases at our tertiary care eye institute, we have observed that graft survival and clarity are paradoxically better in group B patients undergoing combined surgery, provided that other parameters such as glaucoma, infection, and inflammation are controlled. Here, we discuss the mechanisms by which PPV may act as a favorable prognostic factor in terms of graft survival.[2]

TRAUMA DETAILS

The Ocular Trauma Classification Group developed a classification system, based on the Birmingham Eye Trauma Terminology, that classified injured eyes by zones affected by the trauma: (1) cornea and limbus, (2) limbus to 5 mm posterior into the sclera, and (3) > 5 mm into the sclera.[3]

Although it is now several decades old, this classification system is still useful for categorizing the severity of corneoscleral injuries. Generally, scars from the repair of zone 1 injuries do not require corneal transplantation, whereas higher grades of trauma, after primary repair healing, will require corneal transplantation (Figure 1) along with additional procedures such as lensectomy and anterior vitrectomy if the posterior segment is not involved.

Although the initial trauma in group A is limited, reasons for corneal graft failure in these eyes still exist:

- Excessive inflammation and hemorrhage after trauma can lead to an exaggerated fibrovascular response in the vitreous cavity; formation of retrocorneal, ciliary body, and pars plana membranes; and elevated IOP.
- Retinal detachment can occur due to traction from incomplete posterior vitreous detachment and membrane formation. Limited anterior vitrectomy alone may be inadequate for complete removal of the vitreous from the anterior segment and the wound, leading to increased risk of traction and infection.

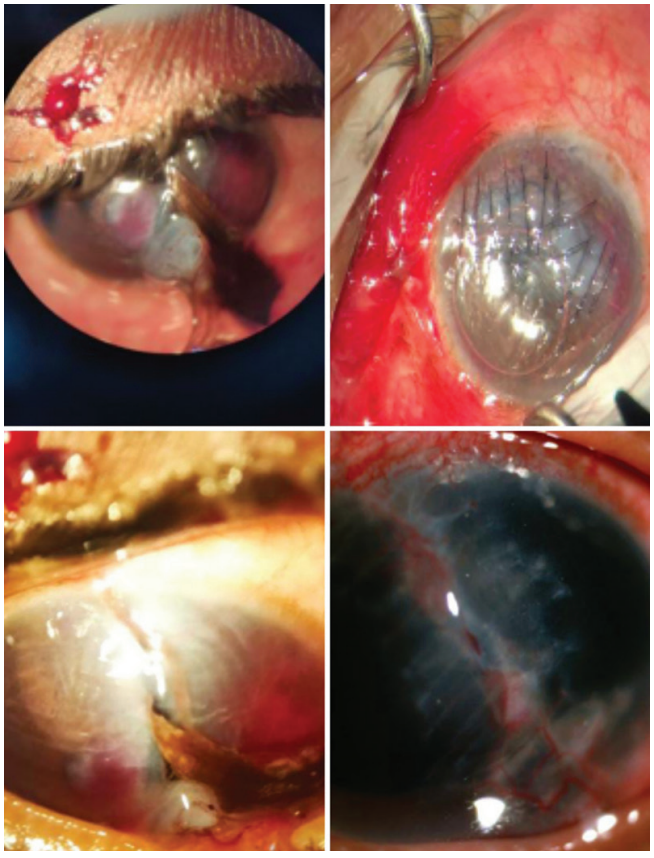

Figure 1. Composite picture showing two eyes with severe corneal injury, at left, and the corresponding distorted anterior segment after initial repair, at right.

Even in eyes in which trauma is limited to the anterior segment, inflammation may involve the vitreous cavity. Further, blood in the vitreous is a potent stimulus for a fibrovascular response, especially in young patients. These factors may lead to retrocorneal membrane formation and graft rejection and failure. Hence, eyes in group A may show initial favorable graft clarity followed by long-term graft failure.

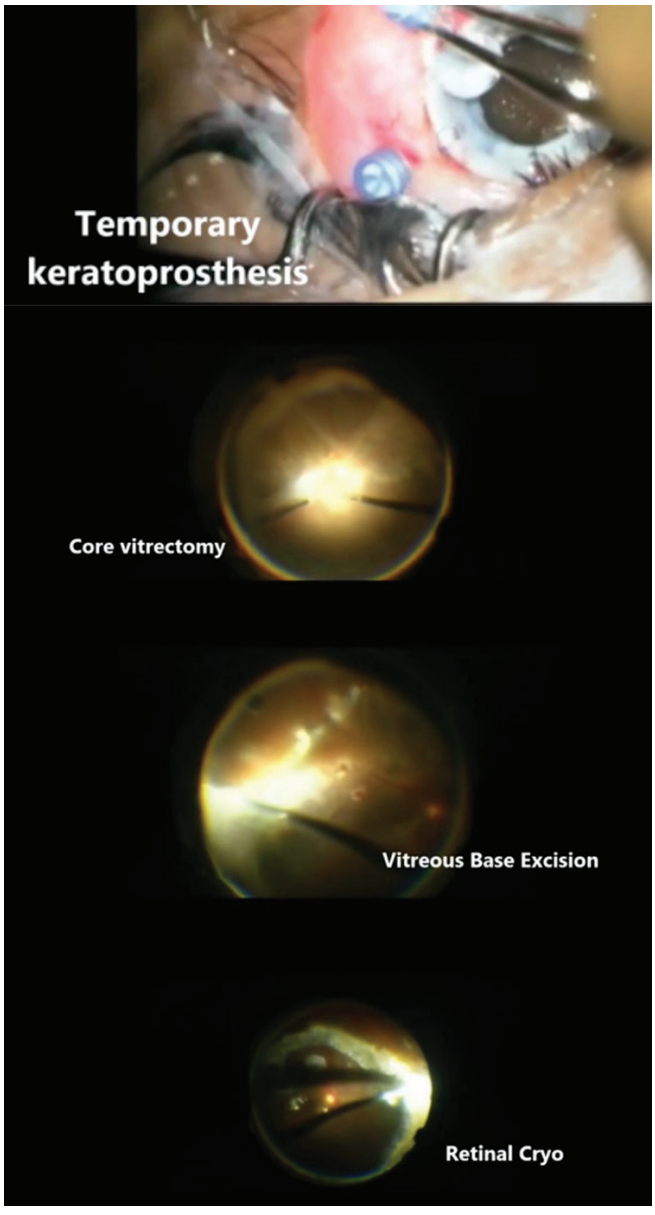

Figure 2. Composite picture showing steps of PPV performed during PKP.

PPV in conjunction with PKP may reduce the risk of corneal graft failure, decreasing inflammation by clearing cytokines, inflammatory cells, fibrin, hemorrhage, and degenerated cells from the eye. Further, vitreous base excision reduces the risk of fibrovascular proliferation by clearing membranes and vitreous from the wound. In addition, induction of a complete posterior vitreous detachment and placement of a scleral buckle can reduce traction on the retina, decreasing the risk of retinal detachment.

TAKEAWAYS

Although PPV has its own possible complications, in appropriate cases the cleanup achieved through PPV may help to reduce membrane formation and facilitate graft survival (Figure 2). In our experience, graft prognosis was better in patients who underwent combined PKP with PPV than in patients who underwent PKP with anterior vitrectomy only.

Some patients require PKP for dense corneal scarring after primary trauma repair. With considerable anterior segment injury or nonresolving hemorrhage, concomitant PPV, even in the absence of posterior segment indications, may improve the chances of corneal graft survival. ■

ALTHOUGH PPV HAS ITS OWN POSSIBLE COMPLICATIONS, IN APPROPRIATE CASES THE CLEANUP ACHIEVED THROUGH PPV MAY HELP TO REDUCE MEMBRANE FORMATION AND FACILITATE GRAFT SURVIVAL.

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FELLOWS' FOCUS

A VIRTUAL RETINA FELLOWS FORUM



The 2021 Fellows Forum went virtual this year due to COVID-19.

BY MATTHEW STARR, MD; LUV PATEL, MD; AND MICHAEL AMMAR, MD

The COVID-19 pandemic has significantly impacted the landscape for educational and research meetings in the field of ophthalmology, and appropriately so. Almost all ophthalmology meetings at present are being held virtually, if at all. Certainly, virtual meetings lack the jovial social interactions that typically come with any conference, but they make up for it with the ability to host many meetings simultaneously and the chance to "attend" a meeting without having to leave one's home.

This year's Annual Retina Fellows Forum was followed a 3-night virtual format. With the benefit of not having to travel to a chilly Chicago in the dead of winter, the online format provided a profoundly educational experience—mingled in with the standard Zoom moments of mic checks and kids running around in the background.

The meeting is typically reserved for second-year vitreoretinal fellows, but the virtual format allowed both first- and second-year surgical retina fellows to experience the Forum this year. This article reports our experiences as the three second-year vitreoretinal fellows at Wills Eye Hospital during this year's virtual Forum.

PART 1. FROM AMD TO SURGICAL DEVICES

The first evening kicked off with a short introduction from Tarek S. Hassan, MD, before diving into the clinical portion of the meeting. The educational content on the first evening covered a diverse range of pathology from AMD to pediatric retina, and from uveitis to tumors.

Rishi P. Singh, MD, discussed topics in the management of AMD and the many exciting treatment modalities on the horizon that will hopefully soon be integrated into the armamentarium of all practitioners. Caroline R. Baumal, MD, and Thomas A. Albini, MD, gave outstanding lectures on two very different topics, uveitis and pediatric retina, offering pearls for vitreoretinal fellows as they begin their careers. Amy C. Schefler, MD, offered her insight and expertise in the management of intraocular malignancies. The evening concluded with the renowned David R. Chow, MD, FRCSC, describing the many new vitreoretinal surgical devices that fellows will soon incorporate into their surgical management of vitreoretinal diseases.

PART 2. ILM PEELING, AMD MIMICKERS, AND MORE

The second night started off with Dr. Chow, who discussed recent articles in the vitreoretinal literature, and included a panel discussion. Specifically, the articles focused on peeling of the internal limiting membrane (ILM) during rhegmatogenous retinal detachment (RRD) repair. Although studies have shown decreased rates of postoperative epiretinal membrane formation and improved single surgery success rates with ILM peeling, most of the panelists said they do not routinely perform ILM peeling at the time of RRD repair. Several panelists offered valid counterpoints against the practice.

Next, David Sarraf, MD, presented striking images of cases that were sent to him as suspected AMD but that were in

AT A GLANCE

- Topics discussed at the 2021 Fellows Forum included the management of AMD and treatment modalities on the horizon.
- Speakers provided insights into when and how to perform macular surgery, how to manage intraocular trauma at the time of injury, and how to approach vitreoretinal surgery after trauma.
- In a survey, about 20% to 30% of participating fellows indicated that they had not finalized a job offer, consistent with previous years.

ALTHOUGH STUDIES HAVE SHOWN DECREASED RATES OF POSTOPERATIVE EPIRETINAL MEMBRANE FORMATION AND IMPROVED SINGLE SURGERY SUCCESS RATES WITH ILM PEELING, MOST OF THE PANELISTS SAID THEY DO NOT ROUTINELY PERFORM ILM PEELING AT THE TIME OF RRD REPAIR.

fact AMD mimickers. The diagnosis du jour is that of pentosan polysufate maculopathy, which was a common AMD mimickers Dr. Sarraf identified.

Dr. Baumal then switched gears to focus on macular surgery and when to operate, presenting a nice array of cases, prompting great discussion among the panelists. Sticking with the surgical approach, Aleksandra V. Rachitskaya, MD, offered pearls for approaching RRDs in a range of situations from primary buckles to RRDs with concomitant macular holes.

Next, Sunir J. Garg, MD, tackled the topic of secondary IOLs. The biggest pearl perhaps was how to handle and interact with the referring providers when fixing dropped lenses: Communication is key!

The night concluded with a lecture by Dean Eliott, MD—his infamous trauma lecture. He provided many insights into how to manage intraocular trauma at the time of injury and how to approach vitreoretinal surgery after trauma. Many fellows will not soon forget the impressive collection of images of trauma cases Dr. Eliott has amassed over his career.

PART 3. LIFE AS A VITREORETINAL SURGEON

The last evening of the Fellows Forum had a slightly different focus from the previous two sessions. Although still presenting plenty of clinical content, the evening included practical sessions on beginning life as a vitreoretinal attending surgeon.

Dr. Hassan kicked things off with a discussion of the management of diabetic retinopathy (DR). A major point of discussion was the role of anti-VEGF agents in the treatment of nonproliferative DR in the absence of macular edema. Discussing the results of the PANORAMA study of aflibercept (Eylea, Regeneron) in nonproliferative DR, Dr. Garg described the evidence as the "strongest data that I have seen yet to incorporate into clinical practice." Dr. Garg then continued the discussion with the presentation of surgical cases, offering pearls and insights into the management of macular holes.

Equally insightful was a group of discussions on beginning practice as a new attending. Alan J. Ruby, MD, led a talk on drug reimbursement, pricing, and management within retina practices. His succinct talk was a welcome illumination into an integral part of the economics of a retina practice that is often obscure to trainees.

The final session was a group discussion led by Carl C. Awh, MD, entitled "The Real World." Discussion topics included the importance of continued learning, communication with the wider retina community, and navigating a new supervisory role over clinic staff. Reassurance was provided through a group poll, in which about 20% to 30% of fellows indicated that they had not finalized a job offer, consistent with previous years, according to Dr. Awh.

Further comfort was provided regarding the daunting mantle of independent practice; an informal poll of the attending faculty suggested that it takes about 3 to 5 years to achieve comfort in practice. Several participants shared valuable early practice advice, such as Dr. Garg's assertion that it is important to have good relationships with patients, staff, local physicians, and referring providers.

The importance and virtues of work-life balance were also discussed, notably by Dr. Sarraf, who said he still plays tennis 1 or 2 hours a day. The practice sessions were a unique, memorable, and cherished facet of the Forum. ■

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OCULAR ENDOSCOPY: A REVIEW

This is an effective tool in eyes with poor media and for visualization and treatment of structures behind the iris.

BY JORGE G. ARROYO, MD, MPH

For retina specialists, standard pars plana vitrectomy (PPV) is the trusted approach to closed surgery for a variety of posterior segment conditions. In some cases—for example, significant trauma to the anterior segment—PPV with the OR microscope can be challenging or impossible. This is where the use of ocular endoscopy can be most advantageous.

The technology is straightforward and recognizable to anyone familiar with endoscopic surgery. Several systems are available in Europe, and two have US FDA approval (Endo Optiks E2 and E4, BVI Medical). A camera, a light, and, in some systems, a laser are incorporated into a single curved or straight housing. The instrument, in sizes from 18 to 23 gauge, is inserted through standard small-gauge vitrectomy incisions.

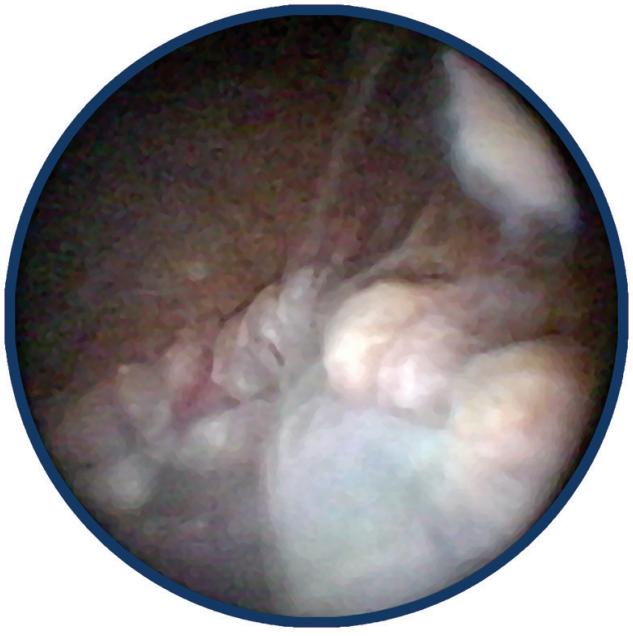
Over the past 25 years, I have had the opportunity to use ocular endoscopy for a range of retina applications. This dive into the literature reviews some of the best evidence for use of this technology.

VISUALIZE THE POSTERIOR SEGMENT

Most patients who require posterior segment surgery can undergo standard PPV using an operating microscope, but when injury or disease prevents visualization of the posterior segment, ocular endoscopy may be a relatively simple and effective option.

In severe open-globe eye injuries, when significant trauma to the anterior segment prevents us from getting a clear view, we can bypass the anterior segment with the endoscope to achieve the necessary visualization. Temporary keratoprosthesis is another much more invasive and complicated option in such cases due to the difficulty of creating a watertight seal in a traumatized eye and the need for suturing of the corneal graft at the conclusion of the case. These patients also have increased risk of needing penetrating keratoplasty in the future.

Studies comparing endoscopic vitrectomy to temporary keratoprosthesis for severe ocular trauma found that surgical outcomes were similar, but patients were treated more quickly with endoscopic vitrectomy because this approach is less invasive and requires less preparation.[1] Patients treated using endoscopy were also less likely to develop retinal detachments or advanced proliferative vitreoretinopathy.[2] One study reviewed outcomes in endoscopic vitrectomy performed on 50 eyes (43 with open-globe injuries and 36 with retinal detachment) for which PPV was not possible and donor corneas were unavailable. Retinas were reattached in about 91% of cases, and about 81% of

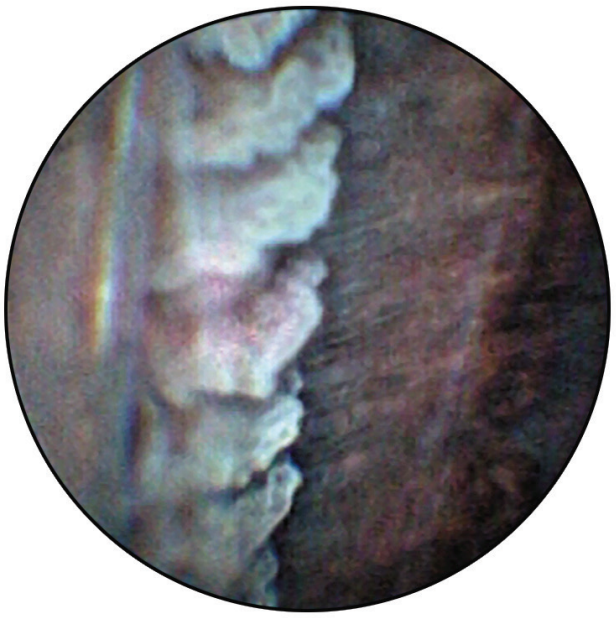


Courtesy of BVI Endo Optiks.

Figure 1. Endoscopic view inside eye with focal abscess associated with endophthalmitis.

AT A GLANCE

- When injury or disease prevents visualization of the posterior segment, ocular endoscopy may be an effective viewing option.
- A key advantage of endoscopy in these cases is that it offers a less invasive method of visualizing the posterior segment of the eye compared with a temporary keratoprosthesis.
- Endoscopy may reduce the chances of iatrogenic lenticular trauma and retinal breaks in pediatric vitrectomy.



Courtesy of BVI Endo Optiks.

Figure 2. Endoscopic view of pars plana and ciliary processes.

patients had improved visual acuity postoperatively.[2]

Endoscopy offers the same advantages for visualization when the posterior segment is obscured due to disease (Figure 1). In posttraumatic endophthalmitis, PPV can reduce pathogens and inflammation and allow repair of retinal detachment,[3] but patients with endophthalmitis often have anterior segment opacities. Endoscopy allows the surgeon to bypass those opacities to visualize the ciliary body (Figure 2) and other anterior structures. This approach has been shown to be safe for diagnosis and treatment.[2,4]

SHORTEN DELAYS FOR TRAUMA SURGERY

In the aforementioned trauma cases, the deciding factor for using endoscopy was the inability to perform standard PPV with the OR microscope, usually due to anterior segment trauma. Limitations of the more invasive temporary keratoprosthesis procedure also influenced decisions. But another key advantage of endoscopy is evident: Patients can be treated sooner with endoscopy than with keratoprosthesis.[1] This is important because the longer surgery is delayed, the more time there is for inflammation to develop, ultimately increasing the odds of developing proliferative vitreoretinopathy, which will affect visual outcomes.

Intraocular foreign bodies (IOFBs; Figure 3) are present in 18% to 41% of open-globe injuries.[5] When trauma involves an IOFB, delays can result in endophthalmitis in 10% of cases. Toxicity is a potential long-term complication; IOFBs that contain iron or copper can cause siderosis bulbi or chalcosis, respectively.[5,6] The longer the IOFB remains in the eye, the greater the chance for it to become encapsulated and more difficult to remove.

Standard vitrectomy using the OR microscope is the first choice of treatment for IOFBs, but when poor visualization due to anterior segment trauma makes this approach impossible, endoscopic vitrectomy is a relatively simple and effective choice compared with temporary keratoprosthesis.[1,7]

REDUCE DAMAGE IN NEOVASCULAR GLAUCOMA

When retinal conditions such as proliferative diabetic retinopathy and central retinal vein occlusion result in neovascular glaucoma, patients typically have an outflow procedure, such as trabeculectomy or tube-shunt surgery (although these approaches have a high failure rate in these patients), or a procedure that limits aqueous production such as cyclophotocoagulation. When cyclophotocoagulation is selected, endoscopic cyclophotocoagulation is the most common approach because its effect is more isolated than that of transscleral cyclophotocoagulation, resulting in less collateral tissue damage and less inflammation.[8,9]

In a comparative study of standard care and endoscopic cyclophotocoagulation, the latter produced a significantly greater reduction in IOP (-28.5 mm Hg) compared with the former (-11.4 mm Hg).[10] Visual acuity and complications were similar. In addition, endoscopic cyclophotocoagulation eliminated the need for medications in nearly three-quarters of patients, compared with 18.5% of patients who had standard care; other studies have shown similar results.[11,12]

IMPROVE ACCESS IN PEDIATRIC CASES

The difficulty of working in the small vitreous cavity of a child increases the risk of iatrogenic lenticular trauma and retinal breaks.[13] Endoscopic vitrectomy allows the surgeon to sustain visualization, potentially reducing the risk of trauma.[8]

A review of the literature shows that endoscopy has been used for a variety of pediatric indications.[13-15] In persistent fetal vasculature, the perpendicular view offered by the endoscope can help surgeons identify safe nonvascular sites for amputation of the fibrovascular stalk.[13] Applications of endoscopy for retinopathy of prematurity include accessing tractional retinal detachment located anteriorly near the standard vitrectomy trocar site, visualizing sclerotomy formation to prevent iatrogenic retinal breaks, and detecting anteriorly located vitreoretinal traction in advanced cases.[13]

OCULAR ENDOSCOPY PEARLS

Use of the endoscopic approach comes with a moderate learning curve, including training and wet-lab time. For practice, the endoscope can be used as a light source during routine procedures, which gives the surgeon time to get used to the medium and compare the views through the microscope and endoscope.

It is essential to hone the ability to identify landmarks seen through the endoscope so that the surgeon can maintain orientation. It gets easier over time to identify the

STANDARD VITRECTOMY USING THE OR MICROSCOPE IS THE FIRST CHOICE OF TREATMENT FOR IOFBS, BUT WHEN POOR VISUALIZATION DUE TO ANTERIOR SEGMENT TRAUMA MAKES THIS APPROACH IMPOSSIBLE, ENDOSCOPIC VITRECTOMY IS A RELATIVELY SIMPLE AND EFFECTIVE CHOICE COMPARED WITH TEMPORARY KERATOPROSTHESIS.

posterior pole and optic nerve and ciliary body structures.

It also takes time to accustom oneself to the endoscope's monovision view. Without stereoscopic depth perception, we can use other observations (magnification, shadows, and reflected light) to comprehend spatial relationships. In the future, stereoscopic endoscopy may be possible with 3D video displays.[13]

Other tips include putting the monitor near the surgeon's line of sight for the microscope to allow comfortable viewing. Also, understand that it will be necessary to use ultrasound to follow patients postoperatively because the anterior segment barriers to visualization will still exist.

The process of learning to use endoscopy is worth the effort for any retina specialist who treats trauma and complex cases. ■

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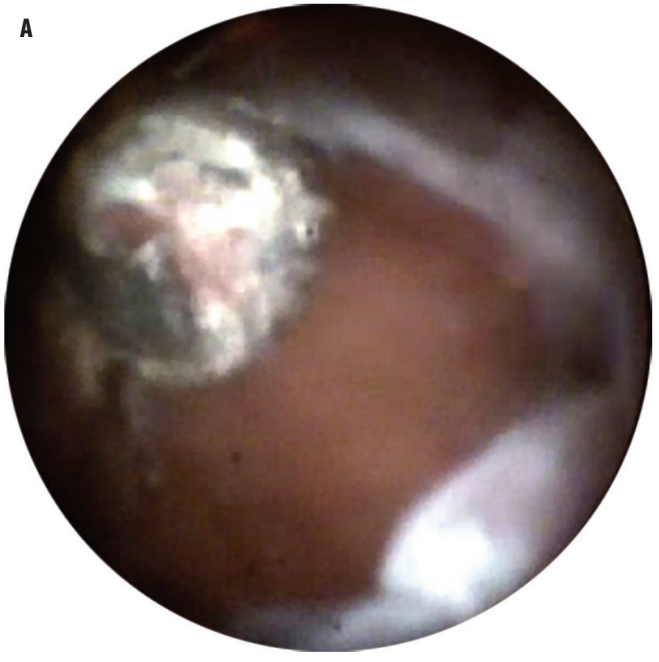

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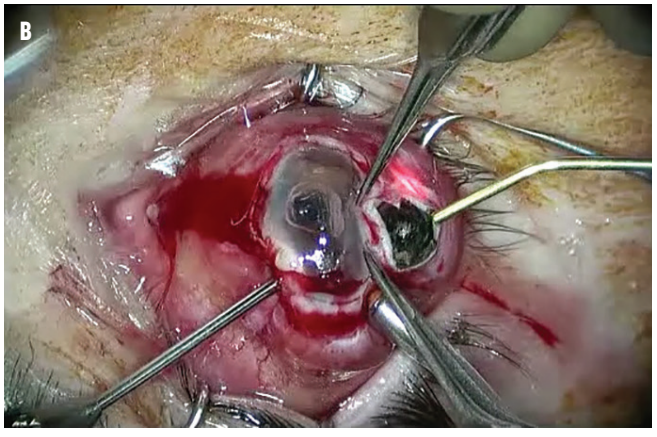
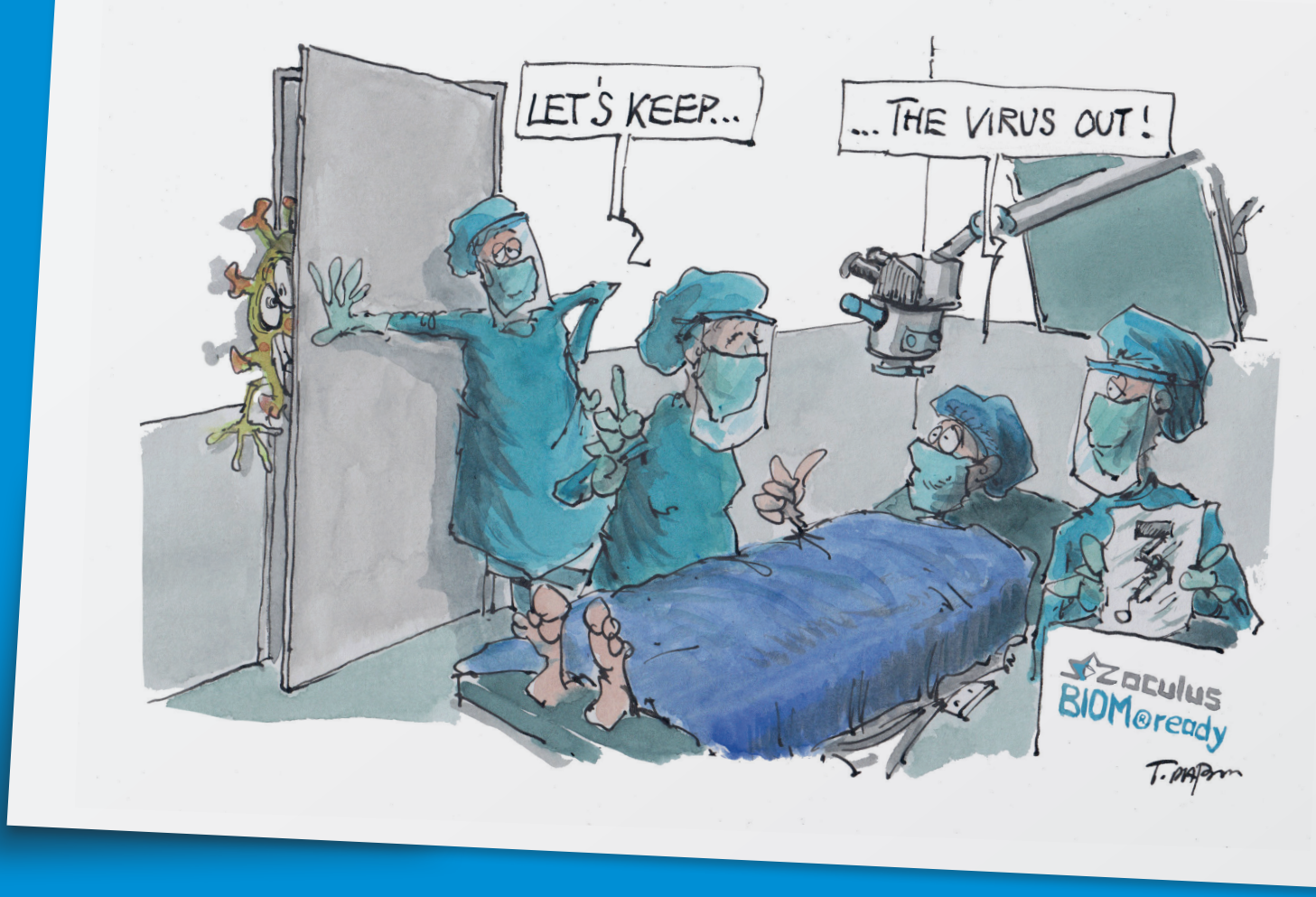


Figure 3. Endoscopic view of a large metallic IOFB (A), and microscopic view of the removal of the large metallic IOFB (B).



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The Ins and Outs of Intraoperative OCT


This tool is changing the way surgeons approach vitreoretinal surgery.

BY MEGAN S. STEINKERCHNER, MD, AND JUSTIS P. EHLERS, MD

OCT has become vital in the diagnosis and monitoring of myriad ophthalmic conditions.[1] The value OCT provides in the pre- and postoperative management of ophthalmic surgical conditions, such as epiretinal membranes and macular holes, led investigators to evaluate the possible role of OCT in the OR itself. In 2005, surgeons first used intraoperative OCT (iOCT), with time-domain technology, to visualize anterior segment structures during lamellar keratoplasty and trabeculectomy procedures.[2] The development of various iOCT technologies followed, ranging from handheld OCT devices to microscope-integrated systems.

The clinical utility of iOCT to date spans anterior and posterior segment applications, and prospective studies suggest that this tool may have the potential to be a future cornerstone of ophthalmic surgery.

iOCT OPTIONS

Portable

The first handheld spectral-domain OCT (SD-OCT) probe was developed by Cynthia Ann Toth, MD, and Joseph A. Izatt, PhD, at Duke University. The device was first described in clinical use during vitreoretinal surgeries in 2009. Using the handheld probe, Toth et al obtained retinal images during macular surgeries involving epiretinal membranes, full thickness macular holes, and vitreomacular traction.[3] The surgeons were able to see operative tissue configurations difficult to detect using traditional en face microscopic views.[3]

Other studies corroborated the advantages of portable SD-OCT, including its use in vitreoretinal indications such as retinal detachment (RD) and proliferative diabetic retinopathy (PDR) surgeries and pediatric retinal examinations.[4-7]

FDA-cleared portable OCT systems include the EnVisu handheld OCT probe (Leica Microsystems) and the stand-mounted iVue system (Optovue). Limitations of handheld probes include the need to devote operating time to the process of obtaining images, as well as motion artifacts, challenges in image stabilization, a steep learning curve for image acquisition, and lack of real-time imaging.

Microscope-Mounted

Mounting a device on the microscope can improve the stability of the scan axis and reproducibility of images and allow foot-pedal control. The first commercially available device offering this function was the Bioptigen EnVisu (Leica Microsystems).[8,9] Microscope stabilization dramatically improved image acquisition time, image stabilization, usability across surgeons, and overall efficiency. This broad accessibility enabled the first multisurgeon large scale prospective study of iOCT, PIONEER.[8] However, like the handheld

AT A GLANCE

- Surgeons first used intraoperative OCT (iOCT), with time-domain technology, to visualize anterior segment structures during lamellar keratoplasty and trabeculectomy procedures.
- The DISCOVER trial supported the clinical utility of iOCT, with 29.2% of posterior segment surgeries reportedly affected by information supplied by iOCT.
- Ongoing advances such as iOCT-compatible instruments, software systems for tissue analysis, and volumetric real-time iOCT may improve this tool's clinical utility.

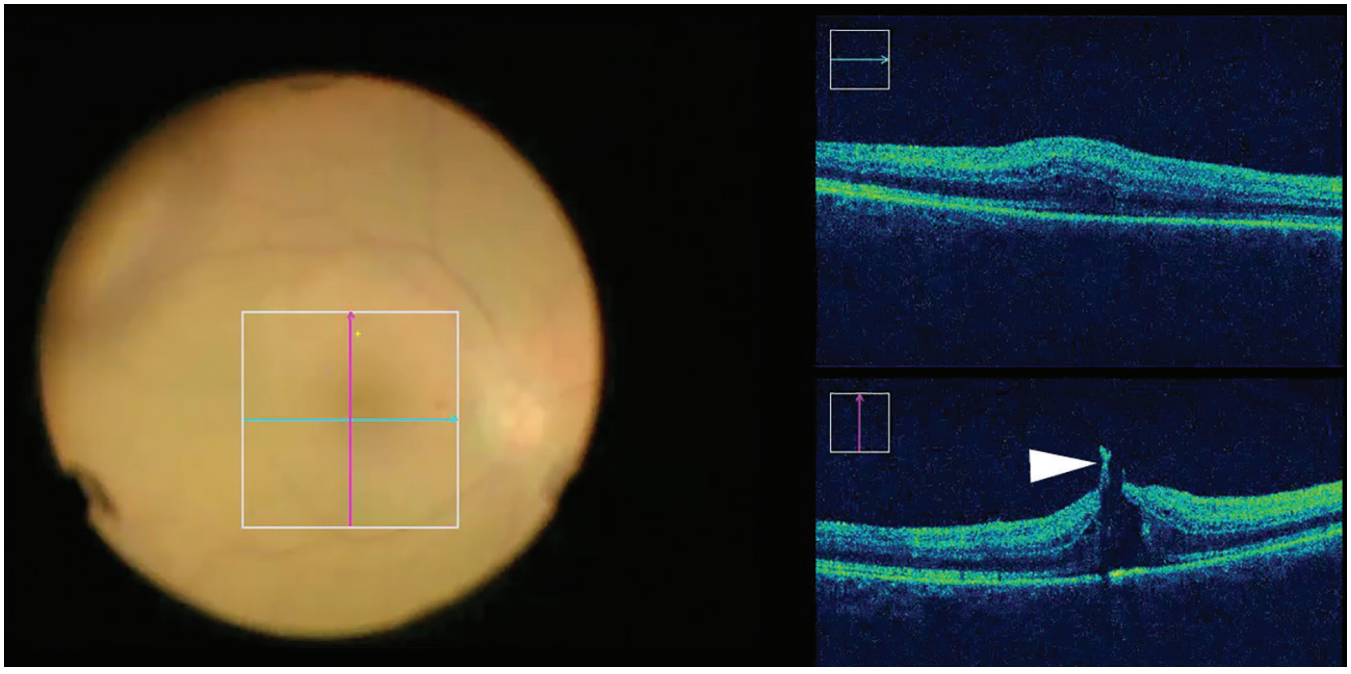

Figure 1. iOCT during macular hole surgery. Following internal limiting membrane peeling, iOCT confirms complete removal of epiretinal membrane and internal limiting membrane. Partially bridging retinal tissue is noted at the hole edge (arrowhead).

devices, microscope-mounted devices did not provide real-time imaging of the instrument-tissue interface.[8]

Microscope-Integrated

In this approach, OCT and microscope optical pathways are integrated, allowing real-time visualization of instrument-tissue interactions with a heads-up external viewing display. Susanne Binder, MD, and Dr. Toth both independently developed early prototypes with this approach. Dr. Toth's team developed an integrated iOCT system using the Bioptigen engine, whereas Dr. Binder's team used the Carl Zeiss Meditec Cirrus engine.

Multiple commercial microscope-integrated iOCT systems are now FDA-cleared and available in many global markets. The Rescan 700 (Carl Zeiss Meditec) is integrated with that company's Lumera 700 microscope platform. The device provides Z tracking and focus controls designed to enhance image quality and stability.[10,11] Haag-Streit's system uses a mounted side port to incorporate the OPMedT OCT system. Finally, the EnFocus system (Leica Microsystems) uses the Leica surgical microscope with extended-range scanning and high-resolution images from the Bioptigen engine.[11]

CLINICAL STUDIES

Two large prospective iOCT trials, PIONEER and DISCOVER, have examined the feasibility, utility, and safety of iOCT across multiple ophthalmic surgeries.

PIONEER evaluated the utility of OCT images derived from a microscope-mounted system in anterior and posterior segment surgeries. OCT images were collected from 98% of the 531 enrolled eyes (256 posterior segment indications) using disease- and procedure-specific imaging protocols with surgeon feedback on the value of the images. The study found that iOCT imaging provided valuable additional information in 43% of membrane peel cases.[8]

DISCOVER evaluated microscope-integrated iOCT using three OCT prototypes, including the Rescan 700, EnFocus, and a research prototype developed at Cleveland Clinic's Cole Eye Institute. Over a 3-year period, 820 individuals were enrolled for either anterior or posterior segment procedures. The DISCOVER trial further supported the clinical utility of iOCT, with 29.2% of posterior segment surgeries reportedly affected by iOCT information.[12-15]

Several studies have since corroborated the clinical efficacy of iOCT. Pfau et al demonstrated a benefit of iOCT in 74.1% of 32 posterior segment and combined cases.[10] Moreover, the addition of iOCT images led to changes in surgical approaches in 41.9% of cases, particularly in surgeries involving membrane peeling and tamponade choice.[10]

Binder et al found that iOCT confirmed procedure completion, depicted macular retinal changes, and helped to identify subclinical pathology that ultimately affected surgical management.[16] Following the success of their initial study, the same group compared the efficacy of iOCT for crucial vitreoretinal surgical steps, including visualizing membranes with retinal dyes. The authors found that iOCT images allowed membrane peeling without the use of dyes

[INTRAOPERATIVE] OCT IDENTIFIED OCCULT RESIDUAL MEMBRANES IN 12% OF CASES—AND CONFIRMED COMPLETE MEMBRANE PEELING CONTRARY TO SURGEON IMPRESSION IN 9% OF CASES.

and helped surgeons detect iatrogenic macular hole formation during vitreomacular traction procedures.[17]

In a recent study led by Drs. Toth and Izatt, the authors reported that real-time iOCT images during vitrectomy for complications of PDR improved dissection of surgical planes and enhanced retinal traction relief by highlighting the need for additional peeling.[18]

VITREORETINAL APPLICATIONS

Macular Surgery

The use of iOCT has been described extensively in macular disease, particularly in vitreoretinal interface disorders, in which the technology provides surgeons with exceptional visualization of the epiretinal membrane and tissue planes throughout the procedure. One study reported that iOCT-guided membrane peeling was possible without the use of surgical staining agents in 40% of cases.[17] Prospective studies of membrane peeling procedures found that iOCT identified occult residual membranes in 12% of cases—and confirmed complete membrane peeling contrary to surgeon impression in 9% of cases.[8]

The DISCOVER trial also demonstrated a disconnect between surgeon impression and surgical anatomy. In 40% of cases in which the surgeon felt that residual membranes were present, iOCT revealed complete membrane removal (Figure 1).[15] Additionally, iOCT has allowed surgeons to characterize subclinical structural changes in procedures such as macular hole closure, providing insights into retinal anatomic configurations that may ultimately influence clinical outcomes.[19,20]

Retinal Detachment

iOCT can enhance visualization of surgical steps during RD repair, including retina or retinal pigment epithelium apposition after perfluorocarbon tamponade and after air-fluid exchange. Specifically, iOCT can assist in locating retinal breaks or occult membranes and differentiating retinal schisis versus detachment. In the DISCOVER study, the feedback provided by iOCT altered the RD surgical procedure in 18% of cases.[15]

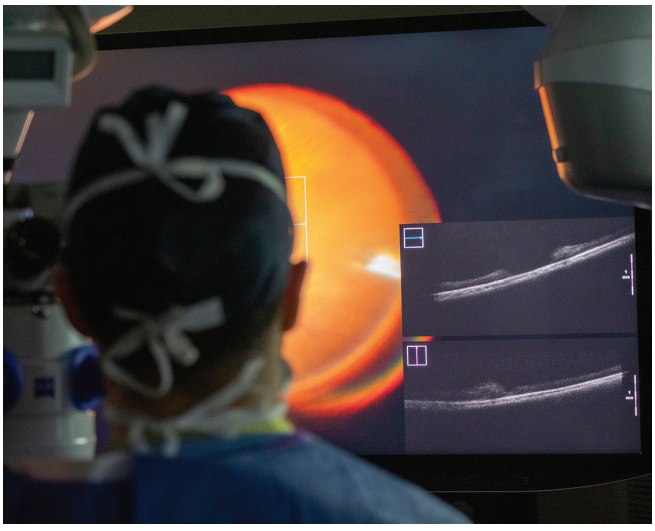

Figure 2. With a 3D immersive system with iOCT integration, the iOCT overlay demonstrates a flat full-thickness retinal hole.

Proliferative Diabetic Retinopathy

In posterior segment surgery involving PDR, iOCT can help surgeons identify difficult-to-visualize surgical planes and facilitate differentiation of RD versus PDR fibrovascular membranes. Static and continuous feedback from iOCT can alter PDR surgery by identifying occult retinal breaks and membrane dissection planes and differenting between tractional and rhegmatogenous RD.[15,18]

Emerging Therapeutics

iOCT can act as a surgical guidance system for subretinal injections, gene delivery, and retinal prosthesis placement.[21-23] For example, surgeons used iOCT feedback regarding the array-tissue interface and prosthetic retinal tack placement when performing Argus II implants (Second Sight Medical Products).[22]

During gene therapy delivery into the subretinal space, iOCT can help identify the location and volume of viral vector injection. In an ongoing phase 2 clinical trial of choroideremia gene therapy, iOCT helped to improve the clinical safety through direct monitoring of foveal stretching and hole formation.[23]

ONGOING ADVANCES

iOCT-compatible Instruments

iOCT images of tissue-instrument interactions are hindered by the properties of most standard vitreoretinal

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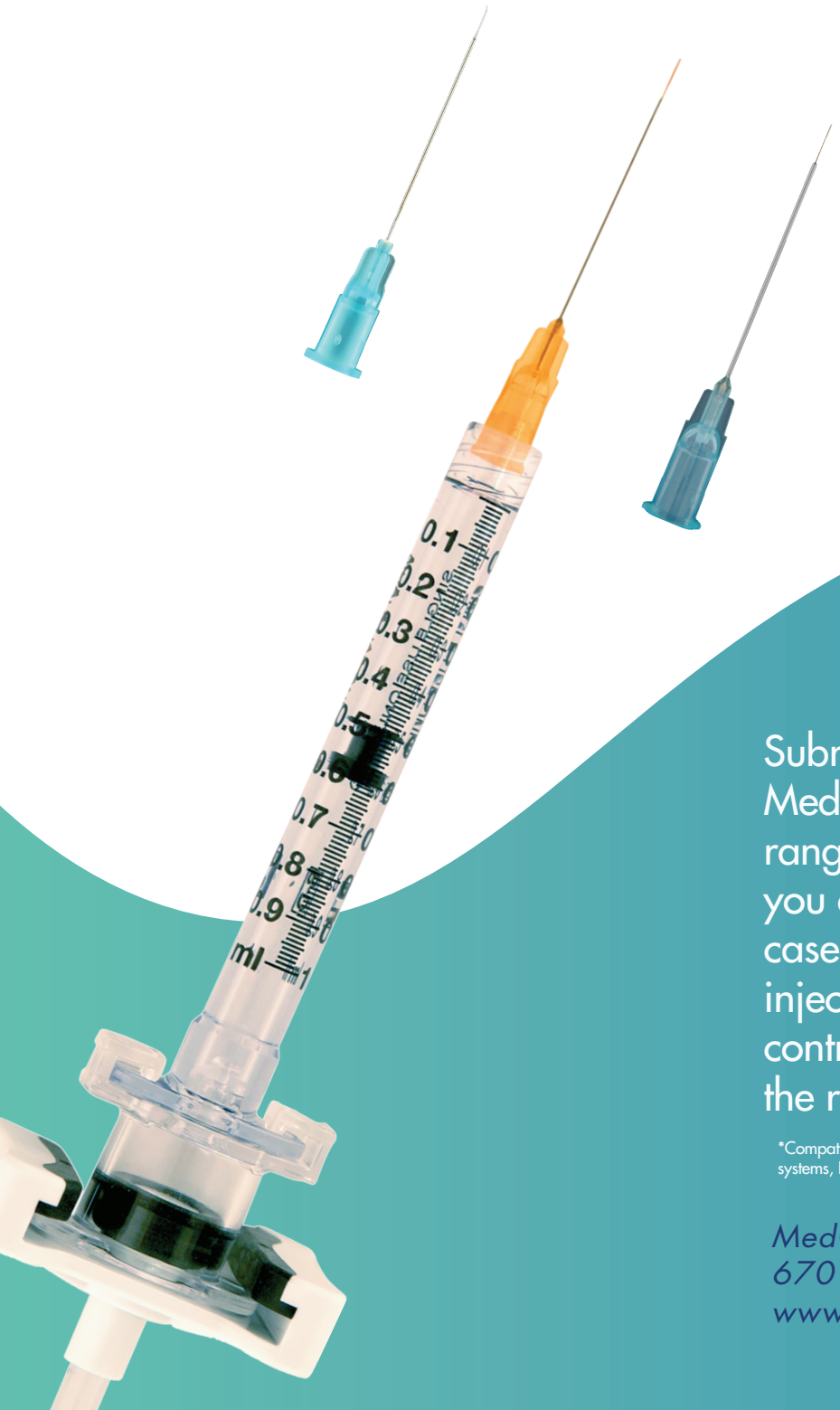

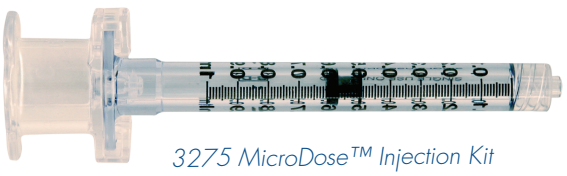

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instruments. Metallic surgical instruments with large profiles (eg, forceps and scissors) result in shadowing of the underlying retinal structures, and light scattering limits the visualization of instrument tip maneuvers with iOCT. The development of iOCT-compatible devices may provide better visualization of instrument tips and surgical manipulation of tissue.[24]

Software Systems for Tissue Analysis

iOCT devices require improved analytical software to enable surgeons to perceive minute tissue alterations intraoperatively. For example, in a study examining the use of volumentric analysis algorithms during macular hole surgery, OCT devices proffered automated analysis of macular hole structural dimensions that correlated with clinical stages and visual outcomes.[25] In addition, iOCT can detail macular hole covariates, which have been shown to be predictive of successful macular hole closure, in ways that are not obtainable preoperatively.[26]

Volumetric analysis using iOCT may also help to determine accurate subretinal therapeutic drug delivery and prevent retinal toxicity. iOCT-derived algorithms measuring bleb volumes after subretinal therapeutic delivery have shown validity and reproducibility, as well as illuminating a stark contrast between intended and actual subretinal drug volumes.[27,28]

Volumetric Real-Time iOCT

Research is under way on the development of microscope-integrated intraoperative swept-source OCT. A research prototype at Duke University can produce real-time volumetric 4D imaging with up to 10 volumes per second while maintaining micron-scale resolution. The images are relayed to microscope oculars using a stereoscopic heads-up device. This platform provides surgical guidance, helping surgeons to visualize retinal pathology and iatrogenic tissue damage in ways not readily visible with current 2D images.[29,30]

CONCLUSIONS

iOCT can provide a better understanding of tissue architectural changes in the OR, thus assisting with surgical maneuvers and guiding the surgeon's decision-making (Figure 2). Researchers are working to enhance certain aspects of iOCT performance, such as instrument integration, software analysis, clinical utility, and image quality. Additional prospective randomized controlled trials would help elucidate the ultimate benefit of this technology for patient outcomes. ■

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Peripheral OCT Imaging in Practice


A new platform mitigates the challenges of image capture and prompts questions about how best to use this data in clinical decision-making.

BY NETAN CHOUDHRY, MD, FRCSC, AND SIMRAT K. SODHI, MSC

For years, obtaining peripheral OCT images has been challenging. For example, the steered image capture of peripheral OCT images relied on variables such as patients' ability to guide their gaze toward a target to capture pathology. Patient cooperation, technician skill, and extended capture time made the tool impractical for many physicians, although the data garnered from the high-quality images were often useful. Assembling montages from contiguous OCT scans similarly faces challenges related to capture time and technical training.

Either method of capturing peripheral OCT—steered image capture or montage—could take, in our experience, as long as 30 minutes. Thus, retina specialists had to weigh the benefits of the peripheral OCT data against the costs of obtaining them.

A new OCT device, the Silverstone (Optos), resolves many of these concerns. This multimodal platform integrates ultra-widefield (UWF) fundus imaging, swept-source OCT (SS-OCT), fundus autofluorescence (FAF), fluorescein angiography, and indocyanine green angiography.

Peripheral OCT capture on this platform takes a few minutes and requires neither image steering nor montaging. The screen-based interface allows technicians to quickly capture 23-mm line scans in the central retina or smaller line or volume scans in the peripheral retina.

Because quantitative data regarding the platform's real-world uses are limited, we conducted a study examining the utility of UWF and peripheral OCT in clinical practice to better understand whether clinical integration of this device would benefit physicians and patients.

DESIGN AND RESULTS

In this single-center, prospective, observational, consecutive case series, presented at the 2021 Macula Society Meeting, we imaged 91 patients (125 eyes) with any of 38 retinal pathologies (eg, retinal detachment, retinoschisis, retinal vein occlusion, retinitis pigmentosa) with disease in the posterior pole, midperiphery, or far periphery.[1]

UWF color, FAF, and peripheral SS-OCT imaging was captured on the Silverstone by two experienced retinal photographers. The photographers captured 6-mm line scans and 6-mm volume scans, as well as a 6-mm HD volume scan and 23-mm extended line OCT as needed. Patients also underwent clinical examination with a Volk digital widefield lens.

The main outcome measures were accessibility of peripheral pathology and the relationship between peripheral OCT images and clinical decision-making.

The average age of study participants was 54 (range, 21–92) years. Of the 125 eyes imaged, 86 (69%) had pathology present only in the periphery. Among those, the addition of peripheral OCT impacted clinical decision-making in 72 (84%) eyes (Figure 1).

AT A GLANCE

- The potential clinical utility of peripheral OCT is significant.
- At the 2021 Macula Society Meeting, data were presented from a study that examined the relationship between peripheral OCT obtained with the Silverstone (Optos) and clinical decision-making.
- A majority (69%) of eyes in the study presented with periphery-only pathology; among that group, data from peripheral OCT aided clinical decision-making in 84% of eyes.

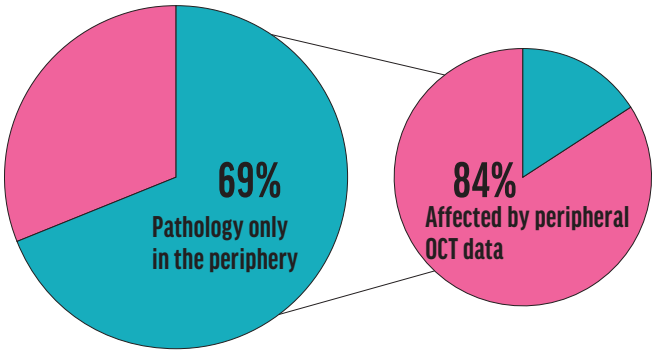

Figure 1. Among 125 eyes imaged in the study, 69% presented with pathology only in the periphery. Of those eyes, peripheral OCT data changed clinical decision-making in 84%.

These results confirmed that peripheral OCT data are clinically valuable and can guide patient care, particularly in cases involving periphery-only pathology. Of course, SS-OCT imaging of the posterior pole continues to be a mainstay of retina care. It should also be noted that peripheral OCT does not serve as a replacement for a clinical examination; rather, it allows for a more robust examination and may provide preoperative data for surgical pathologies.

SURGICAL CASES

We identified several instances in which peripheral OCT informed clinical decision-making in patients with pathologies that had a surgical indication, such as macular hole and retinal detachment. The following case presentations illustrate the real-world utility of peripheral OCT imaging.

Case No. 1

A 45-year-old White woman was referred to our clinic for a macular hole. She presented with BCVA of 20/200 OD. Imaging confirmed the presence of a macular hole, and peripheral OCT imaging captured a retinal hole in the far periphery (Figure 2). The retinal hole was treated with laser retinopexy before macular hole surgery was initiated.

The patient's retinal hole might have been detected without peripheral OCT if a modality such as UWF imaging had been used. However, without OCT, the surgeon would not have known the presence or degree of traction and fluid related to the retinal hole. In this case, there was neither fluid nor traction. These data were used in planning surgery.

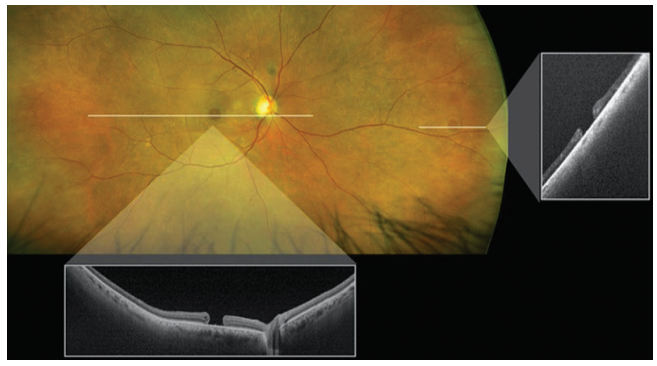

Figure 2. Peripheral OCT detected a retinal hole in the periphery. Early detection of the retinal hole led to its treatment before macular hole surgery.

Case No. 2

A 57-year-old White woman was referred for a retinal detachment with BCVA of 20/200 in the left eye. Peripheral OCT revealed no other retinal breaks or tears, and pneumatic retinopexy was performed. During the follow-up period, peripheral OCT allowed us to track the resolution of subretinal fluid and monitor healing (Figure 3).

In our experience, retinal tears addressed by pneumatic retinopexy may not resolve in the presence of undetected retinal tears or holes. In this case, the surgeon was able to execute treatment with the confidence that no other pathology was present and observe the patient during follow-up using peripheral OCT.

Case No. 3

A 41-year-old White man was referred to our clinic for suspicion of a retinal detachment. He presented with BCVA of 20/20 OD. UWF imaging demonstrated unusual pigmentation in the periphery. Further imaging with peripheral OCT revealed age-related retinoschisis (Figure 4). No retinal holes

(Continued on page 30)

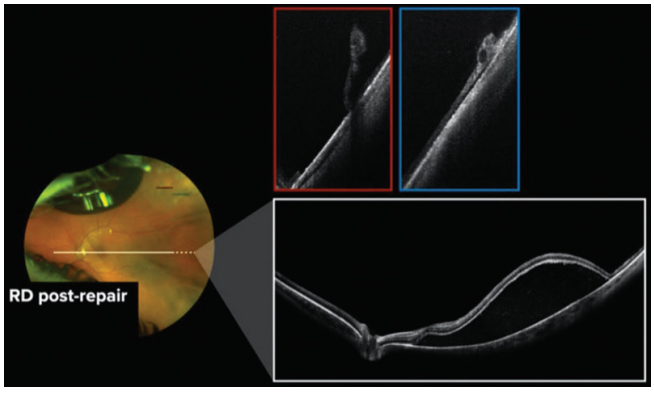

Figure 3. Peripheral OCT allowed visualization of subretinal fluid during follow-up of a patient who underwent pneumatic retinopexy for a retinal detachment.

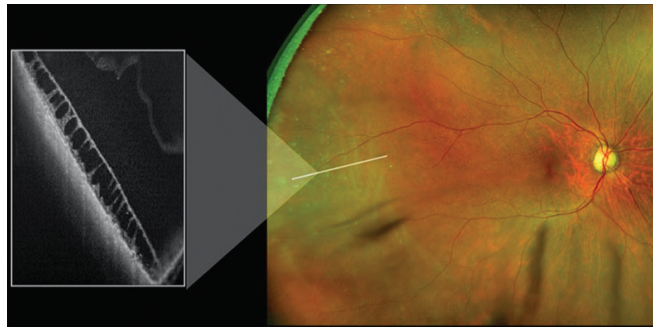

Figure 4. Age-related retinoschisis was detected on peripheral OCT in an asymptomatic patient who was referred for a possible retinal detachment.

Digging Up Buried Drusen

OCT is an excellent tool to capture optic disc drusen that elude you on fundus examination.

BY MEERA S. RAMAKRISHNAN, MD; ROBIN VORA, MD; AND AUBREY GILBERT, MD

Optic disc drusen (ODD)—progressively calcifying deposits within the optic nerve head with a prevalence of 2.4%[1]—are an important consideration in the differential for optic disc elevation. Although superficial ODD are usually easily identified with careful attention to the optic disc on fundus examination, buried ODD can be more difficult to spot. Noting their presence in a timely manner is crucial, however, as this can potentially prevent unnecessary testing and inappropriate treatment for papilledema.

Fundus autofluorescence (FAF) can reveal superficial ODD as discrete hyperautofluorescent lesions, but this imaging modality is not sensitive for buried ODD. B-scan ultrasonography can assess for buried ODD as well as measure optic nerve sheath diameter, but it can be highly operator-dependent and is not sensitive for noncalcified ODD.[2]

Thus, over the past 10 years, OCT has become increasingly useful as an adjunctive tool in the detection of ODD and the workup for possible papilledema.

The benefits of OCT are numerous. It is noninvasive, easily accessible in most clinical practices, and not as operator-dependent as ultrasonography. The evolution from time-domain (TD) to spectral-domain (SD) and now swept-source OCT has been accompanied by significant improvements in image resolution and reduced artifactual findings.

For example, as imaging improved, subretinal hyporeflectivity—previously described in association with ODD on TD-OCT—was ultimately determined to be secondary to poor signal penetration.[3]

The most recently described protocols for imaging ODD, which produce a higher ODD detection rate than B-scan ultrasonography,[4] involve the use of SD-OCT in enhanced depth imaging (EDI) mode to produce a volume scan with either radial or both horizontal and vertical sections.[5] To measure retinal nerve fiber layer (RNFL) thickness, a peripapillary circle scan can be used.

ODD CHARACTERISTICS

The Optic Disc Drusen Studies (ODDS) Consortium has developed a consensus definition of ODD on EDI SD-OCT.[5] ODD must have two key characteristics: They should be

AT A GLANCE

- OCT has become increasingly useful as an adjunctive tool in the detection of optic disc drusen (ODD) and the workup for possible papilledema.
- ODD must have two key characteristics: They should be above the lamina cribrosa, and they should have a hyporeflective core.
- Enhanced depth imaging spectral-domain OCT can refine the diagnostic approach by providing direct visualization of buried ODD.

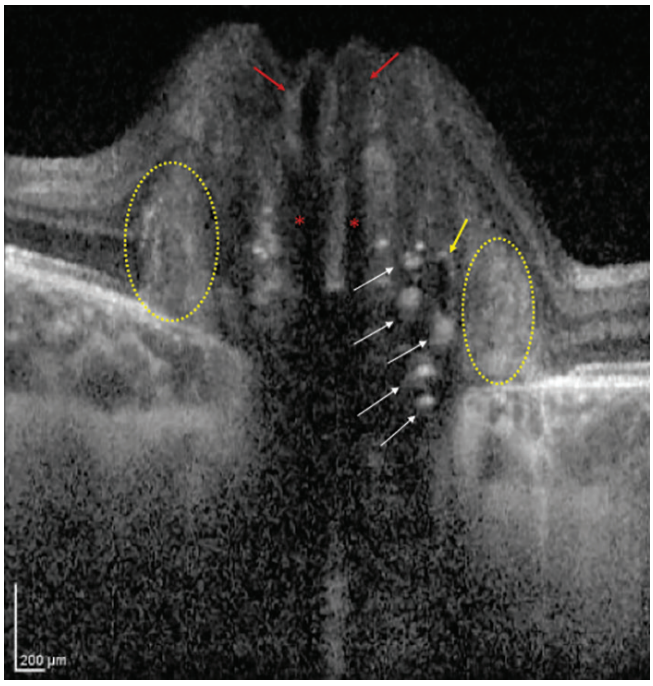

Figure. This EDI SD-OCT of an optic disc reveals several features. ODD (yellow arrow) usually have a hyporeflective core and hyperreflective margin. They are found above the lamina cribrosa. Conglomerates of hyperreflectivity may also represent early disc drusen (white arrows). Blood vessels (red arrows) can be caught in cross-section and often present with trilaminar reflectivity. Arterioles and venules frequently travel together in a figure-eight formation. Vessels are distinguished from ODD by posterior shadowing (red asterisks). PHOMS (yellow circles) are not ODD and instead may represent bulging axons.

above the lamina cribrosa, and they should have a hyporeflective core. In addition, there may be a full or partial hyperreflective margin, often more prominent superiorly, surrounding the hyporeflective signal. Occasionally, multiple smaller ODD can coalesce to form a larger ODD that maintains a hyporeflective core but may also demonstrate patchy internal reflectivity. Clusters of hyperreflective horizontal lines may also be seen in eyes with ODD or in the fellow eyes of patients with unilateral ODD; it is unclear whether these represent early ODD changes.[4,5]

The ODDS Consortium also identified other findings on OCT that can be mistaken for ODD. Blood vessels caught in cross-section can appear as small circular objects with trilayer reflectivity—typically with a hyperreflective wall, an inner hyporeflective ring, and a hypo- or isoreflective core (Figure). However, there will be significant shadowing of the underlying layers, which is not seen with ODD. As arterioles and venules travel together out of the optic nerve head, the two lumina are often seen adjacent to each other in a figure-eight configuration—although this may not be evident if vessels are imaged in an oblique or longitudinal fashion. When in doubt, scrolling through the OCT raster scan can help distinguish between the tubular course of blood vessels and a more discrete ODD.

DISTINGUISHING BETWEEN PAPILLEDEMA AND PSEUDOPAPILLEDEMA CAN HAVE A SIGNIFICANT IMPACT ON THE REST OF A PATIENT'S CARE EXPERIENCE.

Patients with ODD also commonly exhibit peripapillary hyperreflective ovoid mass-like structures (PHOMS) on OCT. In the past, researchers debated whether these represented variants of ODD.[5-7] However, PHOMS are hyperreflective, not hyporeflective, and lack sharp margins. They are also found external to or surrounding the disc. Unlike ODD, they are not visible on ultrasonography or FAF. In addition, OCT detects PHOMS in patients with papilledema without ODD,[8] suggesting that they are not specific to pseudopapilledema. The ODDS Consortium suggested that PHOMS correspond with lateral bulging of optic nerve axons into the peripapillary retina and recommended that they be excluded as a criterion for the diagnosis of ODD unless future histopathologic evidence suggests otherwise.[5]

With respect to RNFL abnormalities, studies show correlation with ODD diameter and location.[6,9] In eyes in which ODD are more superficial, larger, and confluent, visual field defects can result from severe RNFL thinning.[10] Thinning may also be a consequence of ODD-associated ischemic optic neuropathy or chronic axonal injury.[11] However, patterns of RNFL thickness are nonspecific for either pseudo- or true papilledema.[12]

EMBRACING OCT

Distinguishing between papilledema and pseudopapilledema can have a significant impact on the rest of a patient's care experience: Do they receive reassurance and counseling, or a trip to the emergency department for neuroimaging and lumbar puncture?

In severe papilledema, the diagnosis is usually readily apparent from history and fundus examination alone; however, it can be difficult to clinically differentiate mild papilledema from pseudopapilledema due to buried ODD. To further complicate matters, pseudopapilledema and papilledema are not mutually exclusive.

EDI SD-OCT can refine the diagnostic approach by

providing direct visualization of buried ODD. If there is optic disc elevation and no evidence of ODD, it may be reasonable to evaluate further for the presence of increased intracranial pressure; if there are established ODD, clinicians can determine whether further workup is necessary to rule out coexisting papilledema.

Fluorescein angiography, though invasive, can sometimes help in equivocal cases to reveal leakage in optic disc edema that is absent in pseudopapilledema,[13] although mild cases can be challenging to distinguish.

Ultimately, a multipronged approach that includes optic nerve imaging, patient history, visual fields, and examination findings can help clarify the overall clinical picture and determine the necessity for urgent evaluation. As OCT technology continues to advance, so too will our understanding of its role in the diagnosis and management of optic nerve pathology. ■

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(Continued from page 27)

OTHER OCT OPTIONS

Practices looking into devices capable of peripheral OCT imaging can also consider the Heidelberg Spectralis OCT 2 with a 55° lens[1] and the Canon Xephilio OCT-A1, which gained FDA clearance in 2019.[2]

1. Cereda MG, Corvi F, Cozzi M, Pellegrini M, Staurenghi G. Optical coherence tomography 2: diagnostic tool to study peripheral vitreoretinal pathologies. *Retina*. 2019;39(2):415-421.
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or detachments were detected. Because the pathology was not threatening to the fovea and the patient was asymptomatic, we elected observation over treatment.

Without peripheral OCT data in this case, the clinician would be faced with a more challenging and less certain diagnosis that might have required clinical examination with scleral depression or further follow-up. With peripheral OCT, an accurate diagnosis was made quickly and an observation plan was established.

COLLECTING MORE DATA

Use of this new tool for peripheral OCT has expanded our understanding of various retinal conditions. Clinicians particularly benefited from peripheral OCT data when addressing pathologies that required surgery (eg, retinal detachment, macular hole), as surgical planning and postoperative follow-up were more robust.

Further, there were some instances in which UWF imaging combined with peripheral OCT yielded data suitable for an accurate diagnosis, such as in Case No. 3 here, in which peripheral discoloration on UWF color imaging required further exploration with OCT imaging.

As with all new technology, there is room for improvement, particularly for the addition of steered imaging and enhanced vitreous detail. Of course, all devices have a cost, which must be taken into consideration for each practice.

The addition of a peripheral OCT device, especially as the technology improves, may be useful for busy retina clinics, particularly if the device is easy to use with fast data capture. ■

1. Choudhry N. Feasibility and clinical utility of peripheral OCT imaging using a novel integrated SLO ultra-widefield imaging full-field swept-source OCT device. Paper presented at: Macula Society Meeting; February 6-7, 2021.

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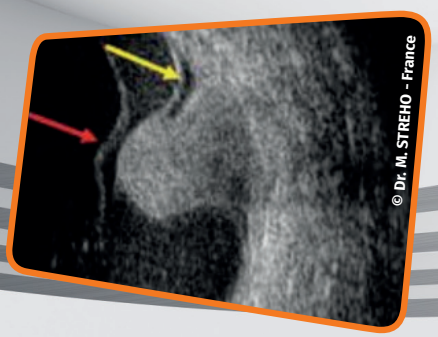

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OCTA: Pearls and Pitfalls

Here's a look at what this new imaging tool can do—and some limitations to be aware of.

BY MEIRA FOGEL LEVIN, MD; ADRIAN AU, MD, PHD; KIRK K. HOU, MD, PHD; AND DAVID SARRAF, MD

OCT angiography (OCTA) is a safe, noninvasive imaging modality that provides depth-resolved imaging of the retinal and choroidal vasculature. With the use of dense volumetric OCT scans, OCTA can detect change (ie, decorrelation) in the OCT signal over very short time periods based on red blood cell motion. The surrounding static tissue remains unchanged on OCT during these short intervals, and the decorrelation information can then be projected in a 2D en face image segmented through the layers of the retina and choroid.[1,2]

The depth-resolved capabilities of OCTA facilitate identification and isolation of the retinal vasculature in both normal and pathologic states that are poorly differentiated by fluorescein angiography (FA).

The normal retinal vasculature is composed of four parallel capillary plexuses divided into two major circulations. The superficial vascular complex (SVC) includes the nerve fiber layer capillary plexus and the superficial retinal capillary plexus (SCP) located between the nerve fiber layer and the inner plexiform layer. The deep vascular complex (DVC) comprises the intermediate retinal capillary plexus and the deep retinal capillary plexus (DCP) located in the inner and outer borders of the inner nuclear layer (INL), respectively.[3]

THE VASCULATURE DISRUPTED

The DVC is difficult to capture with FA, which is primarily helpful to evaluate the SVC.[3,4] In contrast, OCTA can localize the exact layer of ischemia in patients with acute retinal vein and artery occlusions. Specifically, patients with mild forms of retinal vein occlusion can initially present with localized INL hyperreflectivity on OCT (ie, paracentral acute middle maculopathy [PAMM]) with corresponding DCP flow deficit on OCTA.[5,6] This initially develops in the region of the veins and is referred to as perivenular PAMM with en face OCT.

In more severe cases, PAMM can become more diffuse, and the ischemia can extend into the inner retina closer to

AT A GLANCE

- OCT angiography (OCTA) provides depth-resolved imaging of the retinal vasculature in both normal and pathologic states.
- OCTA is a valuable resource to detect macular neovascularization in a wide range of conditions, including AMD, myopia, presumed ocular histoplasmosis syndrome, multifocal choroiditis, panuveitis, pseudoxanthoma elasticum, and placoid diseases.
- Several types of artifacts have been described during acquisition of OCTA images, the most significant being motion, shadow, projection, and pseudoflow artifact.

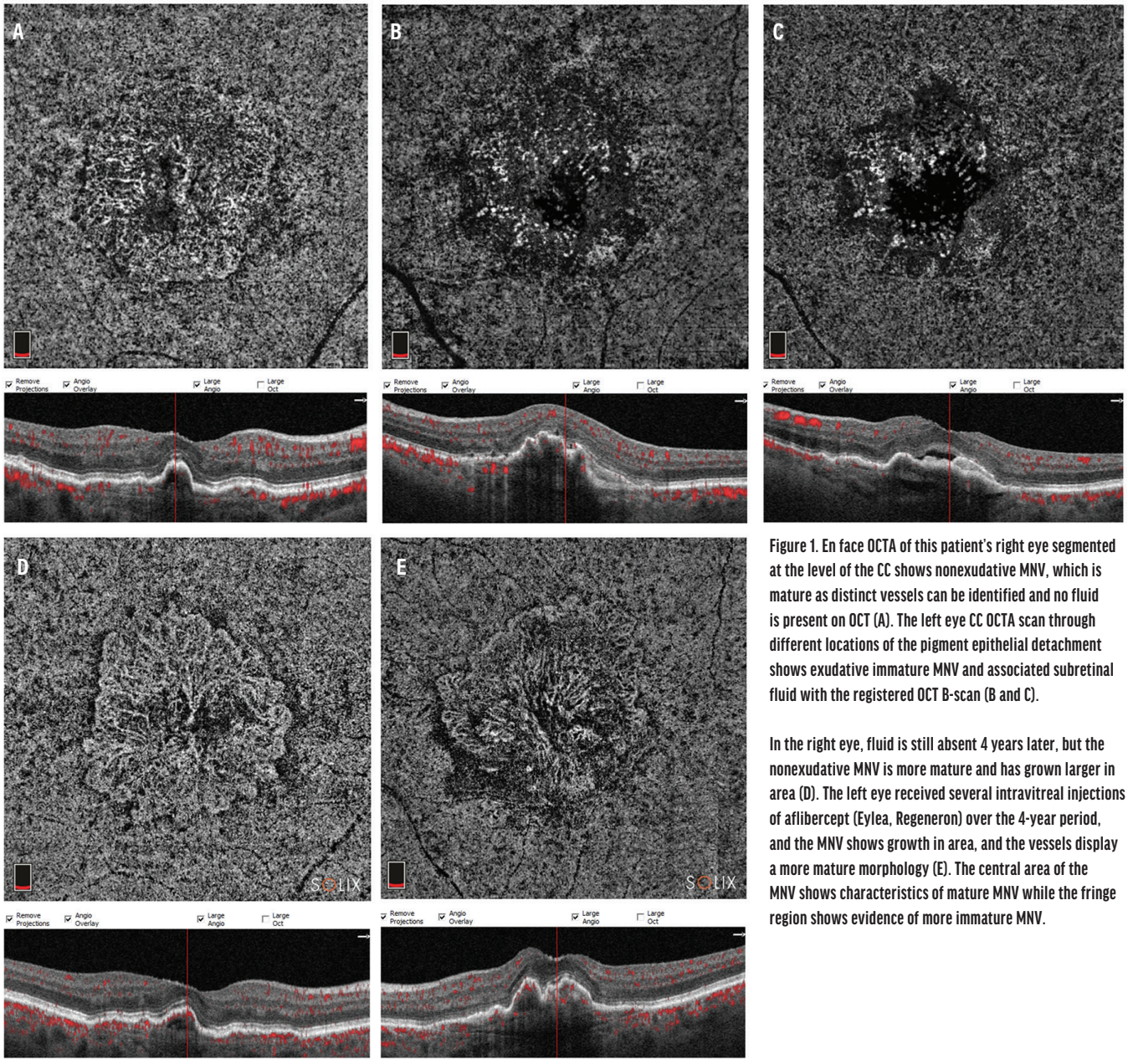

Figure 1. En face OCTA of this patient's right eye segmented at the level of the CC shows nonexudative MNV, which is mature as distinct vessels can be identified and no fluid is present on OCT (A). The left eye CC OCTA scan through different locations of the pigment epithelial detachment shows exudative immature MNV and associated subretinal fluid with the registered OCT B-scan (B and C).

In the right eye, fluid is still absent 4 years later, but the nonexudative MNV is more mature and has grown larger in area (D). The left eye received several intravitreal injections of aflibercept (Eylea, Regeneron) over the 4-year period, and the MNV shows growth in area, and the vessels display a more mature morphology (E). The central area of the MNV shows characteristics of mature MNV while the fringe region shows evidence of more immature MNV.

the arteriole pole, a mechanism recently described as the ischemic cascade.[4,7] These findings illustrate the new insights that en face OCT and OCTA have provided into both pathologic and normal retinal vascular states.

OCTA also provides a greater understanding of the choroid in retinal disease because of its ability to better capture the presence of choroidal ischemia and identify macular neovascularization (MNV).

In placoid spectrum diseases—such as acute posterior multifocal placoid pigment epitheliopathy and persistent placoid maculopathy—OCTA can effectively illustrate inner choroidal ischemia and can help physicians monitor for progression and response to treatment.[8]

OCTA is also an effective tool to quantitate choroidal ischemia in dry AMD. Choriocapillaris (CC) flow deficits can be identified in patients with early and intermediate dry AMD, indicating that CC ischemia is an important driving force in the development and progression of the disease.[9-13]

In neovascular disorders, OCTA can detect MNV in a wide range of conditions, including AMD, myopia, multifocal choroiditis, panuveitis, presumed ocular histoplasmosis syndrome, pseudoxanthoma elasticum, and placoid diseases.[2,8,14-21]

In patients with AMD, OCTA can identify morphologic differences that indicate the maturity of the neovascularization. These morphologic features have been associated with

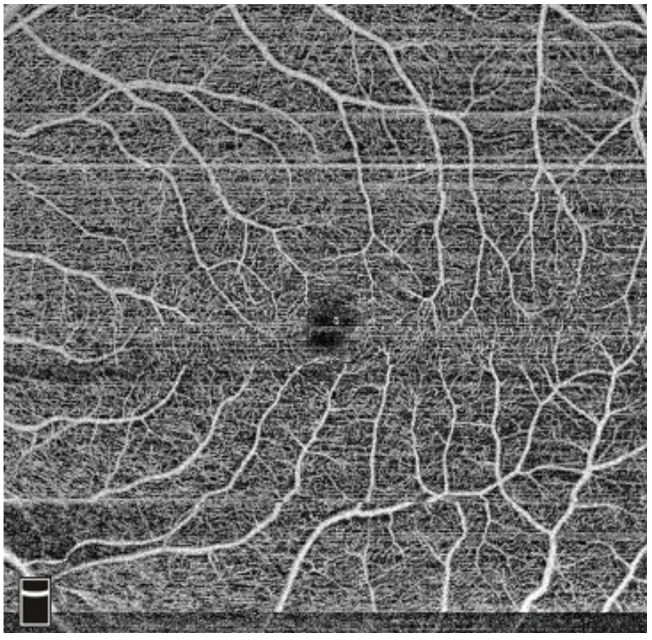

Figure 2. This 6x6 mm en face OCT angiogram of the left eye shows evidence of motion artifact. Note the horizontal lines that are present due to eye movement.

growth of the neovascular lesion, but reliable OCTA markers or predictors of disease activity and response to therapy are lacking.[22] OCTA is also a critical modality to help identify nonexudative MNV and rule out neovascularization in eyes with intermediate AMD and fluid (Figure 1).[23]

IMAGING HURDLES

In addition to the limitations typically encountered with other imaging modalities, such as the need for minimal pupil size, patient cooperation, clear media, and stable fixation, OCTA has unique challenges. For one, the device depends on a threshold level to detect blood flow. To reduce unwanted noise, the manufacturer sets a threshold level of motion detection. If the threshold is set too high, true blood flow signals may be missed; conversely, a low threshold level can cause false-positive flow signals. Thus, OCTA may be less sensitive than FA in detecting microaneurysms and polyps (ie, polypoidal choroidal vasculopathy) because the slow flow can be below OCTA's threshold detection level.[2,24,25]

Another challenge is the presence of segmentation errors. These errors occur more frequently in eyes with pathologies in which the normal retinal architecture is disrupted, requiring manual correction.[26]

Several types of artifacts have been described in the acquisition of OCTA images, the most significant being motion, shadow, projection, and pseudoflow artifact.[2,15,24] Any form of eye movement, including head movement, breathing, blinking, or even minimal fixation changes and micro-motion due to blood flow pulsation, can result in motion artifacts. These movements can cause discrepancies in the consecutive scans that manifest as vertical or horizontal lines on en face images (Figure 2).

A shadow artifact is caused by attenuation of the signal due to light absorption or scattering. It can be caused by any obstacle anterior to the retina such as posterior vitreous detachment, vitreous hemorrhage, or vitritis. Even hyperreflective retinal material such as hard exudate or drusen can obstruct the retinal and choroidal layers.[2,24]

Projection artifact refers to a reflection of superficial blood flow in a deeper layer, generating a false positive flow signal on the en face image.[2,24,25]

Pseudoflow artifact is false-positive flow detected within hyperreflective structures such as hard exudate, drusen, or intraretinal retinal pigment epithelial cells.[2,24,27] False-positive detection of MNV due to the presence of pseudoflow is a common pitfall, and care should be taken when evaluating OCTA to avoid misinterpretation based on artifacts.

Various techniques have been developed to decrease artifacts, including eye-tracking strategy and motion correction and projection removal algorithms, with partial success (Figure 3).[2,24,26,27]

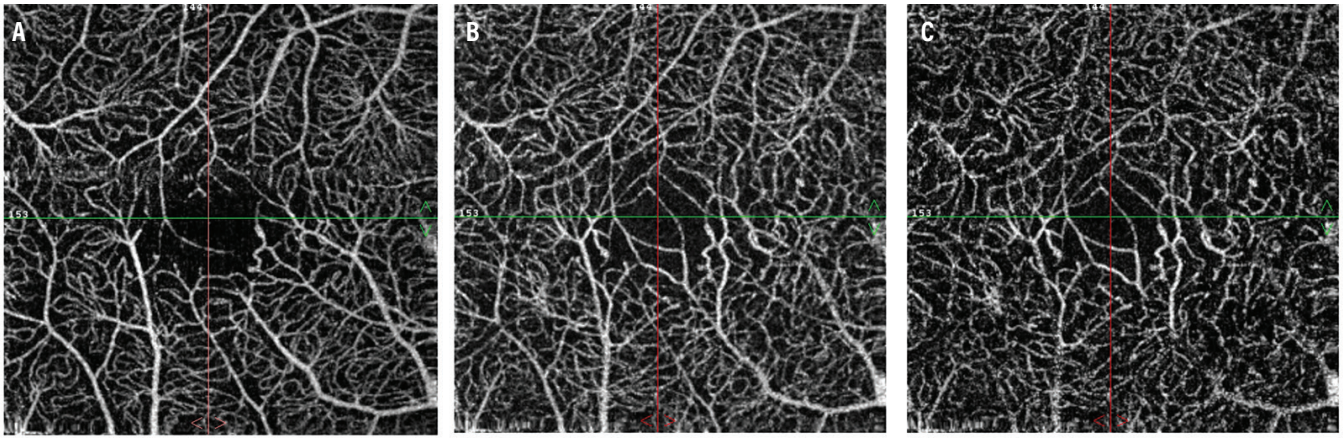

Figure 3. En face OCT angiogram at the level of the SCP (A). En face OCTA scan of the DCP shows projection artifact from the SCP (B). After application of a projection removal algorithm, the superficial vessels are removed, providing a cleaner representation of the DCP (C).

OCTA PROVIDES IMPORTANT INSIGHTS INTO THE RETINAL AND CHOROIDAL VASCULATURE WITH DEPTH-RESOLVED CAPABILITY, AND USES AN APPROACH THAT IS NONINVASIVE, FACILE, AND REPRODUCIBLE.

FINAL TAKEAWAY

OCTA provides important insights into the retinal and choroidal vasculature with depth-resolved capability, and uses an approach that is noninvasive, facile, and reproducible. This modality has generated significant knowledge not only regarding the normal anatomy of the retinal microvasculature but also as pertains to pathologic states, such as retinal vascular occlusions, choroidal ischemia, and MNV.

OCTA can facilitate the depth-resolved detection of ischemia in both the retinal and choroidal circulations and is an indispensable tool to capture MNV, providing more accurate identification and diagnosis and more effective disease monitoring than is possible with conventional systems such as dye-based angiography.

However, as with all imaging modalities, OCTA comes with limitations, the understanding of which is essential to maximize its application for the evaluation and management of retinal disease. ■

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AI: The Missing Link in Telemedicine

New tools are paving the way for timely and cost-effective screening programs.

BY SHARMINA ALAUDDIN, MBBS, DO, FCPS; CATHERINE YE, BA, MBS; OSCAR OTERO, MD; JAKE RADELL, MA; ARUN GOVINDAIAH, MS; ALAUDDIN BHUIYAN, PHD; AND R. THEODORE SMITH, MD, PHD

Despite the widely understood importance of visual health, diagnostic eye care continues to fail a large segment of our population, especially the medically underserved. This often results in catastrophic consequences, such as preventable blindness from AMD, glaucoma, or diabetic retinopathy (DR).

Even with the AAO's recommendation for timely and ongoing vision examinations for patients with type 1 and type 2 diabetes,[1] half of all diabetics do not get the eye examinations necessary to diagnose DR. Left untreated, DR can lead to irreversible blindness.

Likewise, AMD remains the leading cause of blindness in the developed world, followed closely by glaucoma. Both conditions are underdiagnosed in their early stages, with diagnosis often occurring only after irreparable vision loss has already occurred. Vision loss often leads to a downward spiral in overall health: depression, loss of independence and mobility, nursing home care, falls, fractures, bleeds, and, ultimately, death.

AMD INNOVATIONS

Obstacles to early diagnosis can include financial barriers, difficulty accessing care, and a lack of motivation. One proposed solution to overcome these barriers is the adoption of telemedicine.

R. Theodore Smith, MD, PhD, Director of Biomolecular Retinal Imaging at the New York Eye and Ear Infirmary of Mount Sinai and a professor of ophthalmology and neuroscience at the Icahn School of Medicine at Mount Sinai, strongly believes that telemedicine is the answer.

With telemedicine, "Physicians would be able to inform patients if they are at risk for a problem before they even leave the office and, if so, encourage them to get specialized care," he explained. "It could represent a major step for public health by alerting patients to problems that too

AT A GLANCE

- The number of required annual screenings for AMD, glaucoma, and diabetic retinopathy easily tops 100 million, with a prohibitive yearly cost of $23 billion.
- A new deep-learning and telemedicine-based screening tool for AMD detection showed an accuracy of 96.29% on referable AMD and 86% for predicting disease progression within 1 to 2 years.[5]
- The AI-based tools are developed by iHealthScreen, and the current study–led by R. Theodore Smith, MD, PhD–focuses on the prospective trial and offers a portfolio of visual sensory function tests that provide additional information and, potentially, higher accuracy in the screening.

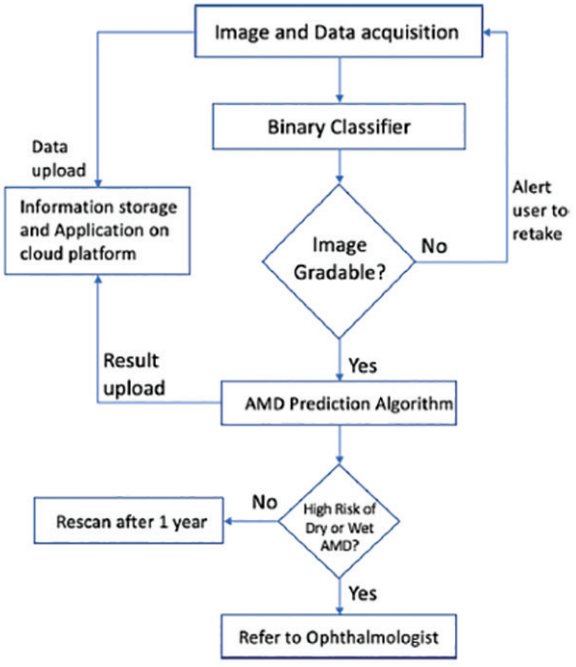

Figure 1. High-level flow chart for overall screening and prediction of late AMD.

often today lead to advanced disease and even blindness."[2]

The development and implementation of a screening tool for early detection of AMD is now of greater importance than ever, as the Age-Related Eye Disease Study has shown that specific antioxidants and vitamin supplements can reduce the risk of progression from intermediate to late-stage AMD. If telemedicine screening can bring about increased use of these supplements by AMD patients, it has the potential to meaningfully decrease AMD progression and associated visual loss.

Considering this urgent need, Alauddin Bhuiyan, PhD, and his team at iHealthScreen developed artificial intelligence (AI)-based AMD screening and prediction tools. Now, Dr. Bhuiyan and Dr. Smith are working on a prospective trial funded by the National Institutes of Health (NIH).

"This technology could be particularly useful in identifying someone who has slipped across the boundary to intermediate or higher-risk AMD and is thus more statistically likely to progress," Dr. Smith said. "By alerting patients and their physicians to the potential dangers ahead, we believe this approach could play a very important public health role."[2]

The tools for this approach are already available and are more affordable than conventional screening and office-based care methods. However, a significant cost worth considering is that of the skilled ophthalmologist integral to telemedicine image evaluation and diagnosis.[3] The number of annual screenings required (AMD for all patients aged 50 or above, glaucoma for all patients over age 40, DR for all diabetics) easily tops 100 million, with a prohibitive yearly cost of $23 billion.

The missing link between affordability and need may

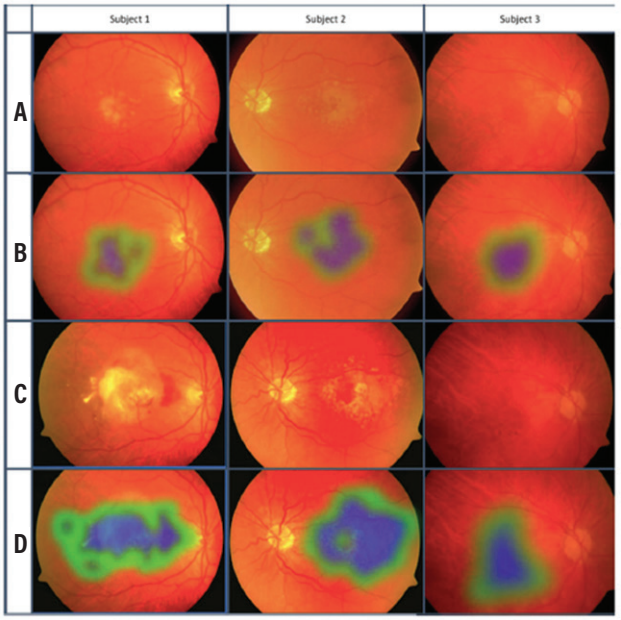

Figure 2. Fundus photos of three patients at baseline (A) and the corresponding heat maps (B) of early AMD signs detected by the classifier. Blue and green colors indicate strong and weaker signs of AMD, respectively. Follow-up photos show conversion to late AMD (C). Follow-up heat maps show larger areas and worse signs signifying late AMD (D).

be AI. Dr. Smith and Dr. Bhuiyan, the founder and CEO of iHealthScreen and an associate professor at Icahn School of Medicine at Mount Sinai, have led the way for several years in building AI systems with deep learning (DL) algorithms capable of making retinal diagnoses (AMD, DR, and glaucoma) using retinal photographs.

"We were able to train these convolutional neural networks on hundreds of thousands of photographs to be able to recognize features that determined if they fell into the broad categories of early, intermediate, or advanced AMD," Dr. Smith explained. "And that's the beauty of AI: it can define patterns and make inferences from gigantic data sets that humans could never wrap their minds around."[2]

Sharmina Alauddin, MBBS, DO, FCPS, presented results with the screening tool for AMD detection at the 2020 AAO Annual Meeting.[4] Prospectively vetted in the clinic setting with inexpensive automated cameras operated by trained staff, the tool uses AMD-specific algorithms to classify patients into early, intermediate, or advanced AMD. A machine learning technique is used to predict progression to late-stage AMD (Figures 1 and 2). The system's accuracy for predicting disease progression within 1 to 2 years is 86%, higher than any other tool currently available.[5]

TARGETING DR

The algorithms for DR screening are also promising, with the ability to grade the severity of DR on a five-point scale (no, mild, moderate, severe, and proliferative DR) based on the presence and extent of microaneurysms, exudates, hemorrhages, and

other abnormalities detectable in fundus photographs. When measured prospectively in the clinic against human expert screening, the AI system achieved a sensitivity of 94.7% and a specificity of 100% for referral-level DR (moderate or worse), which is adequate for FDA approval of a screening system.[6] Larger scale trials are planned to further test the five-point DR algorithm on the path to FDA approval. The federal government, noting the progress being made in AI-based retinal screening, has developed a code for automated retinal diagnosis that will pay $35, not $230,[3] paving the way for a potentially affordable solution.

TARGETING GLAUCOMA

Our group also performed a study for screening glaucoma suspects. Because glaucomatous vision loss may be preceded by an enlargement of the cup-to-disc ratio (CDR), we propose to develop and validate an AI-based CDR grading system that may aid in effective glaucoma suspect screening. The results were presented at ARVO 2020.[7] We tested the system using a dataset constructed from various studies and achieved an accuracy of 89.67%.[7] For external validation, we used the Retinal Fundus Image Database for Glaucoma Analysis dataset, which has 638 gradable quality images, and achieved an accuracy of 83.54%.[7]

FUTURE PLANS

AI is not a panacea. The algorithms can miss vision-threatening disease when left on their own—a concern clinicians and regulators alike must address before any AI system is cleared for independent use. Our team is planning a complementary fail-safe: simple, *functional* vision testing of what the eye actually sees. If a patient fails these tests, regardless of what the AI thinks, something is wrong and the patient must be referred to a specialist. If the BCVA is 20/200 (legally blind), referral is clearly required. Our screening system, therefore, includes a portfolio of visual sensory function tests that are not AI, easily administered on an iPad, creating a safety net for AI errors.

This proposal, then, is a full-fledged assault on the three major blinding eye diseases in primary care settings, particularly in underserved communities, with retinal photography, AI, and *functional* tests.

Machine learning with combined structural and functional data will optimize identification of disease and prediction of outcomes. Our study will be carried out in six clinics by clinic staff under physician supervision: a primary medical clinic for the underserved; a diabetes clinic, a geriatric clinic, and two retina clinics. In total, 2,800 individuals will be enrolled over 5 years, with patient outcomes followed over 3 years, with cohorts chosen to appropriately sample the general population and with enrichment of AMD, DR, and glaucoma patients to focus on these highly prevalent diseases.

The long-term goal is large-scale screening for blinding eye diseases in primary care settings, using telemedicine and AI with nonmydriatic retinal photos unified with functional testing. This will provide cost savings over telemedicine alone and will help to address health care disparities in disadvantaged populations, providing both early detection and efficacious treatment of blinding diseases. ■

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Maximizing the Performance of 3D Visualization Systems

A few key parameter adjustments could significantly improve your OR experience.

BY DAVID R. CHOW, MD, FRCSC

The introduction of 3D visualization systems for vitreoretinal surgery a number of years ago was met with significant enthusiasm and excitement. Surgeons were enticed by the potential advantages these types of systems offered, including enhanced ergonomics, better visual performance, a better teaching platform for educational institutions, greater engagement among the OR surgical staff, overlay of surgical metrics on the display, and the ability to alter the image of the surgical environment (color, contrast, etc.) and to use lower light levels during surgery (reducing the risks of phototoxicity). Overall, it brought a sense of the future with all of its potential.

After a few years on the market, however, the momentum stalled. Many surgeons' initial clinical experiences ended in disappointment because of a number of issues: perceived poor visual performance—either poor resolution, or a sense of too little or too much depth of field (DOF) or "swimming inside the eye"; increased latency, particularly with external work; inconsistent color performance; difficulty with ergonomics because the screen is on the side of the bed; difficulty with the sizing of the large display and control unit in smaller ORs; splitting of the image, particularly on the edges of the display; and high cost that made acquisition a challenge.

A survey of retina fellows during the 2020 Retina Fellows Forum found that 42% of training institutions had access to an Ngenuity 3D visualization system (Alcon), yet nearly half of those institutions never used the system and none of them used it 100% of the time. Only 50% of the responding fellows stated that they would use the system routinely if given a choice on graduation.

Because of this underperformance in clinical reality, I set out with my students to perform a number of studies to determine how to maximize the performance of the Ngenuity system.

PARAMETER SHOWDOWN

Our first study aimed to determine the effect of surgeon-controlled parameters (eg, monitor viewing distance, camera aperture, and microscope magnification) on the lateral resolution of the display. Our data showed that the most important factor in maximizing lateral resolution was maximizing the magnification of the microscope, followed by keeping the display at 1.2 m or, at most, 1.5 m from the surgeon.[1] The camera aperture, when varied between 30% and 75%, had little effect on lateral resolution.

Interestingly, when the display was tested at 2 m (which 54% of fellowships used in 2019 and 17% in 2020, according to the fellow's survey) there was a significant drop in resolution by about 25%, which explains some of the resolution complaints in clinical reality (Figure 1). Our advice from this data is that when the surgeon needs the best resolution

AT A GLANCE

- Early 3D visualization systems met with early adaptation issues, such as inconsistent color and visual performance and questions of latency.
- A recent training survey found that 42% of North American training institutions had access to an Ngenuity 3D visualization system (Alcon), but nearly half of them never used the system and none used it 100% of the time.
- Optimizing surgeon-controlled parameters including monitor viewing distance, camera aperture, and microscope magnification can improve the system's performance.

LATERAL RESOLUTION			
	Zoom 10x	Zoom 15x	Zoom 20x
Monitor Viewing Distance: 1.2 m			
Camera Aperture: 30%	23.6 lp/mm ±3.0	47.1 lp/mm ±3.1	59.3 lp/mm ±4.0
Camera Aperture: 50%	18.0 lp/mm ±2.0	45.4 lp/mm ±0.05	54.9 lp/mm ±0.05
Camera Aperture: 75%	25.7 lp/mm ±4.8	40.5 lp/mm ±4.6	57.0 lp/mm ±0.0
Monitor Viewing Distance: 1.5 m			
Camera Aperture: 30%	21.8 lp/mm ±1.4	41.9 lp/mm ±2.8	59.3 lp/mm ±4.0
Camera Aperture: 50%	20.1 lp/mm ±0.0	41.9 lp/mm +2.8	54.9 lp/mm ±3.5
Camera Aperture: 75%	19.4 lp/mm ±1.2	38.8 lp/mm ±2.4	57 lp/mm ±0.0
Monitor Viewing Distance: 2.0 m			
Camera Aperture: 30%	19.4 lp/mm ±1.2	36.0 lp/mm ±0.0	45.3 lp/mm ±0.0
Camera Aperture: 50%	18.6 lp/mm ±1.2	32.0 lp/mm ±0.0	43.6 lp/mm ±2.8
Camera Aperture: 75%	17.9 lp/mm ±0.0	32.0 lp/mm ±0.0	43.6 lp/mm ±2.8

lp/mm – line pairs per mm
Gonzalez-Saldivar G, Chow DR. Comparison of simulated surgical skills using different camera aperture settings for digitally assisted vitreoretinal surgery. *J Vitreoretinal Dis*. 2019;3(5):328-331.

Figure 1. Lateral resolution changes based on monitor viewing distance.[2]

during peeling of the internal limiting membrane (ILM), he or she should increase magnification on the microscope and make sure the display is 1.2 m distant.

Our next study evaluated the Ngenuity system's DOF with various parameters. The results showed that maximal DOF was obtained at the lowest microscope magnification and with the camera aperture at 30% (Figure 2).[1] A small clinical validation with a surgical wet-lab task with exaggerated 3D requirements in a group of masked test subjects showed better task completion times and accuracy with the camera aperture at 30% than at 75%.[2]

To maximize DOF at any magnification, the surgeon should keep the aperture at 30%. (Interestingly, the survey data in 2020 found that 47% of responding fellows were unaware that the 3D Ngenuity camera had an adjustable aperture.) However, if the surgeon finds the increased DOF of the Ngenuity uncomfortable compared with the conventional microscope, he or she should open the aperture to 50% to collapse the DOF.

The final visual parameter we assessed was depth resolution, which is a 3D system parameter that measures the finest axial depth possible. Our data, pending publication and presented at Euretina 2020, showed that the most important variable to maximize depth resolution was keeping the camera aperture at 30%, followed by maintaining the viewing distance at 1.2 m—the same settings that also maximize lateral resolution.

To peel an ILM, depth resolution is crucial, and the combination of a viewing distance of 1.2 m, a camera aperture of 30%, and maximized microscope magnification will provide the surgeon with the best visual performance with respect to lateral resolution, DOF, and depth resolution.

OVERCOMING DELAYS

Latency, particularly when performing external work, is a frequent complaint from surgeons, but not something I have experienced when using the Ngenuity system.

During the 2020 American Society of Retina Specialists conference, we presented results of our study exploring a titratable latency display on the Ngenuity. Test participants were evaluated objectively and subjectively while performing external suturing tasks or ILM peeling at four latencies: 50 ms (the lowest possible), 70 ms (the current latency of the Ngenuity system), 90 ms (the latency on the TrueVision 3D system, the precursor of the Ngenuity platform), and 122 ms. At 70 ms latency, only 4% of test subjects detected latency for external suturing and 0% for ILM peeling. Objective data revealed no differences in performance at any of the tested latencies, and subjective data suggested that the test subjects found external suturing at 122 ms more difficult, with a 60% drop in usability reported. Overall, our data confirmed to us that there are no clinical performance implications at the current Ngenuity latency of 70 ms.

COLOR IS KEY

Our most recent research explored the color performance of the Ngenuity's camera and display. Ancedotal clinical experience has suggested variability in the color performance

DEPTH OF FIELD – "THE REAL WORLD"			
	Zoom 10x	Zoom 15x	Zoom 20x
Camera Aperture: 30%	3.6 mm ±0.2	2.3 mm ±0.2	1.4 mm ±0.6
Camera Aperture: 50%	2.4 mm ±0.05	1.25 mm ±0.05	1.0 mm ±0.1
Camera Aperture: 75%	1.8 mm ±0.2	1.1 mm ±0.05	0.8 mm ±0.1
Gonzalez-Saldivar G, Chow DR. Comparison of simulated surgical skills using different camera aperture settings for digitally assisted vitreoretinal surgery. *J Vitreoretinal Dis*. 2019;3(5):328-331.			

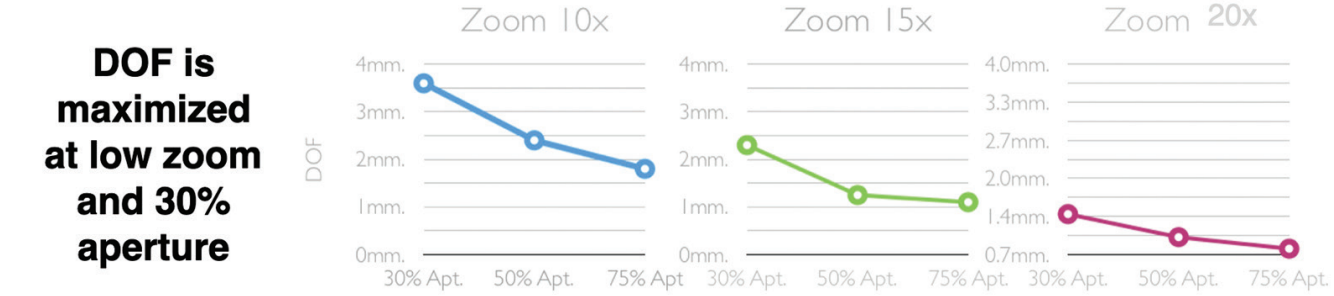

Figure 2. Depth of field parameters based on aperature and magnification.[2]

of the Ngenuity platform (Figure 3). We hypothesized that the white-balance process was contributing to this inconsistency. However, our data revealed consistent color performance when the white-balance process was altered in several ways. The only significant deviation in color performance occurred when white balance was performed using the surgeon's gloved hand.

We also noted that the color performance remained stable over an extended period of time following white balance, suggesting that this process does not need to be performed daily, or likely even weekly. We also noted that color performance was better maintained by white-balancing with the laser filter in place rather than adding the filter intraoperatively. Further studies on the color performance of the platform are onging.

DIM THE LIGHTS

Since the Ngenuity platform's release, many surgeons have reported operating at much lower light pipe levels (some lower than 5%) using the system. Our current work is evaluating the effect of surgeon-controlled parameters (monitor viewing distance, camera aperture, magnification, light pipe power, and use of digital gain on the display) on the display brightness to determine the subjective threshold that surgeons are content with when performing surgery.

NEW OPTIONS

Last year, a second 3D vitreoretinal surgery platform, Artevo (Carl Zeiss Meditec), came to market. Our institution is one of the few centers in the world to have both currently available 3D systems. In my early clinical experience using the Artevo, I have noted many subtle differences between the two. We are now performing the same series of studies just described on the Artevo to determine the ideal settings

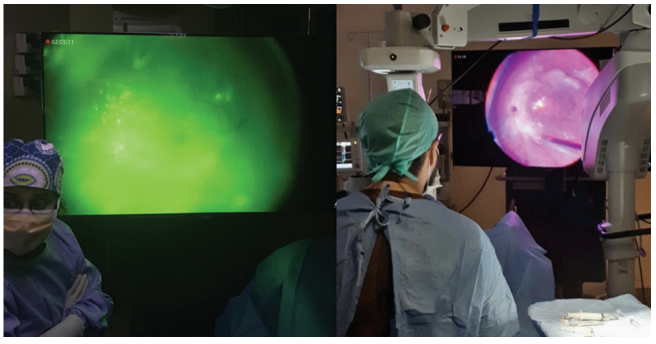

Figure 3. Some surgeons note inconsistency in color performance when using a 3D vitreoretinal surgery platform.

to maximize visual performance on that device. We look forward to presenting these data later this year.

Now that I have been using 3D visualization systems to perform vitreoretinal surgery for several years, I can say without hesitation that I have no intention of going back to a conventional microscope. Our studies have helped me to maximize my visualization with the Ngenuity platform and will shortly allow me to do the same for the Artevo system. I look forward to many wonderful new technologies in development that will take digital 3D visualization systems to the next level. ■

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GLAUCOMA IN THE RETINA PRACTICE: PART 1


Surgeons seeing patients on a monthly basis have the added responsibility of diagnosing and managing open-angle glaucoma.

BY ADAM PFLUGRATH, MD, AND STEVE CHARLES, MD, FACS, FICS

As the treatments for retinal diseases have evolved since the advent of intravitreal injections, and anti-VEGF agents in particular, retina specialists often see patients on a monthly basis. Because of this, we are in the unique but challenging position of also detecting and managing glaucoma in these patients.

This review focuses on managing primary open-angle glaucoma (POAG) in the retina practice. Although neovascular glaucoma has many established associations with retinal vascular disorders, such as proliferative diabetic retinopathy (PDR) and central retinal vein occlusion, coordination is necessary between the retina and glaucoma specialist for surgical management. The topic of glaucoma secondary to vitreoretinal surgery will be reviewed in Part 2 of this series.

EPIDEMIOLOGY

Several diseases encountered in the retina practice, such as diabetes and myopia, are known risk factors for POAG.[1,2] Additionally, patients with macular degeneration can develop glaucoma.[3] Griffith and Goldberg reported that 14.8% of patients in their glaucoma clinic had comorbid retinal disease, with unspecified cystoid macular edema (CME), macular degeneration, PDR, and branch and central retinal vein occlusions being the most common.[4]

DIAGNOSIS AND MONITORING

Diagnosis and monitoring of POAG involves a multifaceted approach with clinical examination and adjuvant testing, such as automated perimetry and OCT. Although many patients with glaucoma also have concurrent retinal pathology, questions remain regarding the reliability of available testing strategies for adequate diagnosis and monitoring.

IOP Measurements

The first clinical sign that indicates glaucomatous damage is IOP. Although Goldmann applanation tonometry (GAT) is the standard measurement tool,[1,5] we use the Tono-pen (Reichert) in our practice. This device has several advantages over GAT, including simplicity of use, portability, absence of fluorescein-related flare, the ability to measure over soft contact lenses, and the fact that measurements are not dependent on patient positioning for those with irregular corneas and irregular tear films.[5]

Handheld rebound tonometers can be used to measure IOP at the peripheral cornea and do not require topical anesthetics.[5] Keep in mind that, in subjects without confounding corneal disease, both rebound tonometry and Tono-pen overestimate IOP compared with GAT.[6,7] Rebound tonometry is affected more by central corneal thickness (CCT) than Tono-pen or GAT.[6] Based on manometric data, the Tono-pen is more accurate than GAT in edematous, irregular corneas and in patients post-penetrating keratoplasty.[8,9]

Optic Nerve Assessment

Clinical assessment of the cup-to-disc ratio is routinely done at the slit lamp. However, prior to clinical examination with biomicroscopy, many retina specialists have access to digital infrared images of the optic nerve head through spectral-domain OCT (SD-OCT). The appearance of the optic nerve in infrared images allows estimation of the cup-to-disc ratio.[10] Further, SD-OCT provides superior anatomic correlation of the optic disc margin to detect remaining neuroretinal rim tissue; clinical examination often overestimates the amount of remaining neuroretinal rim.[11]

OCT is a useful and reliable tool for detecting changes within individual layers of the macula and the peripapillary optic nerve.[12,13] However, decentration of the retinal nerve fiber layer (RNFL) circle scan can lead to significant alterations in RNFL thickness measurements.[14] With continued advances in OCT, interest has grown in the role of macular ganglion cell-inner plexiform layer (GC-IPL) thickness in glaucoma. Macular GC-IPL thickness analysis can detect glau-

comatous changes and is comparable to RNFL.[15] In advanced glaucoma, GC-IPL progression analysis can detect glaucomatous changes better than RNFL progression analysis.[16] However, with macular edema and atrophy, there is lower repeatability in GC-IPL measures, decreasing this metric's accuracy for identifying glaucomatous damage.[17] Thinning of both RNFL and ganglion cell layers are present in neovascular AMD, whereas there is thinning of ganglion cell layers but preservation of RNFL in patients with geographic atrophy.[18]

In patients with diabetic retinopathy requiring panretinal photocoagulation (PRP), there is initial thickening after PRP, followed by progressive, significant thinning of RNFL measurements 2 years after treatment.[19]

Cataracts and other media opacities worsen the repeatability and accuracy of RNFL OCT measurements.[12,20] Further, RNFL thickness appears to increase after cataract surgery secondary to the preoperative underestimation of RNFL thickness related to signal strength errors.[20]

Although RNFL and GC-IPL measurements are affected by retinal pathology and their treatments, some new methods of assessing anatomic correlations of the optic nerve head with SD-OCT are being evaluated.[21] The Bruch membrane opening (BMO) represents a good anatomic landmark that is consistently identifiable with SD-OCT.[11] The assessment of the BMO-fovea axis creates a reproducible anatomy-based reference for more accurate analysis of the RNFL.[13]

Several additional parameters are being assessed using BMO as the anatomic landmark. The BMO-minimum rim width (BMO-MRW) is an assessment of neuroretinal rim thickness, as measured from the BMO to the internal limiting membrane, that is comparable to RNFL in detection of glaucoma.[22] BMO-MRW loss occurs before perimetric vision loss.[23] The BMO-minimum rim area (BMO-MRA) is less dependent on optic disc size.[24] Although both BMO-MRA and BMO-MRW can detect early glaucomatous change, at present RNFL thickness measurements are more reliable in measuring glaucomatous progression.[25]

In myopic patients, GC-IPL is comparable to RNFL in the detection of glaucoma.[26] Further, BMO-MRW is less likely to falsely identify glaucomatous damage in myopic eyes.[27,28]

However, normative data for these structures in most retina pathology are unknown, as are the effects of treatments (eg, PRP) of the neuroretinal rim on these parameters.

Perimetry

Visual field changes and fixation impairment have been noted in patients with diabetic retinopathy and macular degeneration.[29,30] Further, the effect of PRP on visual field assessment has been well documented.[31] In a typical glaucoma population, fixation loss is the primary cause of unreliable visual field assessment.[32] Thus, visual field and automated perimetry testing for glaucoma diagnosis and monitoring have little clinical value in a retina practice.

Intravitreal and Periocular Injections

Periocular injection of steroids can lead to ocular hypertension, and intravitreal steroid formulations also carry a risk of elevating IOP; most of this can be managed medically.[33] However, surgical intervention is more frequent depending on the type of steroid implant.[34] IOP lowering can be achieved with removal of the corticosteroid.

The use of intravitreal dexamethasone as an adjunct to ranibizumab (Lucentis, Genentech) results in an increased incidence of ocular hypertension without improving visual acuity.[35] However, patients who are switched to intravitreal dexamethasone after early recognition of a poor anti-VEGF response have improved visual acuity and anatomic outcomes.[36]

Because glucocorticoids can increase outflow resistance, IOP elevations after the administration of intraocular or periocular steroids should, theoretically, be inconsequential in the presence of a filtering procedure.[37]

Intravitreal injection causes an immediate IOP rise after injection.[38] The elevation is variable depending on the amount of drug injected and needle gauge, with smaller diameter needles leading to higher postinjection IOP.[39]

There is a decrease in peripapillary RNFL thickness after monthly intravitreal injections.[40] Anterior chamber paracentesis at the time of intravitreal injection prevents the immediate postinjection rise in IOP and associated RNFL loss.[40] Prophylactic IOP-lowering medications are ineffective at preventing postinjection IOP increases.[41]

Intravitreal injections of anti-VEGF agents can cause acute and chronic changes to BMO, optic nerve cup deepening, and RNFL thickness when measured by SD-OCT, particularly in the inferior optic nerve head.[42]

Recently, a bimatoprost intracameral implant (Durysta, Allergan) has become available for the treatment of POAG. The implant, injected with a 28-gauge applicator into the anterior chamber, has been shown to be noninferior to topical timolol administration.[43]

CME Secondary to Prostaglandin Analogues

Prostaglandin analogues such as latanoprost are widely used to treat ocular hypertension and glaucoma. Despite their relatively safe profile, there is a small risk of the development of CME. The incidence is around 1% overall, but patients who develop CME are those who have confounding ocular conditions including prior ocular surgery, uveitis, absence of posterior capsule, pseudophakia, aphakia, or retinal inflammatory or vascular conditions such as diabetic retinopathy.[44]

In addition to prostaglandin analogues, timolol and the preservative benzalkonium chloride can worsen CME following cataract extraction.[45] Resolution of prostaglandin-associated CME is achieved by discontinuation of the medication, use of a topical nonsteroidal antiinflammatory drug (NSAID), or both.[45] The concurrent use of a topical NSAID does not affect the ocular hypotensive effects of either timolol or latanoprost.[45]

GIVEN THE LOW INCIDENCE OF PROSTAGLANDIN-ASSOCIATED CME, PROSTAGLANDIN ANALOGUES MAY BE USED SAFELY IN THE PRESENCE OF CONCURRENT MACULAR PATHOLOGY.

CONCLUSION

Technologic advancements allow the potential early detection and monitoring of glaucomatous progression, which can prevent additional peripheral visual field loss. However, a variety of comorbid retinal conditions limit the reliability of conventional testing modalities. In addition, there are limited data regarding the effect intravitreal injections have on the optic nerve head. Thus, further longitudinal studies are needed.

Anterior chamber paracentesis at the time of intravitreal injection may be necessary for an at-risk population to prevent further glaucomatous optic neuropathy. A comprehensive clinical approach assessing IOP trends and optic nerve head status at each visit may help detect early glaucomatous damage.

Advances in OCT measurement algorithms and technologies will continue to be an asset for the detection and monitoring of glaucoma in the retina practice. Given the low incidence of prostaglandin-associated CME, prostaglandin analogues may be used safely in the presence of concurrent macular pathology. Retina physicians should be prepared to assist in the medical management of glaucoma with the continued development of repository medications for lowering IOP. ■

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TRANSRADIAL INTRAARTERIAL CHEMOTHERAPY FOR RETINOBLASTOMA



A new approach may help to improve the delivery of this powerful treatment option.

BY ZAYNAB SAJJADI, BA; ANTONIO YAGHY, MD; AND CAROL L. SHIELDS, MD

Retinoblastoma is the most common primary intraocular pediatric malignancy, with an incidence of 8,000 cases worldwide each year.[1] Goals of care include salvage of life, globe, and vision. Traditionally, this has been attempted through systemic chemotherapy, local thermotherapy or cryotherapy, and plaque or external-beam radiotherapy (EBRT).[2]

In the early 2000s, intraarterial chemotherapy (IAC) was added to the list of globe-conserving measures for retinoblastoma. Delivery of IAC classically involves catheterization of the ipsilateral femoral artery with transit into the aorta, carotid, and internal carotid arteries and then into the ophthalmic artery orifice, with chemotherapy delivered directly to the affected eye.

Studies show that IAC is remarkably powerful, even for advanced retinoblastoma, as it allows delivery of a relatively high drug concentration but is associated with less systemic toxicity (nausea, ototoxicity, neurotoxicity, pancytopenia, myelosuppression) than systemic chemotherapy.[2-4] Ophthalmic complications with vascular occlusion can occur but have been greatly reduced in recent years.[5,6] IAC has revolutionized management and become a mainstay of therapy for retinoblastoma over the past decade.[3]

The conventional method of IAC for retinoblastoma involves the transfemoral approach commonly used in a variety of other neurovascular procedures.[2,7] In the adult population, a different approach is possible through the radial artery with catheterization at the wrist. This is used as an alternative route of access in interventional cardiology and, more recently, neurosurgery.[2,8] The transradial approach is fast, especially in emergency procedures to remove blood clots in stroke victims, and it leads to short recovery times and low incidence of local complications such as hematoma, paresthesia, hand ischemia, and compartment syndrome.[8]

Currently, no established criteria exist for choosing the transradial over the transfemoral approach in neurovascular procedures, but some believe the transradial approach could be beneficial in pediatric patients to reduce bleeding complications. The transfemoral approach has been associated with the risk of retroperitoneal compartment bleeding, and it requires postoperative sedation to avoid lower extremity movement.[2]

In this article, we describe the first case, to the best of our knowledge, of transradial IAC for treatment of retinoblastoma.

CASE REPORT

A 13-year-old White female with no pertinent medical history presented with a report of 5 months of floaters and decreased vision in the right eye. She was found to have a retinal mass in that eye and was referred to the Wills Eye Hospital Ocular Oncology Service for further evaluation and management.

AT A GLANCE

- Intraarterial chemotherapy (IAC) allows delivery of a relatively high drug concentration with less associated systemic toxicity than systemic chemotherapy for retinoblastoma.
- The conventional method of IAC for retinoblastoma involves the transfemoral approach that is commonly used in a variety of other neurovascular procedures.
- This article reports the use of a transradial approach in a patient with group D retinoblastoma.

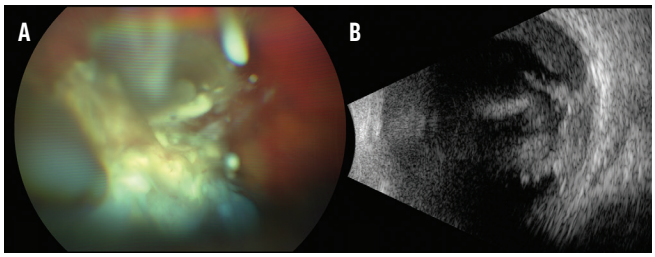

Figure 1. Fundus photograph of the right eye showing group D endophytic retinoblastoma inferotemporally measuring 20 mm in diameter with overlying vitreous seeds (A). On B-scan ultrasonography, the tumor was echodense and measured 8 mm in thickness (B).

On our initial examination, her BCVA was 20/150 OD and 20/25 OS. The anterior segment examination was unremarkable in both eyes, without leukocoria. Fundoscopic examination of the left eye was normal, but the right eye showed an ill-defined, solid, endophytic mass inferotemporally with extensive large overlying active vitreous seeds (Figure 1A). The mass was estimated to be 20 mm in basal diameter and 8 mm in thickness.

On B-scan ultrasonography, the mass blended into the vitreous seeds and demonstrated a few focal areas of calcification (Figure 1B). Orbital magnetic resonance imaging demonstrated no optic nerve invasion. The eye was classified as group D retinoblastoma based on the International Classification of Retinoblastoma system.

Management with enucleation or IAC was discussed with the family, and IAC with the addition of intravitreal chemotherapy was preferred in an attempt to salvage the globe.

Accordingly, IAC was performed. But in this case, the catheterization was achieved through the radial artery, not the femoral artery. Using this method, intraarterial melphalan and topotecan were infused over a span of 30 minutes each into the ophthalmic artery.[2,9]

At 1-month follow-up, the tumor had regressed to 14 mm in basal diameter and 5.9 mm in thickness (Figure 2). However, due to the continued presence of extensive vitreous seeding, additional management with intravitreal chemotherapy was provided.

At 3-month follow-up, the patient was noted to have open retinal holes at the site of previous endophytic tumor with rhegmatogenous retinal detachment. This was repaired with a scleral buckle without drainage.[10]

After four cycles of transradial IAC and five injections of intravitreal chemotherapy, complete tumor control was achieved. At 15-month follow-up, BCVA was 20/70 OD and 20/20 OS. The right eye showed complete regression of the retinoblastoma to a calcified scar with no active vitreous or subretinal seeds and a completely flat retina (Figure 3A and 3B).

Macular OCT of the right eye showed an intact fovea with slight ellipsoid irregularity, likely accounting for the patient's visual acuity of 20/70 OD (Figure 3C). Macular OCT of the left eye was normal (Figure 3D).

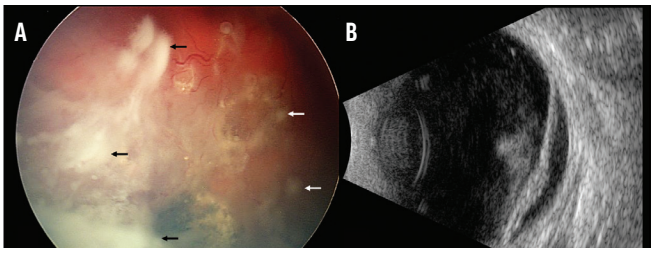

Figure 2. At 1-month follow-up, and after one cycle of IAC using the transradial approach, fundus photograph of the right eye showed significant tumor regression to 14 mm in diameter; however, due to the presence of extensive vitreous seeds (arrows), treatment with intravitreal chemotherapy was initiated (A). On B-scan ultrasonography, tumor thickness had decreased to 5.9 mm (B).

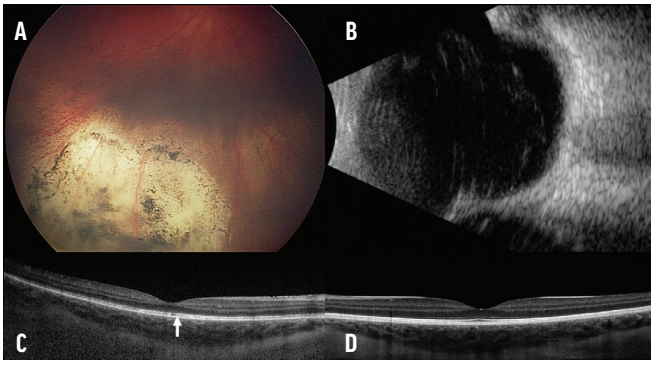

Figure 3. At 15-month follow-up, after four cycles of IAC and five cycles of intravitreal chemotherapy, there was complete regression of the tumor to a flat, calcified scar overlying a recent scleral buckle (A), which can also be seen on B-scan ultrasonography (B). On macular OCT, the fovea in the right eye was intact, but slight ellipsoid irregularity (arrow) was noted, likely accounting for the patient's visual acuity of 20/70 OD (C). Macular OCT in the left eye was normal (D).

DISCUSSION

Retinoblastoma is a life-threatening but curable intraocular malignancy. Over the past few decades, treatment options have evolved to allow remarkable tumor control and globe salvage.[11] Targeted therapy with IAC has quickly gained popularity as a first- and second-line treatment.[3,11] IAC is the preferred treatment for patients older than 3 months with nongermline mutation retinoblastoma, unilateral retinoblastoma, recurrent retinoblastoma after previous therapy, and recurrent subretinal or vitreous seeds.[9]

A recent survey found that 74% of responding centers treating retinoblastoma worldwide use IAC in patients with unilateral advanced disease.[12] The availability of IAC has dramatically altered patient outcomes and reduced the need for enucleation from 80% to approximately 28% to 33% in eyes treated with primary IAC.[2,6,13]

Compared with systemic intravenous chemotherapy for unilateral retinoblastoma, IAC provides significantly better outcomes in control of solid tumor (62% vs 92%, $P = .002$), subretinal seeds (31% vs 86%, $P = .006$), and vitreous seeds (25% vs 74%, $P = .006$), along with significantly higher rates of globe salvage for group D eyes (48% vs 91%, $P = .004$).[14]

Moreover, events of metastatic death are rare in patients

treated with IAC. A multicenter international survey including 1,139 patients with retinoblastoma found a less than 1% incidence of metastatic death after IAC.[15] Similarly, a previous study at a single ocular oncology center analyzed the effectiveness of IAC in patients older than 5 years and found 62% globe salvage with no metastasis or death at 14-month median follow-up.[16]

Although many studies have demonstrated the safety and efficacy of IAC, the procedure remains technically challenging because it requires the involvement of highly specialized neurosurgical or neurointerventional teams.[9,17] For most procedures, including IAC, interventionalists almost exclusively use the transfemoral approach, as data supporting the use of the transradial approach are limited.[2] However, studies in interventional cardiology show that the transradial approach decreases overall adverse clinical events by reducing major bleeding and all-cause mortality.[18]

Al Saiegh et al first demonstrated the safety and feasibility of transradial IAC for retinoblastoma in 10 procedures in five pediatric patients, including our patient described here.[2] Because this patient had reached puberty at the time of her first IAC, the neurosurgery team was able to use the same catheter commonly used for a transfemoral approach. In contrast, the other four patients in the series required a more technical procedure due to the smaller caliber of the radial artery.

The authors concluded that, given the technical nuances and limitations of the transradial approach, the transfemoral approach will remain the first choice for infants and young children. Still, as demonstrated by their case series and this case report, the transradial route can be an effective and feasible method for the treatment of retinoblastoma.[2]

The patient here was discharged home after 1 hour in the postanesthesia care unit and demonstrated treatment results similar to those expected with use of the transfemoral approach. At 15-month follow-up, there was complete regression of the tumor with no evidence of active disease.

CONCLUSION

The emergence of IAC has led to remarkable advances in the treatment of retinoblastoma. Eyes that would previously have been enucleated are now salvaged at rates of 100% for groups B and C, 86% for group D, and 55% for group E at 5 years.[19] Increasing surgical experience and technical advances have allowed the introduction of additional indications for IAC and continued improvements in patient outcomes, including vision salvage.[20]

Although IAC is almost exclusively administered through the femoral artery, implementing the transradial approach could be the next advance in treatment with this modality. As more experience is gained with the transradial approach and more retinoblastoma centers adopt its use, larger studies can further support its effectiveness and safety. ■

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ADOPTING THE 2021 E/M CHANGES

Answers to frequently asked questions from retina practices.

BY JOY WOODKE, COE, OCS, OCSR

After the new evaluation and management (E/M) documentation and coding guidelines were implemented on January 1 and retina practices began to adopt them, several specific scenarios generated unique questions. As the final determination of the proper E/M code is now based on medical decision-making or time, most of the questions I've received recently have been surrounding medical decision-making and these new definitions.

Here are my answers to a few of the most frequently asked questions on the new E/M documentation and coding guidelines that I've received recently from your peers in emails and at virtual coding courses.

NUMBER AND COMPLEXITY OF PROBLEMS ADDRESSED AT THE ENCOUNTER

What is the difference between "1 or more chronic illnesses with exacerbation, progression, or side effects of treatment" in the moderate category, and the same language with the addition of "with *severe* exacerbation" in the high category? Would AMD be considered severe?

According to the American Medical Association,[2] "1 or more chronic illnesses with *severe* exacerbation, progression, or side effects of treatment," as defined in the high category, would be a chronic illness or severe side effect of treatment that has significant risk of morbidity and may require hospital level of care.

AMD is a serious chronic illness severely impacting vision; however, it would qualify for this definition only if the side effects or risk may require hospitalization.

The problems assessed during the patient encounter were proliferative diabetic retinopathy with exacerbation, epiretinal membrane, and posterior vitreous detachment. This is moderate medical decision-making and should be billed as a level 4, correct?

The problems meet the moderate level, with one or more chronic illnesses with exacerbation and with two or more stable chronic illnesses.

However, for the final determination to be moderate and level 4 coding, either the data or risk category would have to meet or exceed the moderate level.

What are some retina examples of one acute or chronic illness or injury that poses a threat to life or bodily function as defined in the problem category as high?

The problem, as assessed during the encounter, would be a threat to bodily function in the near term without treatment. Clinical examples in retina practice would include endophthalmitis, exudative macular degeneration with a new bleed, and macula-on retinal detachment.

AMOUNT AND/OR COMPLEXITY OF DATA TO BE REVIEWED AND ANALYZED

During the encounter, patient testing included fluorescein angiography, fundus photography, and gonioscopy. Would this count as ordering three tests in category 1?

To qualify as ordering of each unique test, each test would need to be a test with a CPT code, not separately billable by the physician, or previously billed within the practice.

Each of the tests mentioned in the question has an assigned code and is separately billable—and therefore is not eligible for this category.

As another example, recommending that a patient with nonexudative AMD use an Amsler grid would not count in this category, as this test does not have an assigned CPT code.

Unique tests that would count include external testing not separately billable in the practice: for example, ordering

magnetic resonance imaging for optic neuritis, a computed tomography scan for a metallic foreign body, or a lab panel for a uveitis consultation (see next question).

For a uveitis patient, I ordered three unique lab tests. Under category 1 for the amount and/or complexity of data, would this count once for the ordering of each unique test, or three?

Each order of the unique lab test would count independently. For this example, this would qualify as three tests and meet the moderate level of data as one of three categories.

Does sending a letter to the referring physician qualify as discussion of management with an external physician?

A letter to a referring physician or primary care provider would not count as discussion. To meet this definition, a two-way conversation (eg, a phone call) would have to be completed and documented. An example could be a phone call to a referring ophthalmologist to coordinate a combined surgical case for a patient with a dislocated IOL.

A patient is unable to provide an adequate history during an encounter due to dementia. The daughter who accompanied her provides the necessary information. Does this count as assessment requiring an independent historian?

Yes. When the retina specialist, based on his or her judgement, is unable to obtain a reliable history from the patient due to developmental stage, dementia, or psychosis, an independent historian (eg, parent, guardian, surrogate, spouse, or witness) can provide the necessary details or confirmatory history. This meets the definition of assessment requiring an independent historian in category 1 of the data category.

RISK OF COMPLICATIONS AND/OR MORBIDITY OR MORTALITY OF PATIENT MANAGEMENT

What are a few examples of prescription drug management in a retina practice?

Prescribing eye drops or pain medication for a surgical patient would be considered prescription drug management. Managing the anti-VEGF medication for a patient receiving intravitreal injections would also qualify.

If a patient has glaucoma but the medication is prescribed and managed by another physician, that would not count, unless the retina specialist initiates a new prescription due to increased IOP and is now managing the disease.

For consultations to evaluate the long-term use of a medication (eg, hydroxychloroquine), the retina specialist is evaluating and monitoring for maculopathy but is not the prescriber of the drug. This would not be considered prescription drug management. Also not qualifying for this risk category is the recommendation of over-the-counter drugs.

Would a fluorescein angiogram be considered a moderate level of risk?

Separately payable tests do not count toward medical decision-making.

How is a minor or major surgery defined in the risk category?

For coding purposes, minor versus major surgery is defined by the global period. However, for medical decision-making definitions, minor or major surgery is based on the physician's expertise and definition and the mutual understanding of those within the same specialty.

What qualifies as an emergency major surgery?

Is the patient scheduled within 24 hours? A surgery that must be performed in the near term, typically later that day and possibly the next morning, is an emergency surgery. These are the cases that cancel your dinner plans or bump another surgical case in the morning to accommodate. The most common example in retina is a macula-on retinal detachment.

If the patient declines scheduling surgery today, does the decision for the major surgery still count?

Yes, when the decision is made to perform surgery, that counts in the risk category for medical decision-making even if the patient declines or if scheduling is delayed due to prior authorization requirements.

FINAL TAKEAWAY

Although it is common during an encounter to focus on the most relevant category of medical decision-making, before making the final code selection be sure to confirm that at least two of three categories meet or exceed the level of medical decision-making.

If the problem level is high and the risk level is moderate, the overall level of medical decision-making would still be moderate, or a level 4: CPT code 99204 or 99214. Just considering the severity of the problem in this case would incorrectly suggest a higher level of service and ultimately lead to inappropriate coding.

To explore more on this topic and master E/M coding for the retina practice, visit aao.org/em for additional resources and frequently asked questions. ■

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AN ELUSIVE CASE OF CYSTOID MACULAR EDEMA



A common IOP-lowering drop can uncommonly be a cause of decreased vision.

BY SAMANTHA SCHILLING, BA, OSC; CURTIS BROBST, BA, COA, OSC; AND BRIAN C. JOONDEPH, MD, MPS

Cystoid macular edema (CME) is a common manifestation of many retinal diseases.[1] Often, the underlying etiology, such as diabetic retinopathy, macular degeneration, or retinal vein occlusion, is obvious based on clinical examination. Recent cataract surgery or active uveitis are other common causes of CME and are readily apparent based on history or examination.

Occasionally, CME may manifest without an obvious cause or underlying condition, perhaps noted on a routine and otherwise unremarkable eye examination. We recently encountered a case of CME with a surprising—although not unheard of—etiology, reminding us to look beyond the obvious and keep elusive etiologies in mind when the usual CME culprits don't apply.

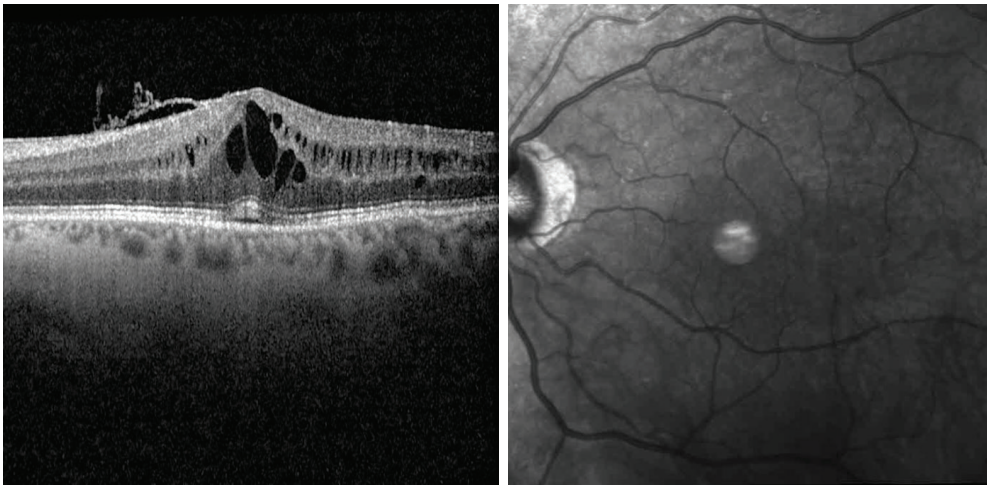

Figure 1. OCT shows CME related to latanoprost administration.

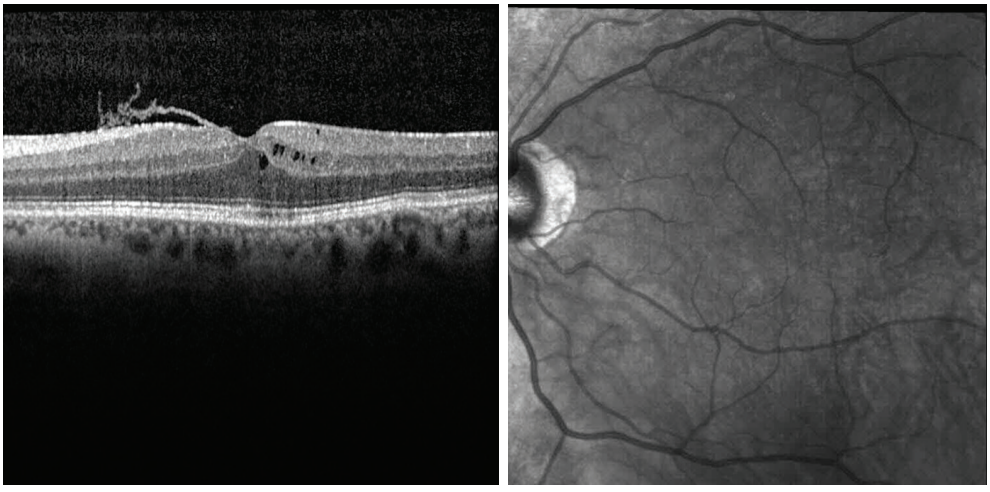

Figure 2. OCT 1 month after discontinuation of latanoprost shows resolution of CME.

CASE REPORT

A 55-year-old man with recently diagnosed glaucoma presented with blurred central vision, redness, and ocular irritation in his left eye. He had been

ALTHOUGH PROSTAGLANDIN ANALOGUES ARE KNOWN TO CAUSE INFLAMMATION, CME IS AN UNCOMMON SIDE EFFECT. THE REASON FOR THIS REMAINS UNKNOWN, BUT GENETIC FACTORS OR UNDERLYING OCULAR DISEASES MAY INCREASE A PATIENT'S SUSCEPTIBILITY.

prescribed several different drop regimens to control his IOP, the most recent being latanoprost 0.005% once daily, which he had been using for several weeks unilaterally in the left eye.

His ocular history included repair of a pseudophakic macula-on retinal detachment in his left eye 5 years ago, with resulting VA of 20/20 OS and a mild, non-clinically significant epiretinal membrane.

On examination, VA was 20/30 OS, with normal IOP and CME noted on OCT (Figure 1). There were no signs of macular degeneration, retinal vascular disease, or uveitis, only the previously noted mild epiretinal membrane. In addition, the timing of the vision decrease, the unilateral CME, and onset of prostaglandin use in the same eye (not bilaterally) was suggestive of a causal relationship.

We recommended discontinuation of latanoprost. The patient saw a glaucoma specialist who substituted brimonidine 0.15% twice daily. One month later, his VA had improved to 20/20 OS with almost complete resolution of symptoms and CME on OCT (Figure 2).

DISCUSSION

Prostaglandin analogues are often used to reduce IOP in patients with ocular hypertension or glaucoma. These drops are often used as first-line therapy due to their convenient once-daily dosing. Common side effects include conjunctival hyperemia, corneal punctate epithelial erosions, and increased iris pigmentation.[2]

A lesser-known side effect of this class of drug is CME, reported with latanoprost and other commercially available prostaglandin analogues.[3,4] Preservative-free prostaglandin analogues can produce this same side effect, ruling out the preservative as the cause of the CME rather than the prostaglandin itself. The CME is reversable after discontinuation of the drug.[5]

Interestingly, prostaglandin analogues can be administered distant from the eye and still cause CME. For example, one group of researchers reported a case of CME several days after intracorporeal injection of a prostaglandin E1 for erectile dysfunction.[6]

Although prostaglandin analogues are known to cause inflammation, CME is an uncommon side effect.[7] The reason for this remains unknown, but genetic factors or underlying ocular diseases may increase a patient's susceptibility. In addition, other confounding ocular pathologies could make a patient more susceptible to CME, such as epiretinal membrane and macular degeneration. Other risk factors for prostaglandin-induced CME are ocular surgery and damage to the blood-retina barrier, as is the case with uveitis.[6] A patient with a healthy blood-retina barrier is less likely to be affected by prostaglandin-induced CME.

Both ocular and systemic use of prostaglandin analogues should remain on the physician's list of possible causes of CME, particularly when a case presents with no other obvious etiology or when standard treatment is ineffective.

Fortunately, treatment is straightforward, as eliminating the causative drop and replacing it with one of many other IOP-lowering drops can lead to complete resolution of CME. This also holds true with discontinuation of systemic prostaglandin use.[6] ■

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THE BENEFITS OF IDENTIFYING PARACENTRAL ACUTE MIDDLE MACULOPATHY

This important OCT sign can be the sole indicator of a significant retinal vascular event with systemic implications.

BY MANAB J. BARMAN, MD; RAGHUDEV BHATTACHARJEE, MD; SAURABH DESHMUKH, MD; AND AWANEESH UPADHYAY, MD

Paracentral acute middle maculopathy (PAMM), first described by Sarraf et al in 2013, typically manifests as a distinct paracentral scotoma with or without diminution of vision.[1] Fundus examination shows a dark gray paracentral lesion that points toward the center of the fovea.[2] The condition can present in conjunction with a number of retinal vascular diseases.[3,4]

Although PAMM was originally described as a variant of acute macular neuropathy (AMN), the two are now regarded as distinct entities.[5] The retinal ischemic cascade of PAMM in its mildest form (known as perivenular PAMM) involves the venular end of the deep capillary plexus (DCP). With increasing severity it may progress to diffusely involve the inner nuclear layer (INL) or even to infarct the inner retina.

AMN, by contrast, displays hyperreflectivity of the outer plexiform layer (OPL) and outer nuclear layer (ONL) and may be associated with disruption of the ellipsoid zone (EZ).[6]

OCT angiography (OCTA) shows reduced flow in the intermediate retinal capillary plexus (ICP) and DCP in PAMM, whereas AMN is associated with reduced flow in the DCP only.[7,8]

New imaging modalities such as OCTA have added substantial knowledge to the pathogenesis of PAMM, but the condition's clinical course and treatment outcome are still under investigation. In a single-center retrospective observational study, we analyzed seven eyes of seven patients with PAMM of varied etiology. The study was conducted following institutional review board guidelines and adhering to the tenets of the Declaration of Helsinki.

CASE NO. 1

A 38-year-old man presented with complaints of blurred vision in the left eye for 7 days. His BCVA was 20/20+. Amsler grid testing identified a small paracentral scotoma inferior to the fixation point, confirmed with visual field testing. Fundus examination revealed a yellowish-white, well-demarcated lesion superior to the fovea (Figure 1A). Multicolor imaging showed a corresponding lesion in green (Figure 1B). Fluorescein angiography (FA) did not show any filling defect. OCT revealed a hyperreflective band involving the inner plexiform layer (IPL) and OPL, indicating PAMM, possibly secondary to cilioretinal artery insufficiency. The EZ was intact (Figure 1C). Systemic workup showed dyslipidemia. The lesion persisted at the 6-month follow-up.

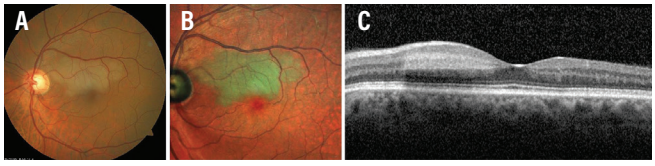

Figure 1. The color fundus photo shows a grayish-white, well-demarcated lesion superior to the fovea (A). Multicolor imaging depicts the lesion in green (B). SD-OCT shows a hyperreflective band in the IPL and OPL (C).

CASE NO. 2

A 52-year-old man presented with blurred vision in the right eye for 15 days despite a BCVA of 20/20. He had a medical history of hypercholesterolemia. Fundus examination showed a well-defined, grayish, wedge-shaped lesion superior to the fovea (Figure 2A). Multicolor imaging depicted the

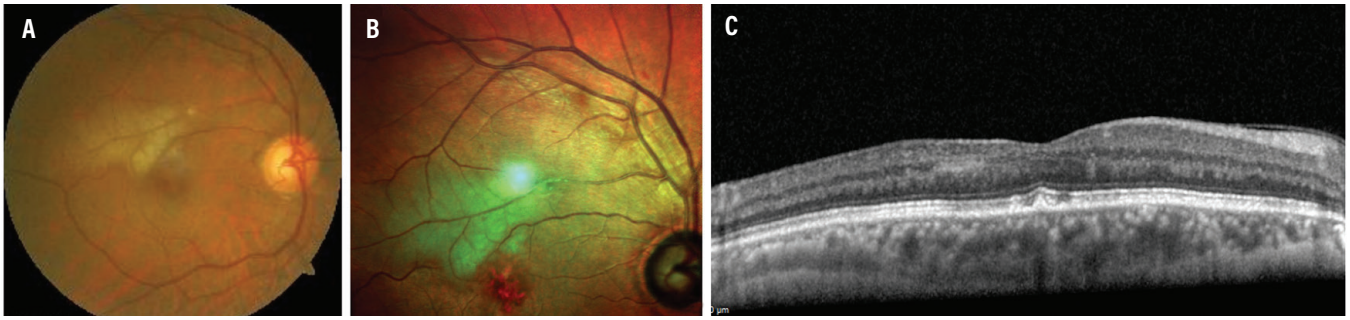

Figure 2. The color fundus photo shows PAMM superior to the fovea (A). Multicolor imaging depicts PAMM in green (B). Thinning of INL is noted on SD-OCT (C).

lesion in green (Figure 2B). FA was inconclusive, but OCT at the level of the lesion revealed thinning of the INL, possibly secondary to branch retinal artery insufficiency (Figure 2C).

CASE NO. 3

A 46-year-old hypertensive man presented with blurred vision in the right eye for 15 days. BCVA was 20/40 OD. Fundus examination revealed evidence of a nonischemic central retinal vein occlusion (CRVO) and a well-defined grayish-white lesion inferotemporal to the fovea (Figure 3A). FA showed inferior extension of the foveal avascular zone. OCT showed cystic changes with a hyperreflective band at the level of the IPL (Figure 3B). OCTA revealed capillary abnormalities in both the DCP and SCP inferior to the fovea (Figures 3C and 3D). The patient received three intravitreal injections of ranibizumab (Lucentis, Genentech) at monthly intervals. After 6 months, fundus examination revealed the persistence of PAMM with cystoid macular edema (CME).

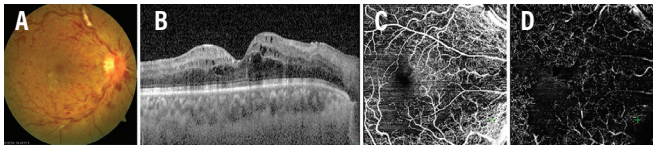

Figure 3. The color fundus photo suggests nonischemic CRVO with PAMM inferotemporal to the fovea (A). SD-OCT shows cystic changes in the center with a hyperreflective band at the level of IPL (B). OCTA shows capillary abnormalities in both the DCP and SCP (C and D).

CASE NO. 4

A 60-year-old woman with diabetes presented with mild blurred vision in the right eye for 3 months. Her BCVA was 20/20+ OD. Fundus examination revealed mild nonproliferative diabetic retinopathy (NPDR) without clinically significant macular edema and a grayish lesion superior to the center of the fovea (Figure 4A). OCT revealed a hyperreflective band at the level of the OPL (Figure 4B). OCTA showed an area of capillary abnormality in the DCP superior to the foveal center (Figure 4C and 4D). After 3 months, the retinal condition was stable with the persistence of PAMM.

CASE NO. 5

A 62-year-old man presented with blurred vision in the left eye for 2 months. He had hypertension and diabetes and was being treated for both. BCVA was 20/80 OS. Diagnosis of branch retinal vein occlusion (BRVO) with CME was made based on the clinical picture and OCT findings (Figure 5A and 5B). FA was deferred. The patient received three intravitreal injections of ranibizumab at monthly intervals. After the first injection, PAMM was detected superior to the fovea and confirmed with OCT (Figure 5C). At 4-month follow-up, PAMM persisted with CME (Figure 5D).

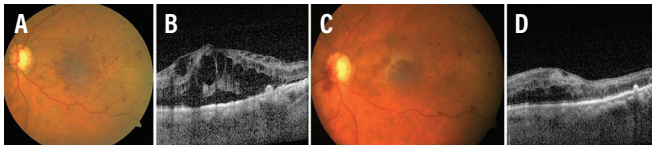

Figure 5. Fundus photo and OCT imaging are suggestive of BRVO with macular edema (A and B). PAMM was detected superior to the fovea 1 month after anti-VEGF injection (C and D).

CASE NO. 6

A 57-year-old man with hypertension presented with blurred vision in the left eye for 2 weeks. BCVA was 20/40 OS. Fundus examination revealed a grayish-white lesion at the distribution of the superior branch retinal artery with evidence of nonischemic CRVO (Figure 6A). FA showed delayed filling of the branch retinal artery (Figure 6B and 6C). OCT revealed

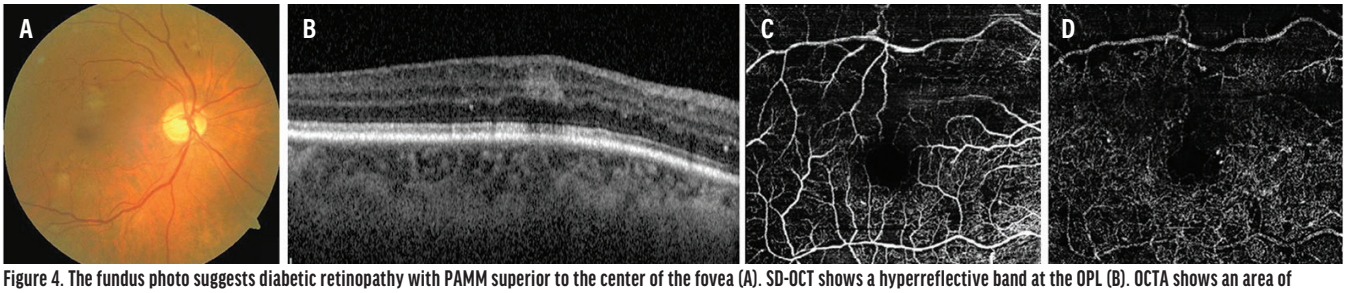

Figure 4. The fundus photo suggests diabetic retinopathy with PAMM superior to the center of the fovea (A). SD-OCT shows a hyperreflective band at the OPL (B). OCTA shows an area of capillary abnormality in the DCP superior to the foveal center (C and D).

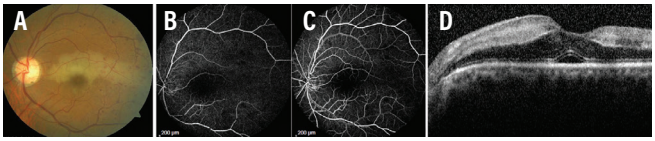

Figure 6. Fundus photo shows PAMM (A). Delayed filling of the branch retinal artery is seen on FA (B and C). SD-OCT shows a hyperreflective band at the IPL and OPL (D).

a hyperreflective band in the inner and middle retinal layers (Figure 6D). A diagnosis of nonischemic CRVO combined with branch retinal artery occlusion (BRAO)-associated PAMM was made. Color Doppler imaging of the carotid and ophthalmic arteries did not reveal any underlying pathology.

CASE NO. 7

A 64-year-old man with hypertension presented with blurred vision in the left eye for 1 day and BCVA of 20/60 OS. Fundus examination showed advanced cupping in each eye and a well-defined parafoveal, intraretinal, grayish lesion with characteristic OCT features suggestive of PAMM (Figure 7A and 7B). Visual field analysis confirmed glaucomatous damage, and the patient was started on medication for primary open-angle glaucoma. The patient presented 3 days later with deterioration of vision to hand movement OS (Figure 7C and 7D). A diagnosis of CRVO with CME and possible central retinal artery hypoperfusion was made based on the findings.

The patient was started on monthly injections of ranibizumab. After 3 months, his VA improved to 20/200, with resolution of the macular edema (Figure 7E and 7F).

DISCUSSION

PAMM is considered a manifestation of focal ischemia of the deep retinal circulation that may herald the presence of a secondary underlying condition. Multicolor imaging can help to detect PAMM, as it creates three simultaneous reflectance images that demonstrate details at different layers of the retina.[9,10] Blue, green, and red reflectance show the inner, middle, and outer retina, respectively. PAMM usually presents with the lesion in green.[11]

OCT is invaluable in confirming a diagnosis of PAMM. On OCT, the condition initially manifests as a hyperreflective band, followed by thinning of the middle retinal layers.[11] En face OCT may demonstrate a remarkable perivenular pattern of PAMM in eyes with retinal vein occlusion even in the absence of significant funduscopic findings.[12] Bakhoum et al described characteristic OCT findings of PAMM suggestive of an ischemic cascade, indicating more vulnerability of the middle retina at the level of the DCP.[13]

FA is a poor imaging modality to illustrate PAMM, whereas OCTA at the level of the DCP detects gross capillary loss.[6,14] OCTA features are described as arteriolar, globular, fernlike, and combination pattern.[15]

Our case series highlights associations between PAMM and other clinical findings, for example dyslipidemia in Case No. 1 and 2.[16] Microcholesterol embolus may lead to the occlusion of DCP in such cases.

CME with PAMM can also occur secondary to CRVO, and research shows that intravitreal injections do not help to resolve PAMM in such cases. [4] Not surprisingly, in Case No. 3, both CME and PAMM persisted after intravitreal injections of an anti-VEGF agent. PAMM secondary to diabetic retinopathy, as seen in Case No. 4, can present without CME.[3]

PAMM can develop secondary to BRVO during follow-up after initiation of anti-VEGF treatment, as in Case No. 5. Pichi et al described a large series of eyes with vascular occlusion, in which PAMM was detected at presentation.[17] This research team also looked at the association of PAMM with cilioretinal artery occlusion.[17] In isolated retinal artery occlusion, initial hyperreflectivity of the inner retinal layers is often seen on OCT. In Case No. 6 of our series, PAMM developed secondary to BRAO with CRVO, and hyperreflectivity was noted in both the inner and middle retinal layers.

Finally, PAMM also may be associated with glaucoma, as

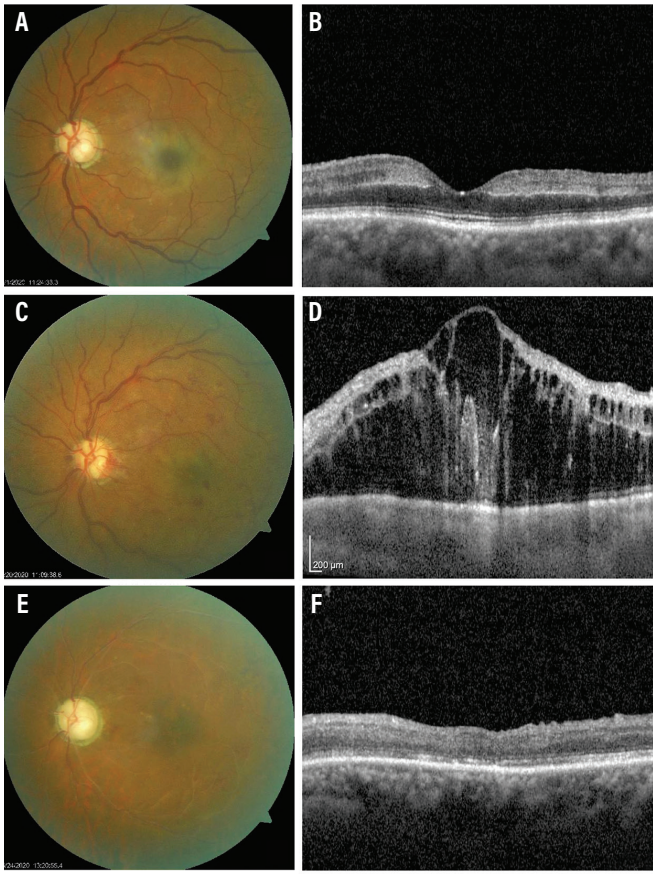

Figure 7. The fundus photograph of this glaucomatous eye shows a perifoveal intraretinal greyish lesion (A), and the corresponding OCT shows hyperreflective band-like lesions in the middle retinal layers of the macula, suggestive of PAMM (B). Fundus photography of the same eye 3 days later shows dilated tortuous vessels with diffuse intraretinal hemorrhages (C), and the corresponding OCT shows macular edema (D). After three anti-VEGF injections, the fundus photograph (E) and OCT (F) show resolution of CRVO and macular edema.

seen in our Case No. 7, and in such cases it may be a premonitory sign of CRVO.[18]

FINAL THOUGHTS

PAMM is a sign of deep retinal ischemia, the duration and severity of which may impact the development of PAMM. Because of its association with other ocular conditions, the presence of PAMM without obvious ocular pathology warrants a thorough systemic evaluation. ■

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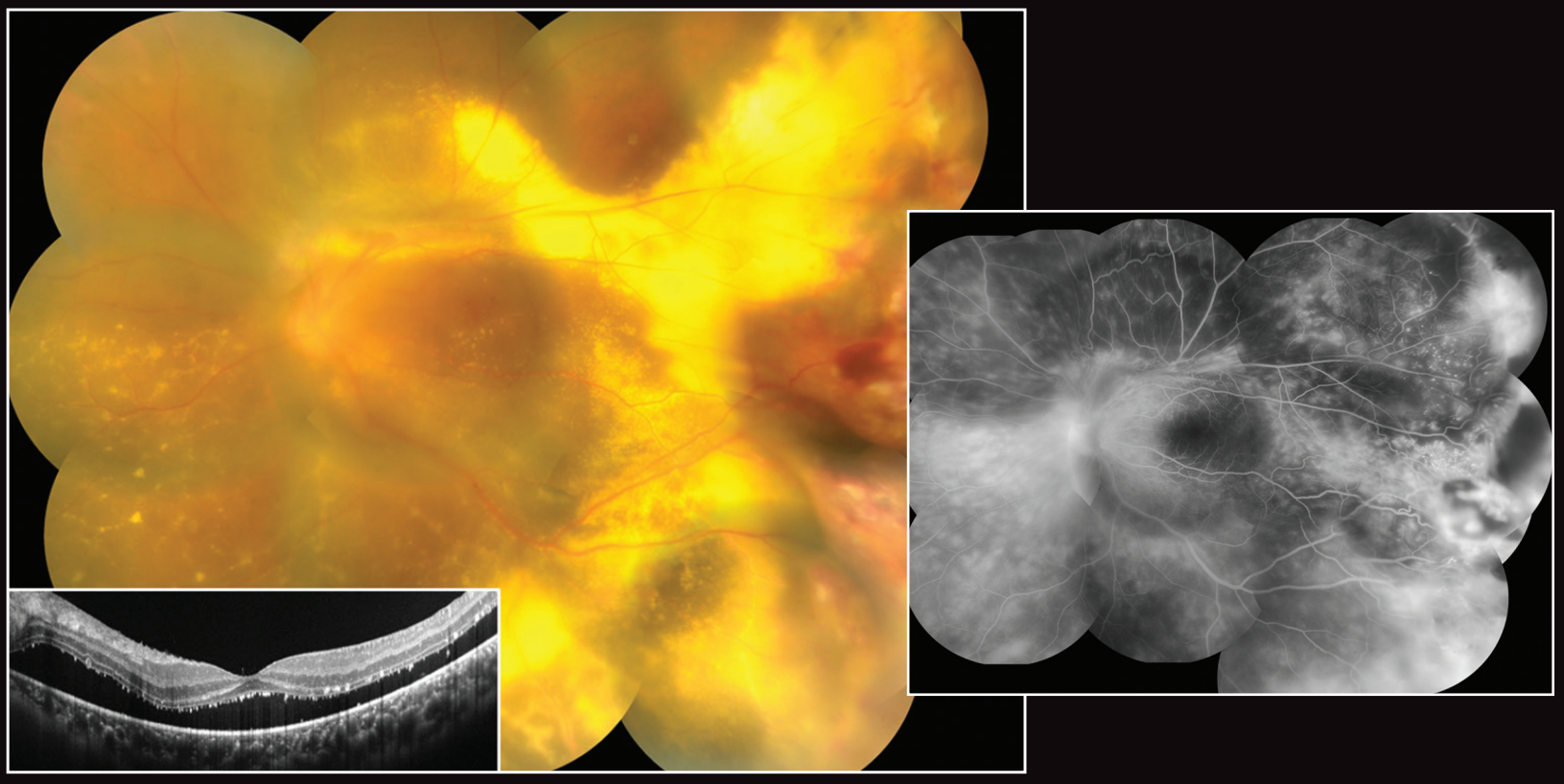


TACKLING COATS DISEASE WITH PPV

Early surgical management can be an effective option to prevent progression.

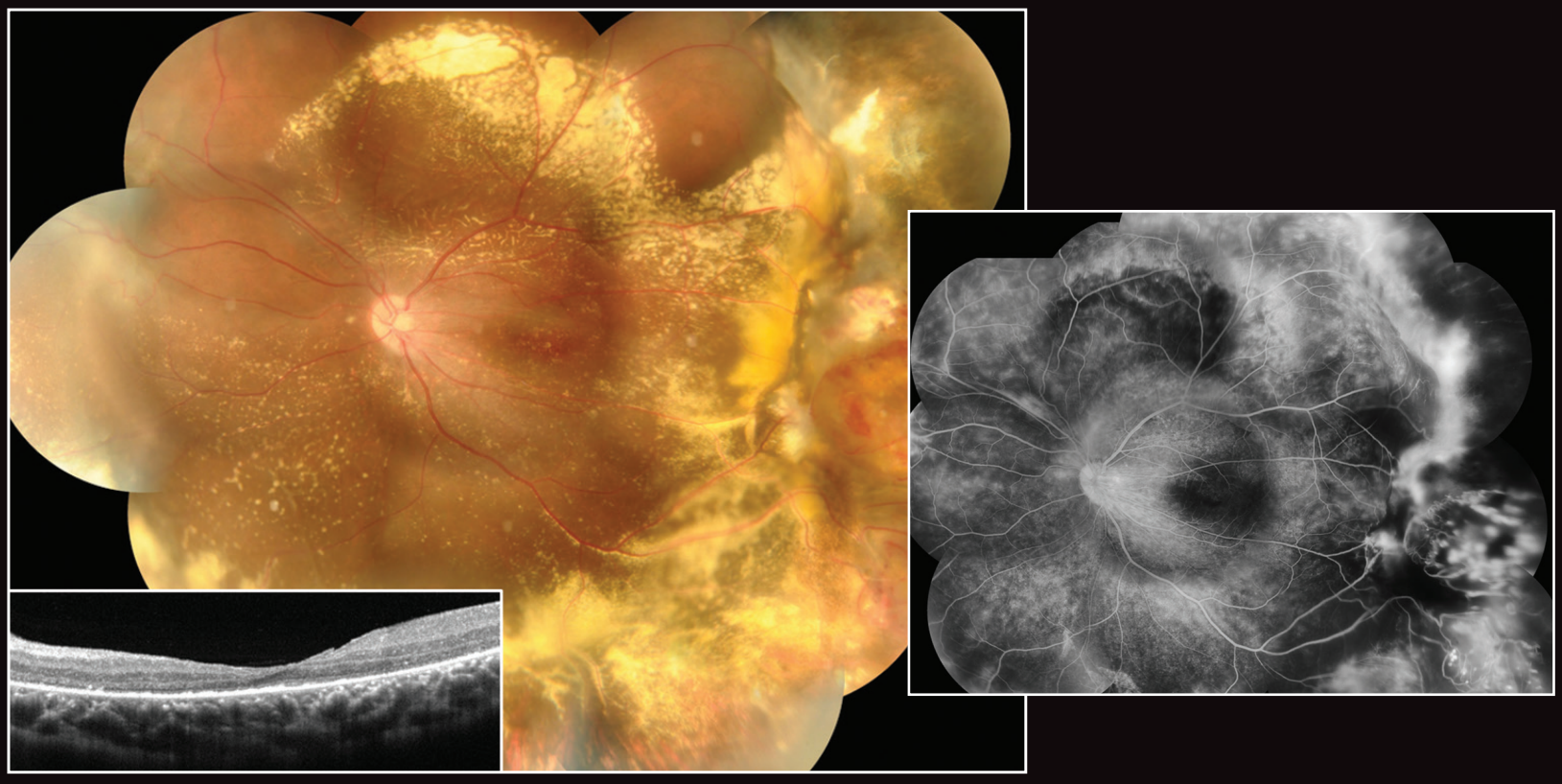
BY SHIN MIZOGUCHI, MD, PHD, AND YUSUKE OSHIMA, MD, PHD

A 16-year-old male presented with a complaint of gradual vision loss in his left eye for the past 6 months. The patient's BCVA was 20/20 OD and 20/400 OS. His ocular history included a diagnosis of Coats disease in the left eye and several sessions of laser photocoagulation at other centers over the past several years.

At the initial visit to our practice, slit-lamp examination showed a normal anterior segment in each eye. Fundus examination revealed a macula-involving severe exudative retinal detachment with accumulation of prominent hard exudates and retinal hemorrhages in the left eye. Retinal folds induced by epiretinal membrane were observed around the upper vascular arcade. Retinal vascular tortuosity and telangiectasia were detected at the temporal periphery with multiple aneurysms, including a large one similar to a retinal hemangioma (Main Figure, Above). Fluorescein angiography (FA) showed prominent diffuse vascular leakage from the telangiectasia and aneurysm (Inset, Above).

We confirmed the earlier diagnosis of Coats disease, now at stage 3A. The patient immediately underwent 25-gauge three-port lens-sparing vitrectomy under general anesthesia. Core vitrectomy with thorough vitreous shaving, brilliant blue G staining–assisted epiretinal and internal limiting membrane peeling, and segmentation and delamination of the peripheral fibrovascular membrane were conducted with a bimanual technique. This procedure was followed by endolaser photocoagulation to the aneurysm and cryoretinopexy to the giant peripheral hemangioma-like aneurysm after fluid-air exchange.

Postoperatively, the patient was instructed to remain in a prone position for 2 days. Two months after surgery, the



retina was completely attached with gradual absorption of the hard exudation (Figure, Above). The peripheral aneurysms had regressed significantly, and minimal leakage was seen on postoperative FA (Inset, Above). The patient's VA recovered to 20/40 OS without any reproliferation.

DISCUSSION

Coats disease is a unilateral retinal vascular disease characterized by retinal vascular telangiectasia and microvascular aneurysmal changes that can cause exudative and tractional retinal detachment.[1] The main treatment option for early-stage Coats disease is laser photocoagulation to the non-perfused retina to stabilize the aneurysms and decrease the permeability of the abnormal vessels.[1,2] Intravitreal injections of anti-VEGF drugs and/or steroids can be used as adjunctive treatments for advanced cases.[3,4]

However, progression cannot always be prevented with medical treatment. Vitreoretinal surgery can more effectively restore visual acuity in eyes with total retinal detachment (stage 3B) or more advanced stages, and these eyes should be treated at the earliest stage possible.[1,5]

In the case presented here, we recommended vitrectomy to induce posterior hyaloid detachment and eliminate the scaffold for vitreoretinal interface proliferation. Extensive endolaser photocoagulation and cryoretinopexy without internal or external drainage may be another effective treatment option for early-stage cases that do not respond to conventional medical approaches. ■

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5. Li AS, Capone A Jr, Trese MT, et al. Long-term outcomes of total exudative retinal detachments in stage 3B Coats disease. *Ophthalmology*. 2018;125(6):887-893.

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

STEVE CHARLES, MD, FACS, FICS

When were you first interested in ophthalmology? When did you know you wanted to become a vitreoretinal surgeon?

I decided on ophthalmology my first week in medical school, and I worked all 4 years at Bascom Palmer Eye Institute. I decided on vitreoretinal surgery during my second year in medical school. The retina is a very complex and elegant structure, with a wide variety of diseases, techniques and technologies; it is a high-tech field perfect for my engineering background, and it is rich in opportunities for product development.

You pursued an engineering degree and are a mechanical and electrical engineer. What made you choose this path? How has it helped with your ophthalmology career?

I planned on using engineering to develop medical products even before starting medical school. I continued my education in engineering throughout medical school, internship, my residency at Bascom Palmer, and my fellowship at the National Eye Institute/National Institutes of Health, as well as my 45 years in practice. I now have more than 100 patents issued or pending and am the principal architect of the Alcon Accurus and Constellation Systems as well as Ocutome 8000 (CooperVision) and MVS (MidLabs) systems. I also invented endophotocoagulation in 1979.

You have developed many techniques and devices used by vitreoretinal surgeons worldwide and also have several patents in engineering. What keeps you motivated to continue to create and improve these fields?

It is about problem-solving for me. It is not about being an inventor per se, money, ego, challenges, or entrepreneurship. Prior to Accurus, we had many individual devices with their own foot pedals, power cords, and small displays. The Accurus system was about system integration, with a single reconfigurable display that is multifunction configurable. I invented linear aspiration to enable foot pedal control of vacuum levels. I pushed for higher and higher cutting rates to reduce pulsatile vitreoretinal traction. I helped develop faster response time fluidics to reduce the incidence of iatrogenic retinal breaks.

How do you maintain a healthy work-life balance?

I have three awesome daughters, work 7 days a week, live alone in an apartment, and have taken no vacation in 25 years, no hobbies, games, movies, fishing, or golf. I lift weights intensely and do that 3 to 4 days per week. I also help domestic violence victims. I have an Airline Transport Pilot rating, six jet type ratings, and have flown corporate jets for business purposes for 30 years. I have no plans to retire.

Figure. Dr. Charles owned and flew a Falcon 50 corporate plane to research and development meetings and medical meetings. He is type-rated in the 3,400 mile range, 480 knot airspeed aircraft.

What has been the most memorable moment of your career?

When I received the AAO's Laureate Recognition Award in 2018 for my work in vitreoretinal surgery. The AAO presents this award to individuals who "have made exceptional contributions to the advancement of eye care, leading to the prevention of blindness and restoration of sight worldwide."[1] ■

1. 2018 Laureate Recognition Awardee: Steven Charles, MD. 2018 Laureate. www.aao.org/about/awards/laureate/steven-charles. Published 2018. Accessed March 3, 2021.

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LUCENTIS®
RANIBIZUMAB INJECTION

Brief summary–please see the LUCENTIS® package insert for full prescribing information.

1 INDICATIONS AND USAGE
LUCENTIS is indicated for the treatment of patients with:

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

1.2 Macular Edema Following Retinal Vein Occlusion (RVO)

1.3 Diabetic Macular Edema (DME)

1.4 Diabetic Retinopathy (DR)

1.5 Myopic Choroidal Neovascularization (mCNV)

4 CONTRAINDICATIONS
4.1 Ocular or Periocular Infections
LUCENTIS is contraindicated in patients with ocular or periocular infections.

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

5 WARNINGS AND PRECAUTIONS
5.1 Endophthalmitis and Retinal Detachments
Intravitreal injections, including those with LUCENTIS, have been associated with endophthalmitis and retinal detachments. Proper aseptic injection technique should always be used when administering LUCENTIS. In addition, patients should be monitored following the injection to permit early treatment should an infection occur *[see Dosage and Administration (2.6, 2.7) in the full prescribing information and Patient Counseling Information (17)]*.

5.2 Increases in Intraocular Pressure
Increases in intraocular pressure have been noted both pre-injection and post-injection (at 60 minutes) while being treated with LUCENTIS. Monitor intraocular pressure prior to and following intravitreal injection with LUCENTIS and manage appropriately *[see Dosage and Administration (2.7 in the full prescribing information)]*.

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

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

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

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

Diabetic Macular Edema and Diabetic Retinopathy
Safety data are derived from studies D-1 and D-2. All enrolled patients had DME and DR at baseline *[see Clinical Studies (14.3, 14.4 in the full prescribing information)]*.

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

5.4 Fatal Events in Patients with DME and DR at baseline
Diabetic Macular Edema and Diabetic Retinopathy
Safety data are derived from studies D-1 and D-2. All enrolled patients had DME and DR at baseline *[see Clinical Studies (14.3, 14.4 in the full prescribing information)]*.

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

6 ADVERSE REACTIONS
The following adverse reactions are discussed in greater detail in other sections of the label:
- Endophthalmitis and Retinal Detachments *[see Warnings and Precautions (5.1)]*
- Increases in Intraocular Pressure *[see Warnings and Precautions (5.2)]*
- Thromboembolic Events *[see Warnings and Precautions (5.3)]*
- Fatal Events in patients with DME and DR at baseline *[see Warnings and Precautions (5.4)]*

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

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

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

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

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

Table 1 Ocular Reactions in the DME and DR, AMD, and RVO Studies

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

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

Table 2 Non-Ocular Reactions in the DME and DR, AMD, and RVO Studies

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

6.3 Immunogenicity
As with all therapeutic proteins, there is the potential for an immune response in patients treated with LUCENTIS. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to LUCENTIS in immunoassays and are highly dependent on the sensitivity and specificity of the assays.

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

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

6.4 Postmarketing Experience
The following adverse reaction has been identified during post-approval use of LUCENTIS. Because this reaction was reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure.
- Ocular: Tear of retinal pigment epithelium among patients with neovascular AMD

7 DRUG INTERACTIONS
Drug interaction studies have not been conducted with LUCENTIS.

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

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
There are no adequate and well-controlled studies of LUCENTIS administration in pregnant women.

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

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

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

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

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

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

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

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

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

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

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

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

LUCENTIS®
[ranibizumab injection]
Manufactured by:
Genentech, Inc.
A Member of the Roche Group
1 DNA Way
South San Francisco, CA
94080-4990

Initial US Approval: June 2006
Revision Date: M-US-00002319(v1.0) 2019

LUCENTIS®
RANIBIZUMAB INJECTION

STRENGTH IN VISION

LUCENTIS has been extensively studied and FDA approved in 5 retinal indications.

INDICATIONS

LUCENTIS® (ranibizumab injection) is indicated for the treatment of patients with:

- Neovascular (wet) age-related macular degeneration (wAMD)
- Macular edema following retinal vein occlusion (RVO)
- Diabetic macular edema (DME)
- Diabetic retinopathy (DR)
- Myopic choroidal neovascularization (mCNV)

IMPORTANT SAFETY INFORMATION

- LUCENTIS is contraindicated in patients with ocular or periocular infections or known hypersensitivity to ranibizumab or any of the excipients in LUCENTIS. Hypersensitivity reactions may manifest as severe intraocular inflammation
- Intravitreal injections, including those with LUCENTIS, have been associated with endophthalmitis, retinal detachment, and iatrogenic traumatic cataract
- Increases in intraocular pressure (IOP) have been noted both pre-injection and post-injection with LUCENTIS
- Although there was a low rate of arterial thromboembolic events (ATEs) observed in the LUCENTIS clinical trials, there is a potential risk of ATEs following intravitreal use of VEGF inhibitors. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause)
- Fatal events occurred more frequently in patients with DME and DR at baseline treated monthly with LUCENTIS compared with control. Although the rate of fatal events was low and included causes of death typical of patients with advanced diabetic complications, a potential relationship between these events and intravitreal use of VEGF inhibitors cannot be excluded
- In the LUCENTIS Phase III clinical trials, the most common ocular side effects included conjunctival hemorrhage, eye pain, vitreous floaters, and increased intraocular pressure. The most common non-ocular side effects included nasopharyngitis, anemia, nausea, and cough

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

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

Randomized, double-masked clinical trials conducted for the 5 LUCENTIS indications included the following: **wAMD:** *MARINA, ANCHOR, PIER, HARBOR*. **DR and DME:** *RISE, RIDE*. **mCNV:** *RADIANCE*. **RVO:** *BRAVO, CRUISE*.[1-10]

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