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Retina Today
SEPTEMBER 2020 VOL. 15, NO. 6 | RETINATODAY.COM

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DIABETIC EYE DISEASE AND COVID-19

FIRST REPORT OF CENTRAL RVO ASSOCIATED WITH COVID-19

NEW PHASE 2/3 DATA ON GEOGRAPHIC ATROPHY

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Reference: 1. Data on File. Alcon Laboratories Inc; May 2018. **2.** Data on File. Alcon Laboratories Inc; September 2017.

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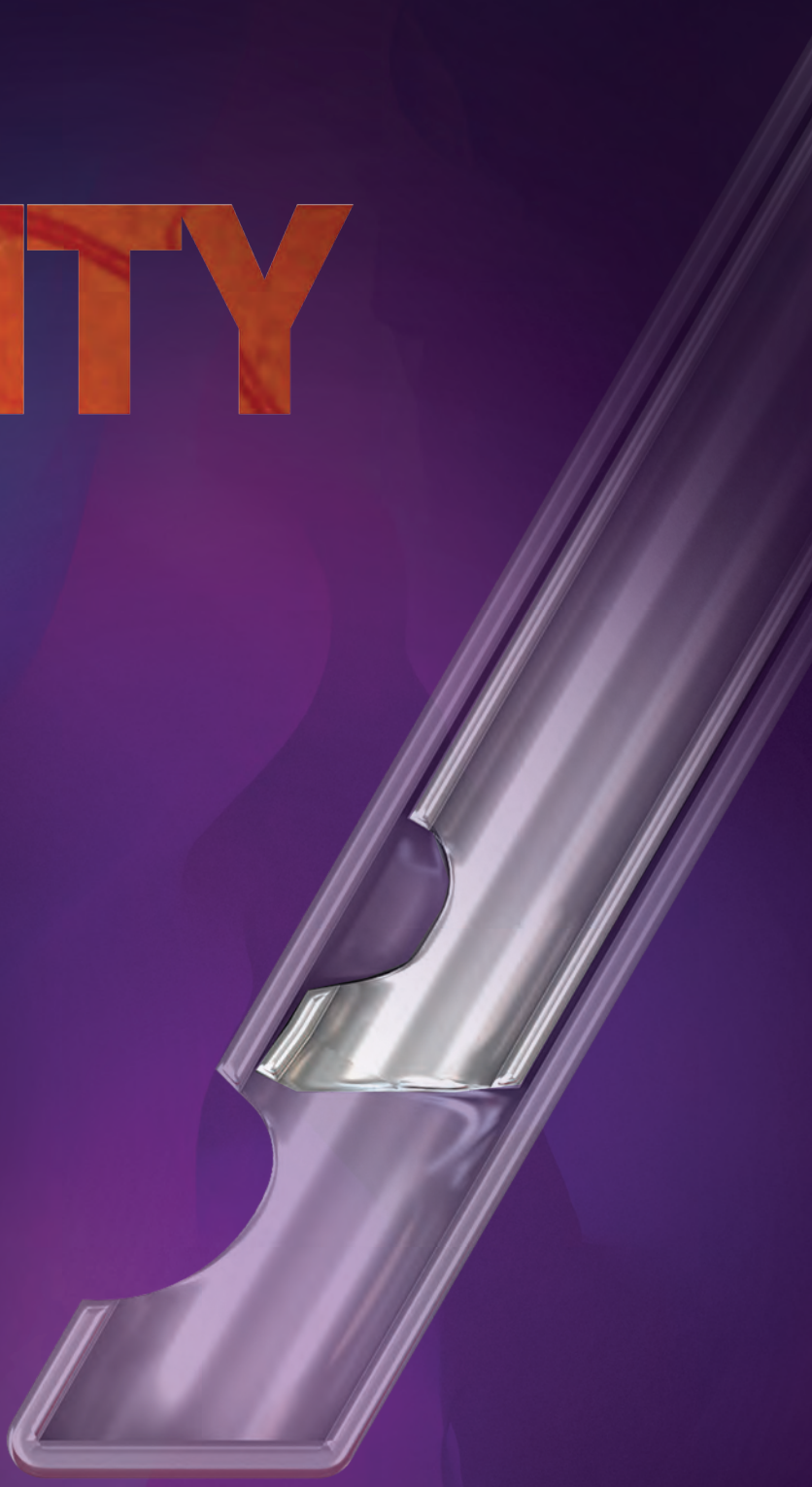

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References: 1. Irannejad A, Tambat S, Abulon DJK. Retropulsion and mass flow of 27-gauge vitrectomy probes: comparison of dual-blade/flat-tipped probes and single-blade/beveled probes. Poster presented at: 18th Congress of the European Society of Retina Specialists; September 20–23, 2018; Vienna, Austria. **2.** Alcon data on file. Alcon Laboratories, Inc; June 2018. **3.** Alcon data on file. Alcon Laboratories, Inc; June 2018. **4.** Alcon data on file. Alcon Laboratories, Inc; June 2018. **5.** Alcon data on file. Alcon Laboratories, Inc; May 2017.

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References
1. Data on file – Results of HPLC purity tests performed on samples of compounded BBG dyes available in the U.S. **2.** Total DORC Global Sales data for ILM Blue since launch – available on file.

IMPORTANT INFORMATION ABOUT TISSUEBLUE™ (Brilliant Blue G Ophthalmic Solution) 0.025%

BRIEF SUMMARY This summary contains important information about TISSUEBLUE™ (TISH-OO-BLU) Solution. It is not meant to take the place of the full Prescribing Information. Read this information carefully before you prescribe TISSUEBLUE. For full Prescribing Information and Patient Information please see package insert.

WHAT IS TISSUEBLUE? TISSUEBLUE™ (Brilliant Blue G Ophthalmic Solution) 0.025% is a disclosing agent indicated to selectively stain the internal limiting membrane (ILM). The drug product will be administered by health care professionals only and should never be given to patients to handle.

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FORGING AHEAD

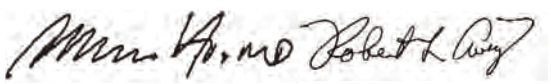

We retina specialists are lucky enough to be in a position to continue to treat patients during the pandemic. Yes, protocols have changed. Yes, volumes have dropped. And yes, altered treatment patterns may affect patients. All of these are concerning. It is worth mentioning, though, that in the aggregate we provided (and can still provide) a level of care that some of our colleagues elsewhere in medicine were unable (or not allowed) to administer.

We have dedicated the past three issues of *Retina Today* to the COVID-19 crisis—and for good reason. The events of 2020 will forever reshape medicine. To ignore this public health emergency would have been editorial malpractice. As our understanding of the virus evolves, the need for continued coverage persists. Still, as we get back to semi-normal practice, we have decided to return a portion of our focus to the practice of retina itself. For our next several issues, we'll be covering the art of retina during the pandemic.

In this issue's suite of cover articles, we've included some COVID-19 topics (such as two retina fellows' perspectives on how their training has been affected by the crisis) some diabetic eye disease topics (such as a contrasting review of two clinical trials for drugs that address diabetic eye disease), and some retina-during-COVID topics (such as a piece on how to treat diabetic eye disease during the pandemic). Among our jewels this issue: a photo essay from Nuha Kapatayes, BS, and Brian C. Joondeph, MD, MPS, in which they share what they believe to be the first reported case of a patient presenting with central retinal vein occlusion associated with COVID-19.

As always, our columns are worth investigating. Matthew R. Starr, MD, interviews Carl D. Regillo, MD, about the latest data regarding dry AMD therapy. Daniel L. Chao, MD, PhD; Arshad M. Khanani, MD, MA; and Charles C. Wykoff, MD, PhD, summarize the COOL-2 trial, which may lead to a new type of anesthetic for intravitreal injection. And the Eyetube team checks in with the latest videos from around the globe.

A final note: Check out *Retina Today*'s new website. Its sharper, cleaner articulation of the publication's content is designed for mobile reading and quick searches. We think you'll like it. While you're there, sign up for the publication's print version or opt in to our emails so that you can stay up-to-date on all things *Retina Today*. ■



CHIEF MEDICAL EDITOR ASSOCIATE MEDICAL EDITOR

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DIABETIC EYE DISEASE AND COVID-19

DEPARTMENTS

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PORT DELIVERY OF RANIBIZUMAB WAS NONINFERIOR TO MONTHLY INJECTIONS IN WET AMD TRIAL

Patients with wet age-related macular degeneration (AMD) receiving ranibizumab via a permanent refillable implant delivery system achieved visual acuity outcomes noninferior to those of patients receiving monthly injections of 0.5 mg ranibizumab (Lucentis, Genentech). These and other results from the phase 3 Archway study of the Port Delivery System (PDS) were announced by Roche ahead of their presentation at the American Society of Retina Specialists Virtual Annual Meeting in July.[1]

In the Archway trial, 98.4% of patients implanted with the PDS were able to go 6 months without needing additional treatment and achieved visual acuity outcomes equivalent to patients receiving monthly ranibizumab injections, according to a press release from Roche. Patients in the study had received ranibizumab therapy previously and were known responders to anti-VEGF therapy. The PDS was generally well-tolerated, with a favorable risk-benefit profile.

The primary endpoint of the study was change from baseline in BCVA averaged over week 36 and week 40. In the PDS arm, patients gained an average 0.2 letters from baseline, with 244 of 248 patients (98.4%) maintaining the fixed 6-month refill schedule within the first refill period. Patients treated monthly with ranibizumab injections gained an average 0.5 letters from baseline. The PDS also controlled retinal thickness as effectively as monthly injection, with patients in both arms achieving a mean change in center point thickness within 10 µm from baseline.

The Roche release noted that the PDS contains a customized formulation of ranibizumab not approved by regulatory authorities. It is different from the ranibizumab for intravitreal injection marketed as Lucentis. The PDS is designed to continuously release this formulation of ranibizumab into the eye over time.

WATCH IT NOW

BIT.LY/EYEWIRE0920

In addition to Archway, the PDS is being evaluated in the Portal long-term extension safety and tolerability study in patients with wet AMD; in the phase 3 Pagoda trial in patients with diabetic macular edema (DME); and in the recently initiated Pavilion phase 3 trial in patients with diabetic retinopathy (DR).

1. Campochiaro P. Primary Analysis Results of the Phase 3 Archway Trial of the Port Delivery System With Ranibizumab for Patients With Neovascular AMD. Paper presented at: American Society of Retina Specialists Annual Meeting; July 24-26, 2020.

FDA: REGENXBIO CAN BEGIN PHASE 2 TRIAL IN DIABETIC RETINOPATHY

An open-label study to evaluate the efficacy, safety, and tolerability of suprachoroidal delivery of RGX-314 (Regenxbio) in individuals with DR has been cleared to begin by the US FDA, the drug's developer announced in August.

Regenxbio plans to begin dosing patients in the phase 2 ALTITUDE trial this year. The multicenter, randomized, controlled dose-escalation study is expected to enroll 40 patients with DR. Patients will be randomly assigned to one of two doses of RGX-314 or control. The primary endpoint will be the proportion of patients who improve on a DR severity scale at 48 weeks.

RGX-314, which incorporates a viral vector encoding an antibody fragment designed to inhibit VEGF, is being developed as a potential one-time treatment for DR and other retinal conditions.

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PHASE 2 STUDY OF PLASMA KALLIKREIN INHIBITOR IN DME BEGUN

The first patient has been treated in a phase 2 trial of a plasma kallikrein inhibitor for treatment of DME, the drug's developer announced in September. The two-part KALAHARI trial will evaluate THR-149 (Oxurion), first in a dose-escalation phase and then in a safety and efficacy phase.

THR-149 acts through inhibition of the plasma kallikrein-kinin system, a validated VEGF-independent target for DME, according to Oxurion. The compound was well-tolerated in a phase 1 trial and showed promising signals of efficacy, the company said. The phase 2 study will recruit approximately 120 patients with center-involved DME who respond suboptimally to anti-VEGF therapy. Part A data are expected next year, and top-line Part B results in 2023.

FDA CLEARS AI SYSTEM FOR DETECTION OF DIABETIC RETINOPATHY

An artificial intelligence (AI) system for detecting DR received marketing clearance from the FDA, the system's developer announced in August. The EyeArt autonomous AI system (Eyenuk) is indicated for use by health care providers to automatically detect more than mild DR and vision-threatening DR in the eyes of adults diagnosed with diabetes who have not been previously diagnosed with more than mild DR, the company stated.

The system is the first autonomous AI technology cleared by the FDA that can detect both more than mild DR and vision-threatening DR in one test performed in primary care and eye care settings, according to Eyenuk. The EyeArt system is indicated for use with two Canon models of fundus camera. Eyenuk plans to expand the list of compatible imaging devices.

Autonomous AI for DR screening will likely be covered by payers starting in 2021, the company said in a press release. Last year, the CPT Editorial Panel created a new CPT code, 9225X, for point-of-care automated analysis that uses AI technology to perform the interpretation of an eye exam without requiring that an ophthalmologist interpret the results. Medicare is considering CPT code 9225X to be a diagnostic service under the Physician Fee Schedule and is creating separate payment for it, according to Eyenuk.

GENE THERAPY FOR GA IN PHASE 2 TRIAL

A phase 2 study of an investigational gene therapy for geographic atrophy (GA) has been initiated, according to the therapy's developer. GT005 (Gyroscope) is designed to restore balance to an overactive complement system by increasing production of the complement factor I (CFI) protein. The CFI protein regulates the activity of the complement system. The multicenter randomized EXPLORE trial will enroll approximately 75 patients with GA secondary to dry AMD and with a mutation in the CFI gene. The primary endpoint will be progression of GA at 48 weeks after a single injection of one of two doses of GT005 or control.

ORPHAN PRODUCT GRANT AWARDED FOR STARGARDT DISEASE CANDIDATE

An FDA orphan products clinical trial grant has been awarded to Kubota Vision to support its ongoing phase 3 study of emixustat in Stargardt disease, according to the company. The multicenter, randomized, double-masked, placebo-controlled study was initiated in 2018. Patients in the study are randomly assigned to emixustat 10 mg or placebo once daily for 24 months.

Orphan product clinical trial grants support studies that will contribute to the essential data needed for development of medical products that will meet the needs of patients with rare diseases.

FORWARDVUE PHARMA SECURES FUNDING TO ADVANCE PRECLINICAL DEVELOPMENT

ForwardVue Pharma has secured funding to advance the preclinical development of its antiangiogenic small molecule directed against diabetic eye disease and wet AMD, the company announced in August. ForwardVue is developing a small synthetic compound, caroboxyamidotriazole, that acts via the novel mechanism of ORAI-1 inhibition and can be formulated to deliver potent antiangiogenic effects for 6 to 12 months, according to the company. The compound has been used in the treatment of advanced cancer.

ANOTHER ORPHAN DRUG DESIGNATION FOR OCUGEN

Ocugen received a fourth orphan drug designation from the FDA for its gene therapy product candidate OCU400, this time for treatment of *PDE6B* gene mutation–associated retinal diseases, according to the company. Retinitis pigmentosa can be caused by *PDE6B* mutation, and a mutation in the *PDE6B* gene has been found to cause an inherited form of night blindness. Ocugen's OCU400 platform is designed to address multiple diseases with a single product. It has been assessed in preclinical studies but not yet in the clinical setting. ■

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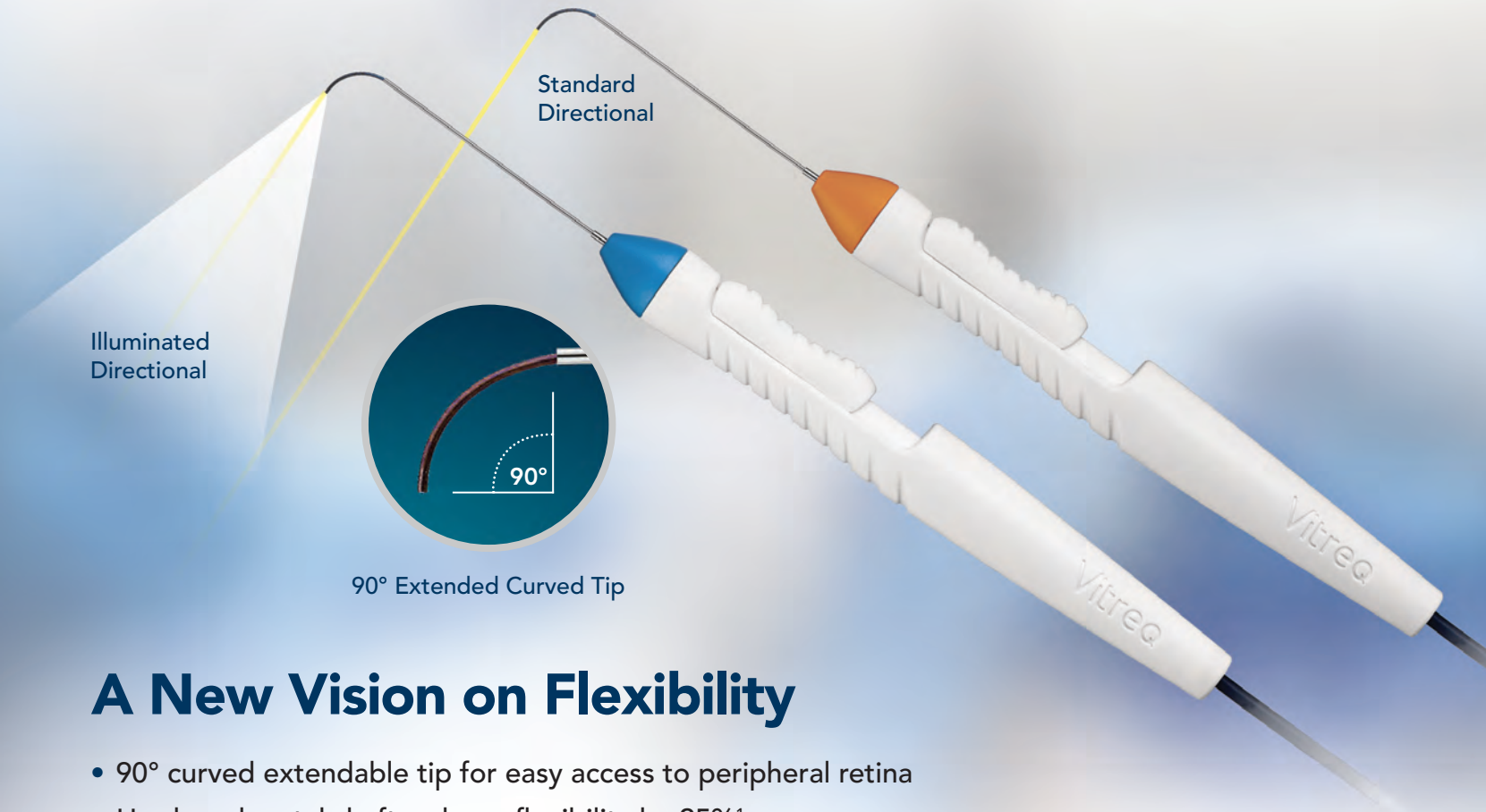

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[1] Data on file

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FELLOWS' FOCUS

CLINICAL IMPACT OF THE GATHER1 TRIAL FOR GEOGRAPHIC ATROPHY


New data show that a treatment for this disease may be on the horizon.

INTERVIEW BY MATTHEW R. STARR, MD, WITH CARL D. REGILLO, MD

Results of GATHER1, a phase 2/3 trial evaluating the efficacy and safety of the novel complement C5 inhibitor avacincaptad pegol (Zimura, Iveric bio), were announced in June.[1] (The trial was re-named in June. It originally was called OPH2003.[2]) Avacincaptad is administered via intravitreal injection. The study reached its primary efficacy endpoint of reducing the rate of geographic atrophy growth over 12 months as compared with sham injections, according to a release from Iveric.

To learn more about the results of this trial, I interviewed Carl D. Regillo, MD, Chief of the Retina Service at Wills Eye Hospital.

—Matthew R. Starr, MD

Matthew R. Starr, MD: How do you interpret the results of the GATHER1 trial?

Carl D. Regillo, MD: GATHER1 was a phase 2/3, double-masked, prospective, sham-controlled study. Researchers in the study found that monthly doses of 2 mg and 4 mg of avacincaptad resulted in a reduction by 27% to 28% in the rate of geographic atrophy (GA) growth. This reduction was statistically significant ($P = .007$ and $P = .005$ for the two doses, respectively) at the primary endpoint of 12 months. A favorable safety profile was reported. Both doses showed a similar benefit compared with the control group. Furthermore, the treatment and sham curves showed early separation for both doses, evident by month 6, with continued divergence and an increasing magnitude of effect through 18 months. The drug was well tolerated, and no intraocular inflammation or endophthalmitis were reported.

Dr. Starr: Given these results, what do you expect from the phase 3 trial GATHER2?

Dr. Regillo: GATHER2 (also known as ISEE2008[2]) will be a confirmatory phase 3 study that is designed similarly to GATHER1. Both studies have enrolled patients with

nonfoveal GA in the study eye and have a primary endpoint of 1 year. Patients in GATHER2 will receive 2 mg avacincaptad monthly. Based on similarities in study design and the definitive statistical significance of the data in GATHER1, there is a high likelihood of having a successful trial that meets its primary endpoint of significantly slowing the growth rate of GA at 1 year.

What is different in GATHER2, however, is that after month 12 researchers will randomly reassign patients to either monthly or every-other-month dosing. This information will provide data on the need to continue monthly dosing beyond the first year to maintain the same degree of benefit on the rate of GA growth in practice.

Dr. Starr: What is different about avacincaptad compared with lampalizumab (Genentech), the compliment inhibitor that showed promise for treating GA in early trials but then faltered in later phase trials?

Dr. Regillo: Lampalizumab showed evidence of some reduction in GA growth compared with sham in an exploratory hypothesis-generating phase 2 study, but the *P* value for significance in that study was 0.2, and thus the study did not provide a high level of certainty that the effect was real. Subsequently, in the pivotal phase 3 Chroma and Spectri studies, the differences in GA reduction observed between lampalizumab and control were not statistically significant.[3] It could be that the mechanism of action of lampalizumab (ie, binding complement factor D) focused on a portion of the complement system that was too far upstream, potentially leaving downstream pathologic complement processes unchecked.

With avacincaptad, the effector components of all three arms of the complement cascade are potentially blocked by targeting C5, which, in turn, ultimately inhibits both inflammasome and membrane attack complex formation. This broader mechanism of action may be more effective in treating GA.

Dr. Starr: If the phase 3 trial is successful and avacincaptad is approved by regulatory bodies for the treatment of GA, how do you envision it changing management of GA and dry AMD?

Dr. Regillo: Having a drug that reduces the growth rate of GA would fulfill a major unmet need in our patients with GA. The US FDA has not approved a treatment for the treatment of GA growth; even AREDS formula supplementation has no known effect on GA. When we have an effective therapy, I envision using it in potentially all patients with vision-threatening GA.

WATCH IT NOW

EyewireTV's Ranna Jaraha reports on Iveric bio's latest data.

BIT.LY/STARR0920

Dr. Starr: Would you begin treating patients with small, nonfoveal-involving islands of GA with monthly injections?

Dr. Regillo: This drug may be an option for any patient with nonfoveal GA in which the GA represents a threat to visual acuity. GA lesions are areas of cell death in the macula, and our goal is to prevent the enlargement of this area to prevent or slow progression of patients' difficulties with certain visual tasks such as reading, driving, and cooking. I believe that any patient with nonfoveal GA could potentially benefit if one or both eyes meet the eligibility criteria used in GATHER1 and GATHER2.

Dr. Starr: What do you make of the higher rates of choroidal neovascularization (CNV) seen in avacincaptad-treated eyes compared with sham eyes in GATHER1?

Dr. Regillo: Dose-related higher rates of CNV in eyes with GA being treated with a complement blocker were first seen in the phase 2 Filly study,[4] which evaluated the safety and efficacy of the C3 blocker pegcetacoplan (APL-2,

(Continued on page 17)

AT A GLANCE

- The phase 2/3 GATHER1 trial evaluated the safety and efficacy of avacincaptad pegol (Zimura, Iveric bio) for the treatment of geographic atrophy (GA). Researchers found that avacincaptad significantly reduced GA growth at 1 year compared with sham treatment.
- The phase 3 GATHER2 study will also evaluate the safety and efficacy of avacincaptad for GA treatment and will closely resemble the structure of the GATHER1 trial.
- Potential side effects of complement inhibition may be treatable with anti-VEGF agents.

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*Diabetic macular edema. †Retinal vein occlusion: branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO). ‡Best-corrected visual acuity.

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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.

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.

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.

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

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

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

CALL OZURDEX®

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® (dexamethasone intravitreal implant) 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® (dexamethasone intravitreal implant) 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.

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

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

Treat early with

Ozurdex®
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implant) 0.7 mg

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OZURDEX®

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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 Studies Experience: Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies 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 studies (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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(Continued from page 13)

Apellis Pharmaceuticals). Higher rates of CNV were detected in avacincaptad-treated eyes in GATHER1, although the differences in CNV rates between the sham arm and the avacincaptad monthly dose arms were lower than has been reported for monthly pegcetacoplan.

We will know more about the exact rates of this potential side effect when we acquire additional phase 3 data. Without any treatment, patients with GA will lose vision over time. The good news is that CNV in the setting of GA appears to progress slowly. Eyes in the clinical trials that converted to neovascular AMD still did well, thanks in large part to the anti-VEGF treatment options we already have. Of course, for a patient receiving avacincaptad therapy, treating CNV in the presence of GA could require two intravitreal injections. Physicians and patients will need to weigh this risk when considering the use of a complement blocker in practice. ■

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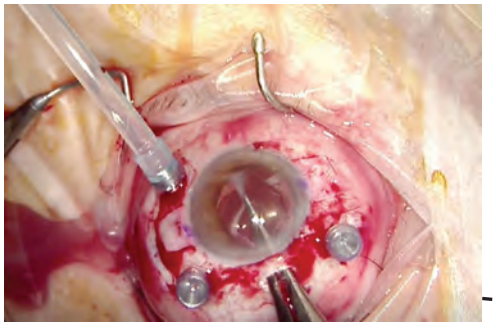
- Financial disclosure: None

EYETUBE AROUND THE GLOBE

A roundup of the latest Eyetube highlights from across the world.

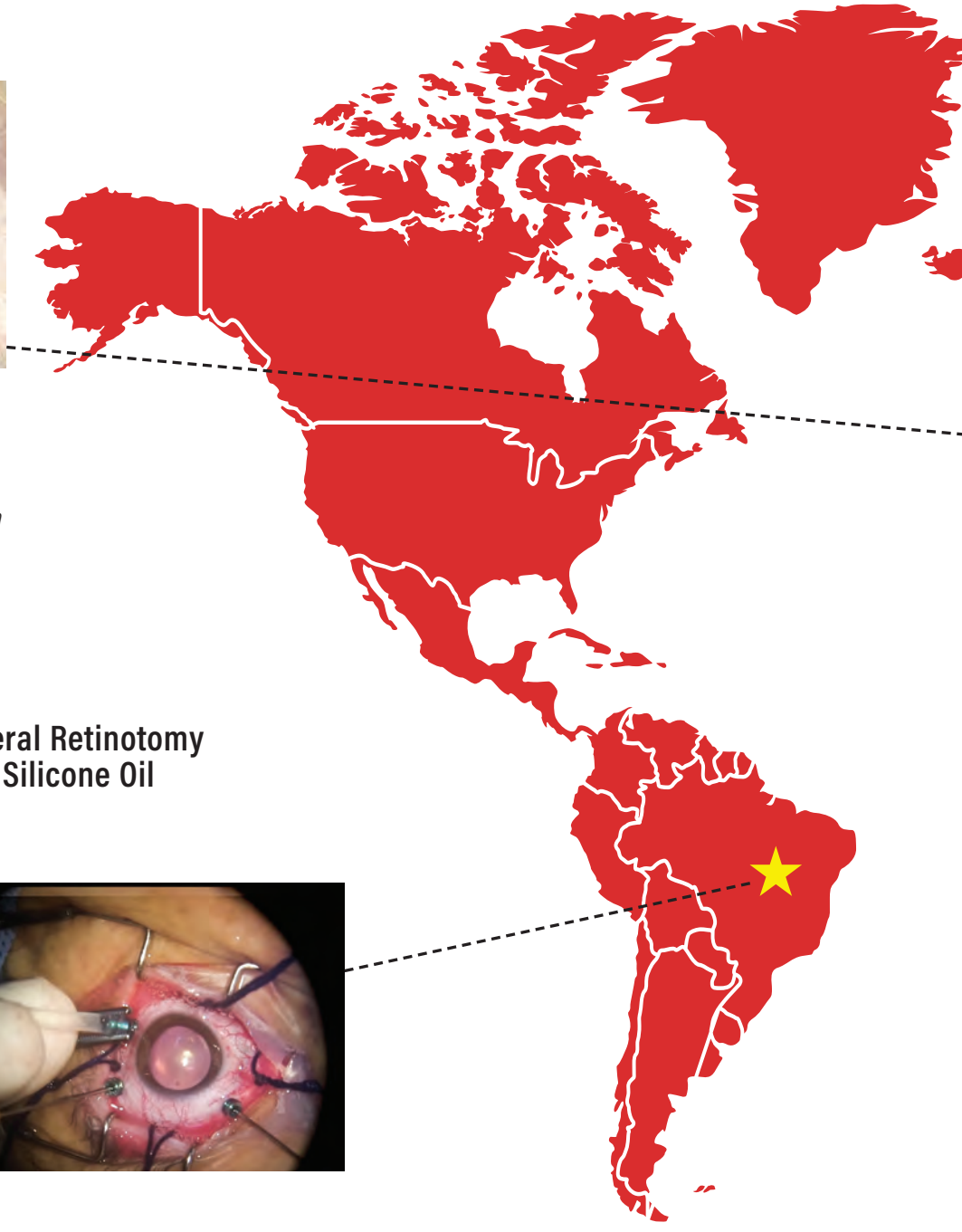


Scleral IOL Fixation

Frédéric Aissani, MD
Centre Hospitalier de Cambrai
Cambrai, France

This patient had a previous cataract surgery and then suffered a blunt trauma 1 month later, resulting in decreased vision.

WATCH IT NOW: BIT.LY/0920AISSANI



Buckle Vitrectomy With Peripheral Retinotomy for Retinal Shortening PVR and Silicone Oil

Hudson de Carvalho Nakamura, MD
Goiás Eye Bank Foundation
Jardim Da Luz, Goiânia, Brazil

A case in which proliferative vitreoretinopathy caused retinal shortening in a phakic patient. A buckle-vitrectomy was used in order to decrease the likelihood of a peripheral retinal redetachment secondary to another PVR. By putting a buckle around the eye, the free temporal retina will find a wall and support for its periphery, and that helps support that area with the appropriate indentation from the buckle.

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Multifunctional Use of 27-Gauge Vitreous Cutter in Combined Tractional-Rhegmatogenous Retinal Detachment

Gurkan Erdogan, MD
Beyoglu Eye Training and Research Hospital
Istanbul, Turkey

This video presents unimanual and bimanual approaches with 27-gauge vitrectomy in combined tractional-rhegmatogenous retinal detachment. The need for instrument exchange is decreased even when peeling the membrane from the mobile surface of the combined tractional-rhegmatogenous retinal detachment.

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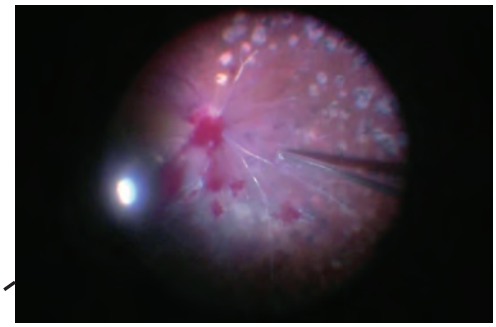
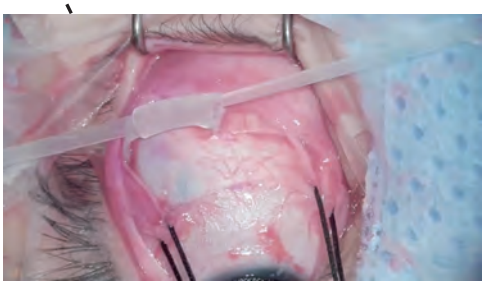


Heads Up: Sutureless Chandelier-Assisted Scleral Buckle

Adel AlAkeely, MD
King Khaled Eye Specialist Hospital
Riyadh, Saudi Arabia

This procedure offers a better visualization of the fundus through chandelier light illumination, improved ergonomics through a heads-up 3D display system, and less discomfort to the patient by eliminating the use of nonabsorbable sutures.

WATCH IT NOW: BIT.LY/0920ALAKEELY



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COOLING ANESTHESIA: A NEW FORM OF ANESTHESIA FOR INTRAVITREAL INJECTIONS?

This rapid, nonpharmacologic form of anesthesia may improve the patient experience and decrease toxicity to the ocular surface.

BY DANIEL L. CHAO, MD, PHD; ARSHAD M. KHANANI, MD, MA; AND CHARLES C. WYKOFF, MD, PHD

Intravitreal (IVT) injection is the most common procedure performed by retina specialists, with estimates of more than 6 million injections performed in the United States annually.[1] That number is only expected to increase as new therapeutics are developed for expanding indications.

Due to the large volume of IVT injections in the retina clinic, significant efforts have been focused on making the workflow for performing IVT injections as efficient as possible and improving the patient experience.

CURRENT TRENDS

Despite the safety and efficacy of IVT injections, patients can experience significant anxiety and discomfort while undergoing a procedure. Indeed, in a survey of patients undergoing IVT injections, the step most associated with significant discomfort was the injection itself, as opposed to the preparation or waiting.[2] Another study found that needle penetration was one of the highest points of concern for patients during IVT injection.[3] These findings suggest that improving anesthesia may improve the patient experience for IVT injection.

Current methods of anesthesia for IVT injection include the application of topical anesthetic drops, a pledget soaked with lidocaine, topical lidocaine gel, and subconjunctival lidocaine injection. All of these methods have benefits and tradeoffs in terms of patient comfort and time of onset of anesthesia, and there is no consensus choice for anesthetic use in IVT injections. This is reflected in the most recent American Society of Retina Specialists (ASRS) Preferences & Trends (PAT) survey, which found that 23% of responding retina specialists used topical drops, 18% used pledgets soaked with lidocaine, 25% used lidocaine gel, and 34% used

AT A GLANCE

- Emerging data suggest that cooling anesthesia is a rapid, nonpharmacologic approach to anesthesia that can be safely and effectively used for intravitreal injection.
- A clinical trial, COOL-2, demonstrated the safety and efficacy of cooling anesthesia over the course of six injections.
- Of patients in the study who received cooling anesthesia at -15° C for 10 seconds, 80% preferred that method to their previous form of anesthesia, subconjunctival lidocaine.

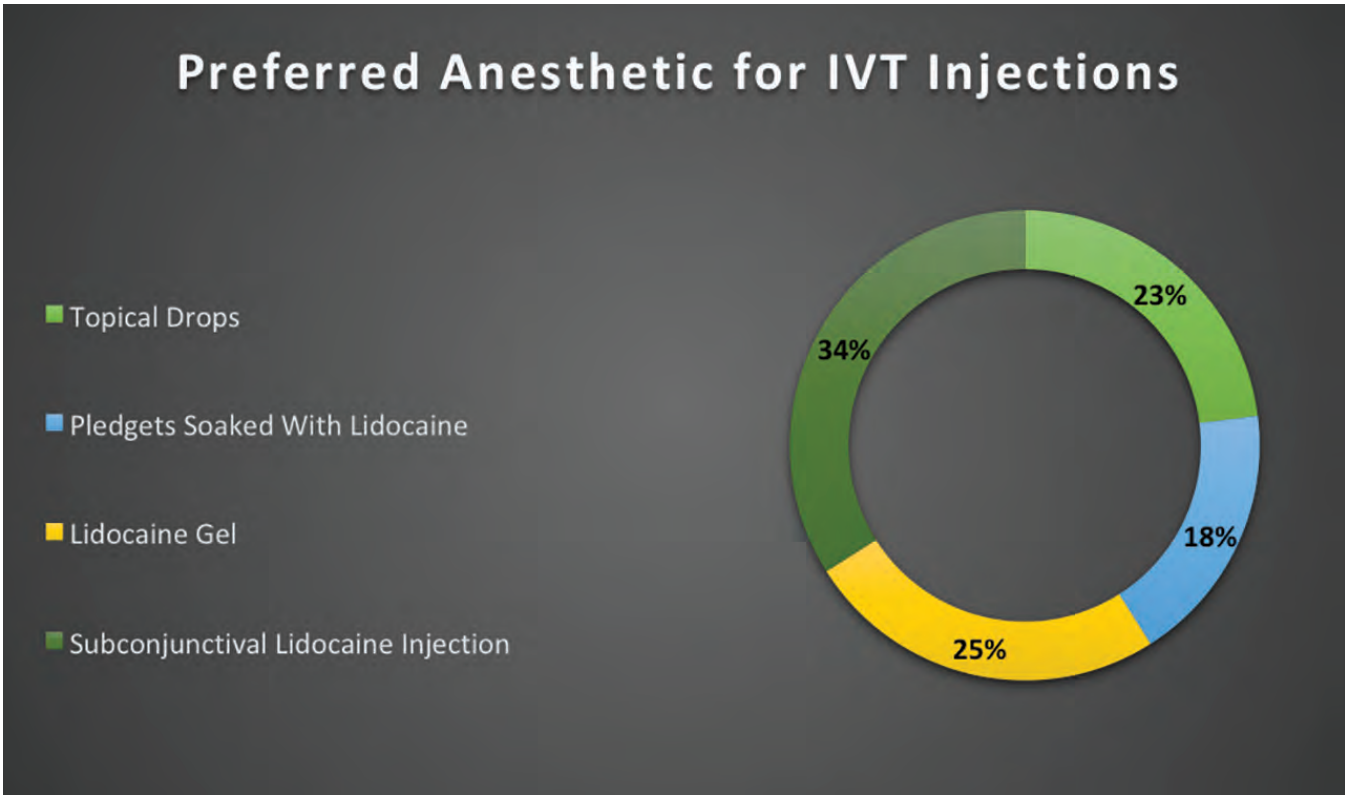

Figure. The 2019 ASRS PAT Survey found that respondents used a variety of anesthesia methods for IVT injection, with no clear consensus choice among retina specialists.

subconjunctival lidocaine injection (Figure).[4] These numbers are similar to those in other surveys of IVT anesthesia preference by retina specialists.[5]

Prospective studies comparing the efficacy of different methods of anesthesia have been mixed; one study suggested that subconjunctival lidocaine is more efficacious than lidocaine gel or topical anesthesia, whereas others found no difference in pain scores among those three methods.[6-9] Systematic reviews of IVT injection anesthesia have also not identified superiority of one type of anesthesia over another in pain scores.[10,11]

Considerations for anesthesia for retina specialists include the efficiency of the procedure, the comfort of the patient, and the best utilization of resources and costs. An alternative method of anesthesia that is fast, tolerable to patients, and has minimal adverse events could help to improve both the patient experience and the workflow of retinal physicians.

A COOLER APPROACH

Cooling anesthesia is a form of nonpharmacologic anesthesia that has shown promising results in clinical studies. We define cooling anesthesia as the local application of temperatures slightly below freezing (usually between -10° and -20° C) as an anesthetic agent. This temperature is much warmer than temperatures that have been shown to cause tissue damage to the eye.[12-14]

Using low temperature to anesthetize human tissue is not a new idea, and this approach is sometimes used as anesthesia for injection of dermal fillers.[15,16] The mechanisms by which anesthesia using low temperature works include decreasing nerve conduction, which inhibits the firing of pain receptors, and the release of endorphins.[16,17]

Recent publications have suggested that cooling the surface of the eye, in lieu of pharmacologic agents, might provide effective anesthesia for IVT injections. A case report demonstrated that ice in a glove, applied to the conjunctiva and sclera for 2 minutes, was sufficient to effectively anesthetize the eye for a patient with a lidocaine allergy.[8] A clinical study with a prototype cooling device demonstrated that, as measured by a visual analog scale (VAS), cooling anesthesia was well tolerated and that pain with cooling anesthesia was not significantly different from pain with lidocaine gel use.[18]

Recently, results of a longitudinal study with a clinical-grade device manufactured by RecensMedical were presented at the 2020 ASRS Meeting.[19]

COOL-2 DESIGN AND RESULTS

The COOL-2 trial (NCT03956797), sponsored by RecensMedical, was an open-label longitudinal study assessing the safety of cooling anesthesia over a series of six injections. Pain scores as measured by a VAS and data from a patient preference instrument were collected. Participants had received at

COOLING ANESTHESIA IS AN ALTERNATIVE, RAPID, NONPHARMACOLOGIC FORM OF ANESTHESIA THAT MAY HAVE DIFFERENTIATING CHARACTERISTICS THAT MAKE IT ATTRACTIVE TO PATIENTS AND PHYSICIANS ALIKE FOR IVT INJECTIONS.

least three IVT injections before enrolling in the study. In the study, for six consecutive injections, participants received cooling anesthesia at either -15° C for 10 seconds or -15° C for 15 seconds.

The study has been fully enrolled, and 39 patients have finished the study. For these patients, pain as measured by VAS was not different from standard of care historical controls in previous studies, and VAS scores from cooling anesthesia did not change over the course of the study. Cooling anesthesia was well tolerated, and there were no ocular serious adverse events or adverse events unrelated to the injection or the device. The average injection time from start of anesthesia to injection was less than 2 minutes.

Interestingly, more than 80% of patients who received cooling anesthesia at -15° C for 10 seconds preferred that over their previous form of anesthesia. (All patients had previously received subconjunctival lidocaine as anesthesia.)

A multicenter masked randomized trial comparing cooling anesthesia to standard of care is planned to start in the near future.

DISCUSSION AND CONCLUSION

These studies demonstrate the proof of concept and safety of using cooling anesthesia for IVT injections. The rapid, nonpharmacologic nature of this anesthesia may improve the patient experience, decrease toxicity to the ocular surface, and facilitate a more rapid workflow and improved time and space efficiency for retina specialists.

Cooling anesthesia is an alternative, rapid, nonpharmacologic form of anesthesia that may have differentiating characteristics that make it attractive to patients and physicians alike for IVT injections. We look forward to the emergence of additional data on cooling anesthesia and its potential for the safety and comfort of our patients in the future. ■

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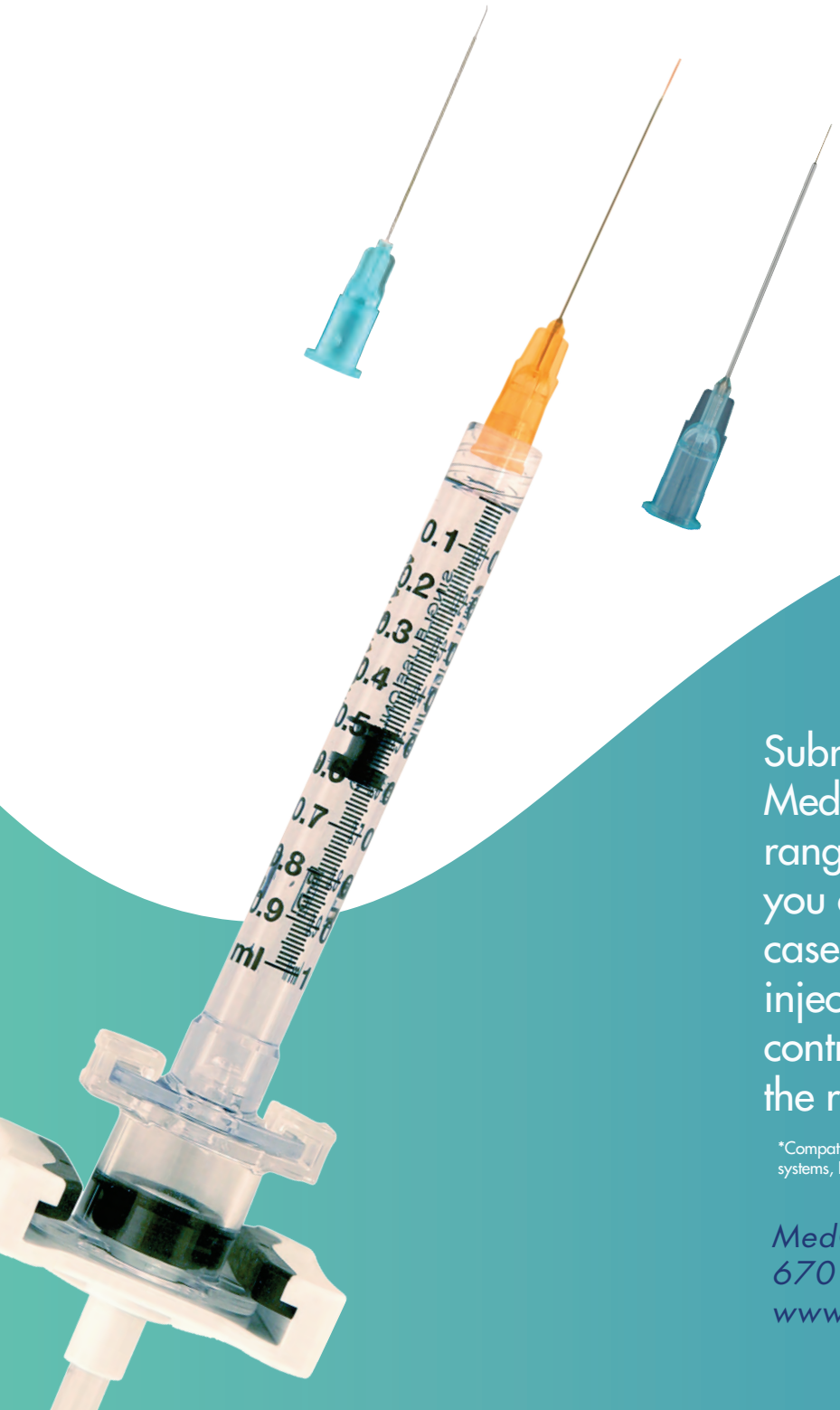

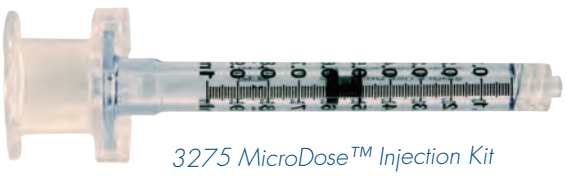

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New Retina Radio: Are Today's Protocols Tomorrow's Routines?

Selected excerpts from a recent edition of *New Retina Radio*.

INTERVIEW BY JOHN W. KITCHENS, MD; WITH MURTAZA ADAM, MD; DAVID R.P. ALMEIDA, MD, PHD, MBA; AND CHRISTINA Y. WENG, MD, MBA

As the host of New Retina Radio's *COVID-19 coverage, I've had the opportunity to speak with a number of leaders in our field about the present and future challenges the COVID-19 pandemic presents. I am curious whether, in some ways, we are witnessing the future of retina in our present moment.*

Protocols have changed significantly during the COVID-19 pandemic. Which of those procedures are here to stay and which will disappear as the pandemic subsides? To find out, I invited three of retina's rising leaders—Murtaza Adam, MD; David R.P. Almeida, MD, PhD, MBA; and Christina Y. Weng, MD, MBA—to New Retina Radio *to discuss which changes implemented in 2020 might become permanent fixtures in retina practice.*

Portions of our discussion are presented here, edited for brevity and clarity.

You can find audio of this episode (and others in the series) in the New Retina Radio *podcast feed. Just navigate to the podcast in your preferred app, subscribe, and listen.*

—John W. Kitchens, MD

PRACTICE LAYOUT

John W. Kitchens, MD: Describe how you normally see patients and then how you have modified that during COVID-19.

David R.P. Almeida, MD, PhD, MBA: We were lucky that our practice setup was already prepared to handle the COVID-19 crisis. Our practice has two floors. The pre-COVID routine saw patients interacting with physicians on the first floor, where diagnosis, imaging, and a treatment plan occurred. Treatment was administered on the second floor, which had a negative pressure system with multiple lanes.

During the pandemic, we have obviously adjusted waiting rooms, PPE requirements, and masking protocols. And we've tried to minimize contact opportunities. Luckily, our layout required patients who needed treatment to head directly to the second floor, and for most of our patients that's what we're doing. They come in for their injection and then they leave.

Dr. Kitchens: And are you doing more or fewer treatments now compared with before the pandemic?

Dr. Almeida: We're providing the same level of care. Our injection clinic was already set up, and so, other than extending intervals for a few patients, we're sticking to pre-pandemic treatment regimens. We use the first-floor imaging stations for selected patients, but the injection clinic is running at full tilt.

Dr. Kitchens: Dr. Weng, can you walk me through the hypothetical first visit for a patient with wet age-related macular degeneration (AMD)? Tell me what your protocols were before the pandemic so we have a basis for comparison.

Christina Y. Weng, MD, MBA: Our pre-pandemic check-in process required a technician to gather patient history, assess vision, and administer imaging. All of this was performed before the patient and the physician interacted.

Before the pandemic, we imaged any referred patients with OCT and occasionally fluorescein angiography to confirm diagnosis. I asked that a family member join the patient, if possible, so that another listening ear can absorb the information I'm delivering. At that point, I usually had the patient initiate therapy on their next visit because I needed pre-authorization to start injecting in most cases.

Now, our policy at Baylor does not allow patients to bring family members to appointments, unless that family member is there to assist with something like translation or a physical handicap. We try to streamline patient intake, too, which minimizes the number of surfaces a patient touches and the number of rooms that need to be turned over between patients. Many of our patients only receive OCT testing; ancillary testing such as fluorescein angiography and fundus photography are performed only if it will change clinical management.

I see patients in the same room where they are worked up, and I'm often administering treatment on the same day to eliminate the need for a return visit. I'm not sure how sustainable this is from a financial and insurance perspective, but it's what we're doing at Baylor now.

AT A GLANCE

- Some protocols implemented during the COVID-19 era may stay in place after the pandemic subsides.
- In an interview with *New Retina Radio*, three retina specialists share what's happening at their clinics, explain why some new processes may become permanent fixtures, and discuss which therapies and technologies in the pipeline would be particularly useful to have right now.

Murtaza Adam, MD: Dr. Weng's description of a *lean* facility is easier to implement in a smaller practice, and kudos to her team for thinking on their feet and adjusting quickly in the university setting. Luckily, at Colorado Retina, we had a lean system in place, and our adjustments looked more like Dr. Almeida's.

In the past, we didn't have to think about such high levels of safety measures in the clinic. Gone are the days of only wiping alcohol on an applicator to address contamination. Our entire framework has shifted.

PATIENTS AND BILLING

Dr. Kitchens: If we reserve imaging for only those patients whose disease management may be altered after the results, as Dr. Weng has described, then some patients may feel like we're not providing a full workup. Is that your experience, Dr. Adam?

Dr. Adam: Not at all. In fact, most of my patients are appreciative of getting in and out so quickly. Injection-only visits take about 30 minutes—a far cry from some of our previous turnaround times. For patients who report visual change, we check visual acuity and perform imaging. I wonder how we'll transition back after the pandemic's intensity is reduced.

Dr. Almeida: Have you run into difficulty with billing? Payers sometimes want to see vision checks or pressure checks on an assessment.

Dr. Adam: We don't bill for visits during injection-only visits. We bill only for the injection and, if needed, the OCT.

Dr. Kitchens: Drs. Adam and Almeida are in private practice. Does their experience with injection-only visitation mirror your experience at Baylor, Dr. Weng?

Dr. Weng: We check vision and pressure in all of our patients, and the vast majority of our patients receive OCT imaging. Our wet AMD patients are on treat-and-extend regimens, and we use that imaging to guide treatment. Luckily, OCT images are quickly acquired, so they do not disrupt our processing flow as long as they are ordered correctly.

TELEMEDICINE

Dr. Kitchens: How have you engaged with patients via telemedicine during the pandemic?

Dr. Adam: The day before a patient is scheduled for an in-person visit, we call them to gather information usually acquired during their in-person intake. History, medications, review of symptoms—all of that is included in their chart. When their visit starts, they get their pressure checked and then I see them immediately. I think we'll continue with this model even after the pandemic.

Dr. Kitchens: Telecommunication with some of our patients can be challenging.

Dr. Adam: Agreed. Sometimes it's a matter of getting a family member to help them with technology. Not uncommonly, the patient has trouble hearing you. It's not a perfect system—I would say it works for 50% to 60% of my patients. Still, it does lend itself to increased efficiency in the clinic.

Dr. Almeida: We use the same system that Dr. Adam just outlined. We gather as much information as possible over the phone before bringing patients in, and then we instruct them to visit our injection clinic for treatment visits. Telehealth, in that way, creates a quick and safe visit for our patients. But we have not done anything like video conferencing. We haven't had the need yet.

Dr. Weng: We have the ability to videoconference with patients via our EHR system, but I've found it challenging. It can be useful for triaging patients, and some patients find it reassuring to know a doctor is listening to their symptoms. But when a patient reports a change in vision, I can't say, "Oh, I don't think it's really anything," without the aid of an OCT or a dilated examination.

Dr. Kitchens: Are there any technologies that you wish you had?

Dr. Weng: Home OCT is something that would revolutionize retina. If we had that, we could tell patients with accuracy how quickly they need to be seen.

Dr. Kitchens: Agreed. Home OCT would be a game-changer. We have the Amsler grid, obviously, and we also have the ForeseeHome device (Notal Vision). Dr. Almeida, has your practice used the ForeseeHome?

Dr. Almeida: Our practice covers such a huge area that we have chosen to concentrate on efficiency and on supporting our local referral base. Unfortunately, we don't have the bandwidth for something like ForeseeHome.

Dr. Adam: My practice also hasn't embraced ForeseeHome, or any home-based monitoring system for that matter. Has your practice looked into these, Dr. Kitchens?

Dr. Kitchens: We're believers in it. We were in the HOME study, which evaluated the ForeseeHome device's efficacy. About 70% of my patients can use it, and they love it; the other 30% have difficulty with it. We have found it an effective monitoring tool for patients.

A Return to In-Person Meetings?

In-person education is one of the jewels of retina, and a dynamic of the job that many physicians miss. What concerns do you have about the resumption of in-person meetings, which will presumably happen in 2021?

Murtaza Adam, MD
Colorado Retina Associates
It's going to take a lot to convince me that in-person meetings should be resumed. I need to see evidence of a nationwide paradigm shift on how travel and business is conducted before I can comfortably attend a convention.

David R.P. Almeida, MD, MBA, PhD
Erie Retinal Surgery
It's tricky. Obviously, I want to go and see my colleagues and learn about their research. But I also don't want to acquire the virus while traveling, become an asymptomatic carrier, and then pass it along to my patients.

Christina Y. Weng, MD, MBA
Baylor College of Medicine-Cullen Eye Institute
Our facility requires people who visited certain states to quarantine for 14 days. Even if I visit a state that isn't on the list when I leave, I would be required to quarantine if that state is added to the list while I'm there. I must consider this when traveling to any potential events.

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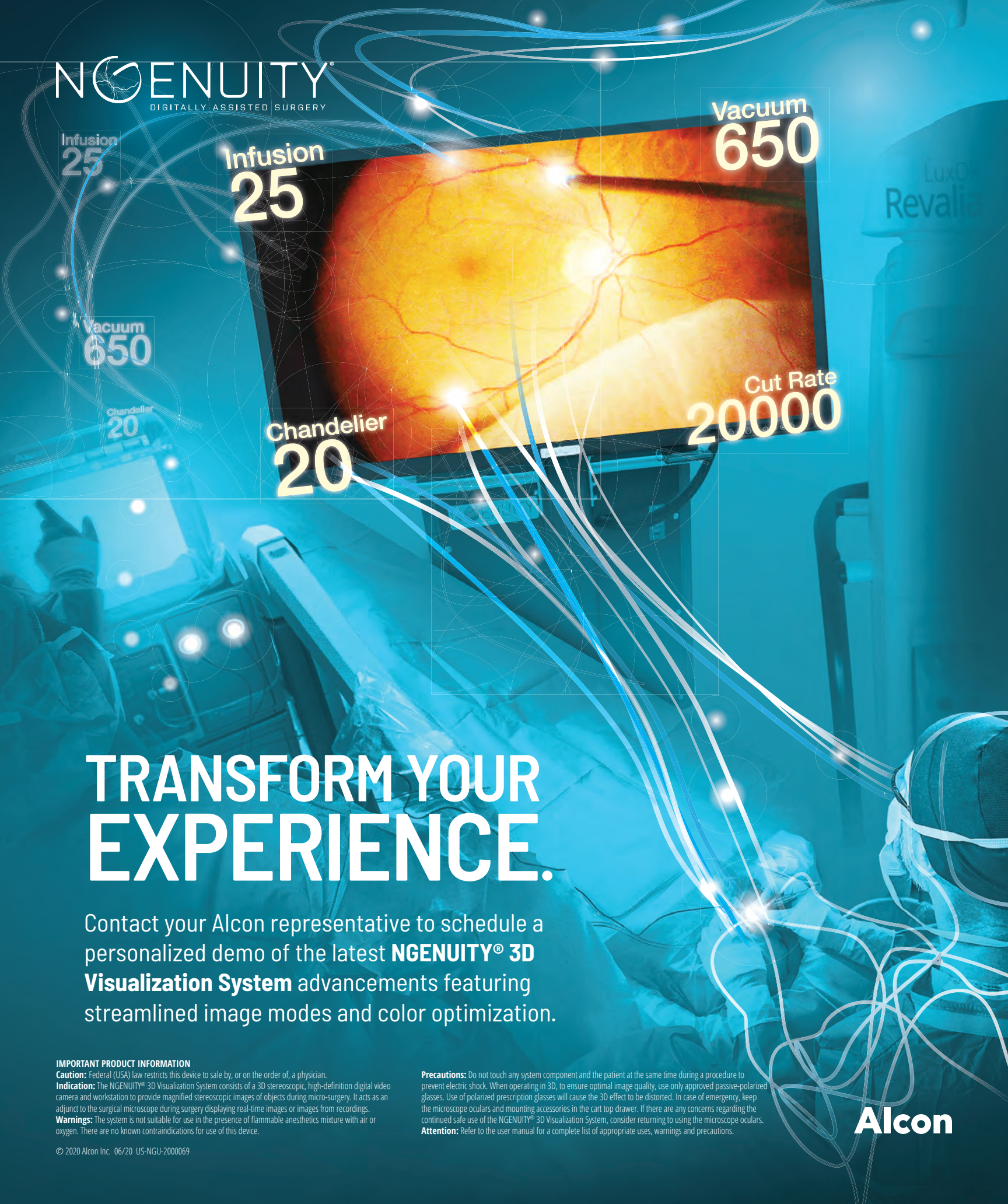

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DRUG CHOICE

Dr. Kitchens: Has the pandemic affected your choice of drug—say, allowing more steroid use in patients with diabetic eye disease, or using a different anti-VEGF agent for wet AMD patients?

Dr. Adam: Before the pandemic, we had plenty of patients who received bevacizumab (Avastin, Genentech) and were happy to come in every 4 or 5 weeks for an appointment. Now, given that every appointment is a risk of exposure, our practice has shifted our anti-VEGF agents of choice, particularly for patients in long-term care facilities, as they are at the greatest risk for complications should they contract COVID-19.

Dr. Weng: Drug durability was already a hot topic, and now it's even more important. Longer-duration drugs could allow us to avoid a situation like we had at the beginning of the pandemic, when we had to strictly enforce social distancing and decide which patients we were able to see. Technology that could get us to quarterly intervals or longer would be great. That is part of the reason the Port Delivery System (PDS, Genentech) excites me so much. Regarding steroid use, I am generally a proponent of it, but given that it may also be harder for patients to return to our clinic if there is an IOP spike, it is important to select patients carefully.

Dr. Kitchens: Are you switching anti-VEGF agents?

Dr. Weng: I've considered it. Some patients with wet AMD experience longer duration of effect if they receive aflibercept (Eylea, Regeneron), for example. And of course, now there is brolucizumab (Beovu, Novartis). The patients I've started on brolucizumab have responded wonderfully, and many have moved to quarterly treatments. Given the safety considerations around brolucizumab, however, I think a lot of doctors are hesitant to start patients on this agent, especially during this time.

Dr. Almeida: With respect to neovascular AMD, we have significant experience with longer duration of effect and stable efficacy intervals with aflibercept, although we use all the available anti-VEGF agents. We started using brolucizumab in November 2019. When some safety concerns arose, we revised our consent process and monitor those patients closely.

THE FUTURE OF RETINA

Dr. Kitchens: Some of the changes we made will be here for the long term. Others will fade away with time. Does the panel have any ideas about which protocols will stay in place?

Dr. Weng: Cleaning practices and hygiene routines will probably stick around for a while. It's hard to justify going back to a less-clean workplace. I think that wiping down rooms with bleach and wearing masks will be around for a while. Forever, maybe.

Dr. Adam: Creating a less-clean practice—that's going to be a hard sell.

Dr. Almeida: As someone who loves staying involved with clinical trials, I look forward to enrolling patients and gathering data. We have a completely separate area for our clinical trials division, which facilitates pandemic preparedness in research patients. I can see this division of clinical roles (eg, imaging, diagnosis, treatment, research, etc.) remaining for the long term.

Dr. Adam: The challenge with recruiting for clinical trials at the moment is that patient volume is down. Patient enthusiasm is still present, which is key. But, in Colorado, our referrals fell sharply when optometry offices closed. ■

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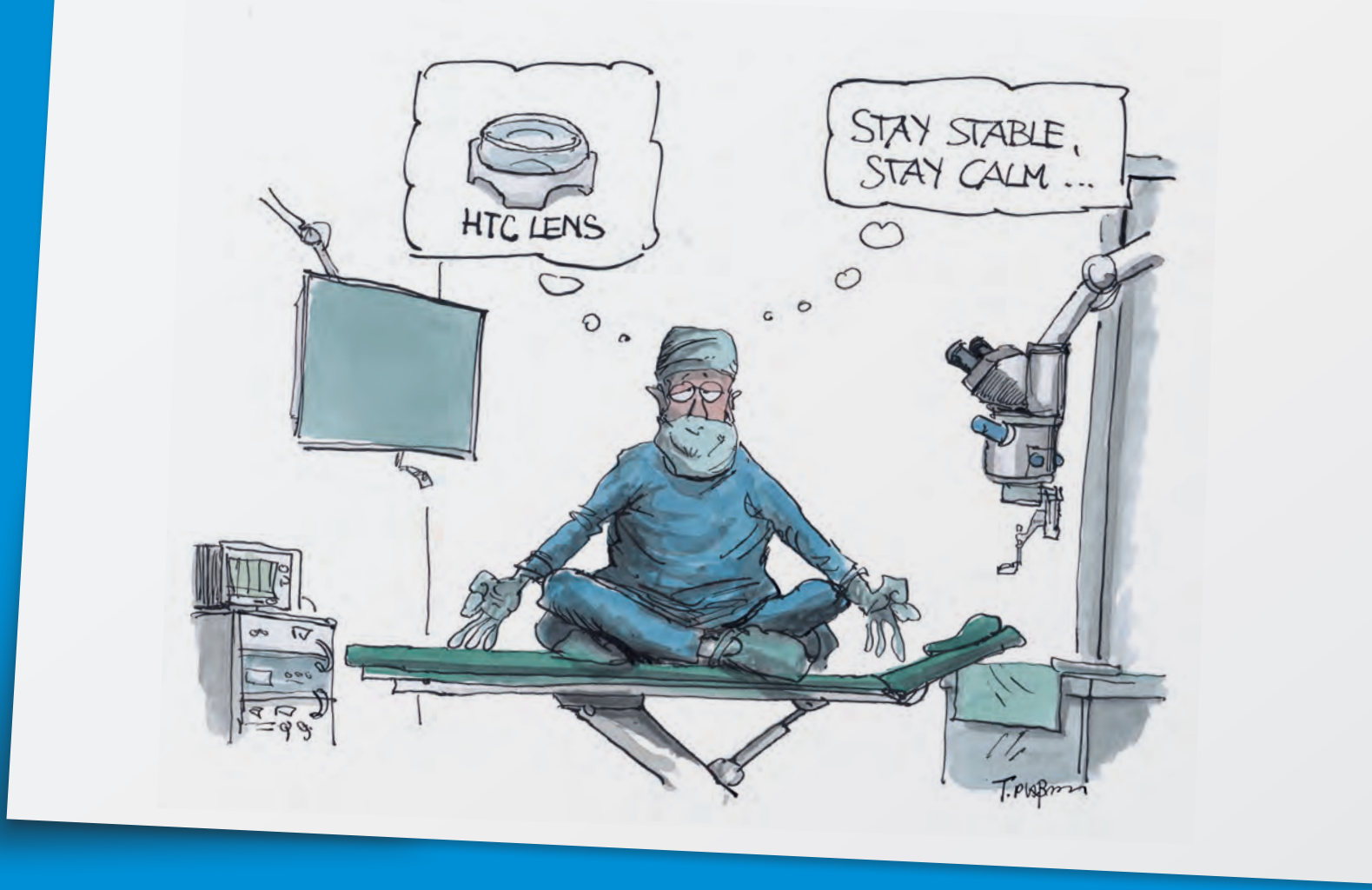

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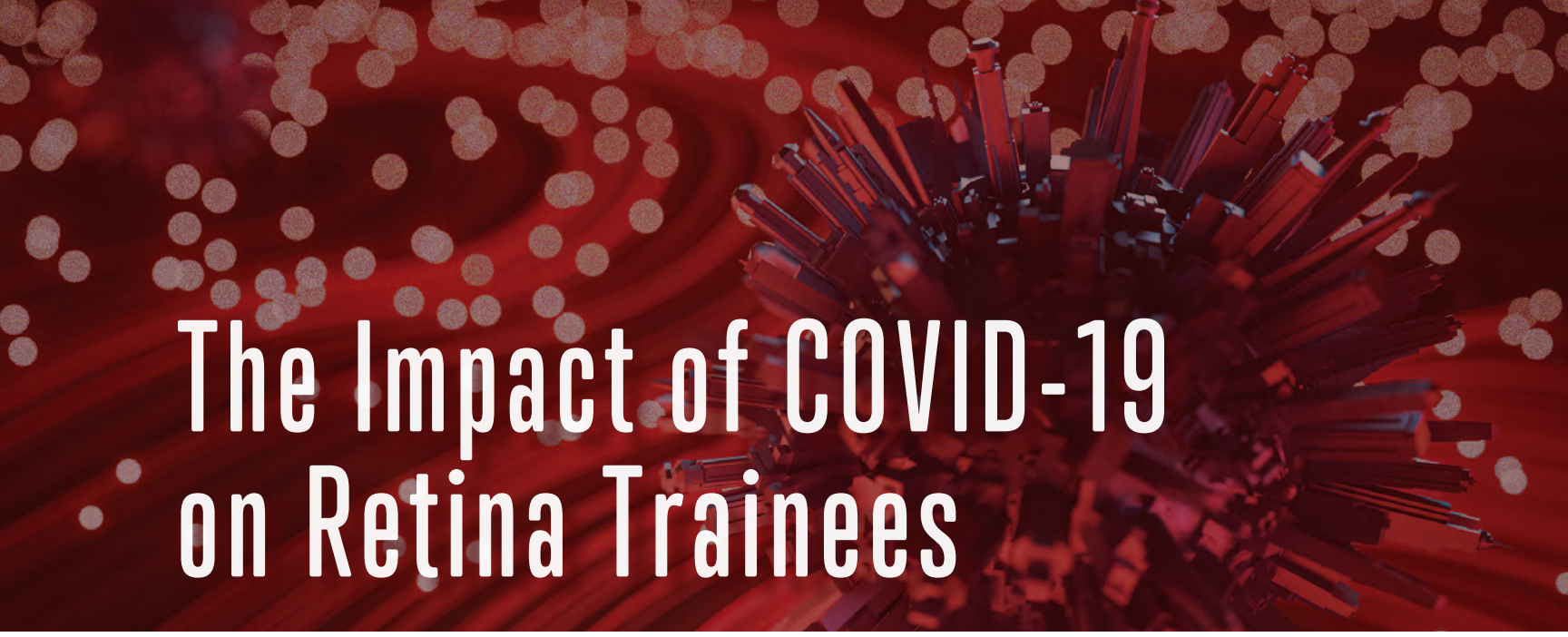

The Impact of COVID-19 on Retina Trainees


As if the training wasn't hard enough.

BY GIULIA CORRADETTI, MD, AND FEDERICO CORVI, MD

For many, 2020 is a year with special meanings. It marks the beginning of a new decade, a time for new beginnings, exciting resolutions, and big dreams. For many doctors in training, 2020 will mark the year of their graduation from medical school, residency, or fellowship. This is the culmination of many years of hard work and studying on their way to becoming an intern, a resident, a fellow, and ultimately to starting a new life as a practicing physician and surgeon.

Many also looked forward to 2020 as the year of ophthalmologists, as 20/20 VA is the hallmark of good vision. However, as we all know by now, it has been a year full of challenges. As the new decade started unfolding, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and its associated disease, COVID-19, were reported in Wuhan, China, leading to a rapid epidemic outbreak. On March 11, the World Health Organization declared COVID-19 a pandemic,[1] with sustained risk of further global spread.

In the following months, COVID-19 spread worldwide to 188 countries, with more than 25 million cases confirmed and 280,000 deaths as of early September.[2] From an isolated outbreak to a pandemic labeled the worst public health crisis since the 1918 flu pandemic in a matter of months.

Soon after its auspicious beginning, 2020 became the year of pandemic with all dreams and resolutions put on hold. Many countries ordered lockdowns to avoid rapid transmission of the virus. Social distancing measures were implemented worldwide, and everyone was encouraged to wear a mask when in public. Health care systems across the world experienced unprecedented burdens, and all specialties of medicine have been profoundly affected. All individuals have been involved in the fight against this disease.

Ophthalmologists soon learned that the use of personal protective equipment (PPE) was necessary to limit the transmission of the virus. Given the requirement in our specialty to be physically close to the patients' eyes during routine eye exams, use of PPE was key to allowing us to safely perform ophthalmologic examinations.

In a recent report, ophthalmologists were noted to be one of the medical specialties most profoundly affected by COVID-19.[3] During this exceptionally challenging time, we

AT A GLANCE

- As it did with all other aspects of society, the COVID-19 pandemic upended the process of ophthalmic education in 2020.
- Clinic visits and surgeries were canceled, but learning has still taken place through remote and virtual means.
- Some of the changes instituted due to the crisis this year show promise to be carried forward for future trainees.

THE GROWTH OF WEBINARS, PODCASTS, AND ONLINE TEACHING TOOLS ALLOWED US TO EXCHANGE IDEAS, INTERACT WITH OUR COLLEAGUES, NETWORK, PRESENT CHALLENGING CASES, AND BUILD A NEW MODEL FOR ACQUIRING MEDICAL EDUCATION REMOTELY.

were called upon to make difficult decisions for which we did not receive any formal training. Ultimately, we faced the challenge of optimizing our clinical practice to try to balance the benefit of treating patients to prevent vision loss against the maintenance of a safe clinical environment for all.[4] We also experienced a notable reduction in clinic volume as routine visits and elective surgeries were canceled or postponed in order to protect asymptomatic patients and providers.[5]

TRAINING AFFECTED

The outbreak inevitably affected all ophthalmologists-in-training and our educational experiences. To the challenges of the training itself we had to add the challenges of being in training during this global health crisis: the uncertainty of the future, the fear of not being able to learn everything, the need to rapidly acquire new learning methodologies, the stress of transitioning from in-person visits to virtual interviews for future positions, the challenges of conducting research projects remotely and with reduced clinical volume.

Conferences and in-person meetings were canceled with the introduction of physical distancing norms, reducing networking and collaborative opportunities for trainees. On the other hand, the great progress in communications technologies during recent decades gave us the possibility to connect to our mentors using virtual platforms.

In order to provide high standards in ophthalmic research while ensuring safety during the pandemic, our research institution transferred our activity remotely and planned weekly virtual meetings to connect us to our mentors to present ongoing research and to discuss future proposals. Grand rounds, seminars, and conferences were also transferred online. The growth of webinars, podcasts, and online teaching tools allowed us to exchange ideas, interact with our colleagues, network, present challenging cases, and build a new model for acquiring medical education remotely.

Furthermore, the use of social media to communicate scientific information, educate patients, and build new professional connections increased exponentially.[6] These virtual opportunities compensated for the lack of in-person meeting and learning due to the pandemic.

NEW FRONTIERS

The events of 2020 have introduced a series of changes in the mentoring of future ophthalmic professionals. These changes have pushed us to discover new frontiers in ophthalmic education. Even though they were forced on us by a crisis, some of these changes appear to hold promise to positively impact the training of future young ophthalmologists. Perhaps they will be adopted as part of the academic education model of the future. ■

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Retinal Vein Occlusion Associated With COVID-19


CRVO is commonly seen in association with a hypercoagulable state.

BY NUHA KAPATAYES, BS, AND BRIAN C. JOONDEPH, MD, MPS

Infection with SARS-CoV-2, the virus that causes COVID-19, is known to induce a hypercoagulable state with resulting venous thromboembolism.[1] Central retinal vein occlusion (CRVO) is commonly seen in association with a hypercoagulable state, which may contribute to the pathogenesis of retinal vein occlusion (RVO).[2] We report, to the best of our knowledge, the first case of CRVO associated with COVID-19 infection.

A 59-year-old man was referred to our clinic with blurred vision in his right eye concurrent with cough and abdominal pain. COVID-19 infection was suspected, but polymerase chain reaction testing was not performed because he was not ill enough for hospital admission, which at the time was required for testing. Several weeks later, his systemic symptoms resolved, and he was tested for COVID-19 antibodies. He was positive for SARS-CoV-2 immunoglobulin G and negative for immunoglobulin M.

The patient's medical history was significant for a 5-year history of microscopic colitis. His only medication was aspirin 81 mg/day.

An eye examination revealed 20/20-1 VA OD, with normal IOP and slit-lamp examination. His right fundus showed a mild CRVO (Figures 1 and 2). His left eye visual acuity and examination were normal. OCT imaging did not show macular edema (Figure 3), and therefore he was not treated.

DISCUSSION

CRVO is due to a thrombus in the central retinal vein as it exits the globe within the optic nerve. Often patients with CRVO have systemic risk factors such as hypertension, diabetes. cardiovascular disease, or a hypercoagulable state. Our patient had none of these risk factors for CRVO. Although ulcerative colitis has been reported as a rare association with CRVO, no such association has been reported with microscopic colitis, a less severe form of inflammatory bowel disease.[3] As noted, COVID-19 infection can cause hypercoagulability.

Retinal microvascular changes have been reported with COVID-19, including subtle cotton wool spots and microhemorrhages but not a retinal vascular occlusion.[4]

The timing of COVID-19 infection, as documented by antibody testing in this patient, with visual symptoms and findings of a CRVO, suggest an association between the two conditions. The pathogenesis is consistent with COVID-19

AT A GLANCE

- The hypercoagulable state induced by COVID-19 may be linked with CRVO, which itself is associated with the presence of hypercoagulation.
- The authors share what is possibly the first reported case of a patient with COVID-19 who presented with CRVO.

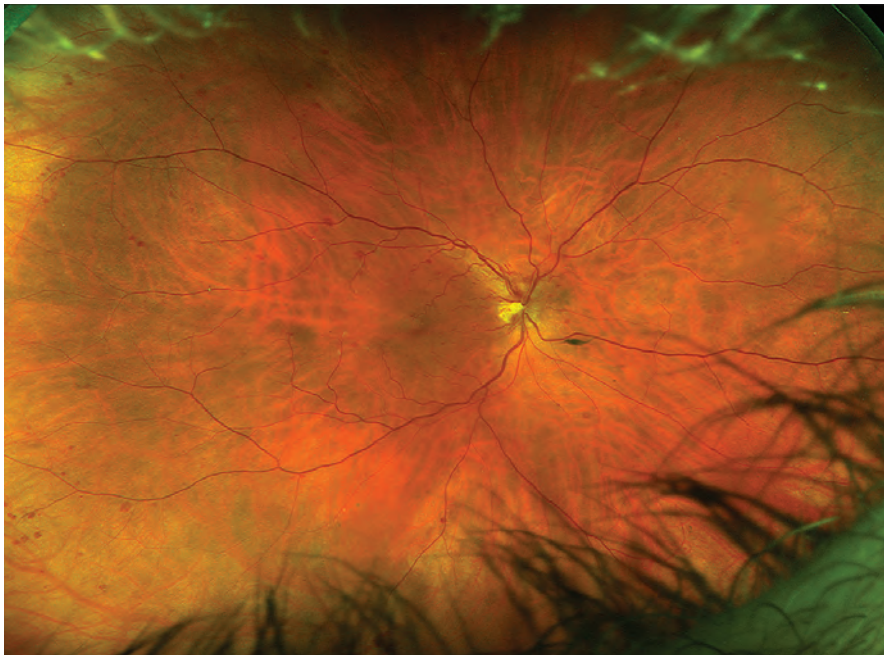

Figure 1. A CRVO can be seen in the patient's right eye.

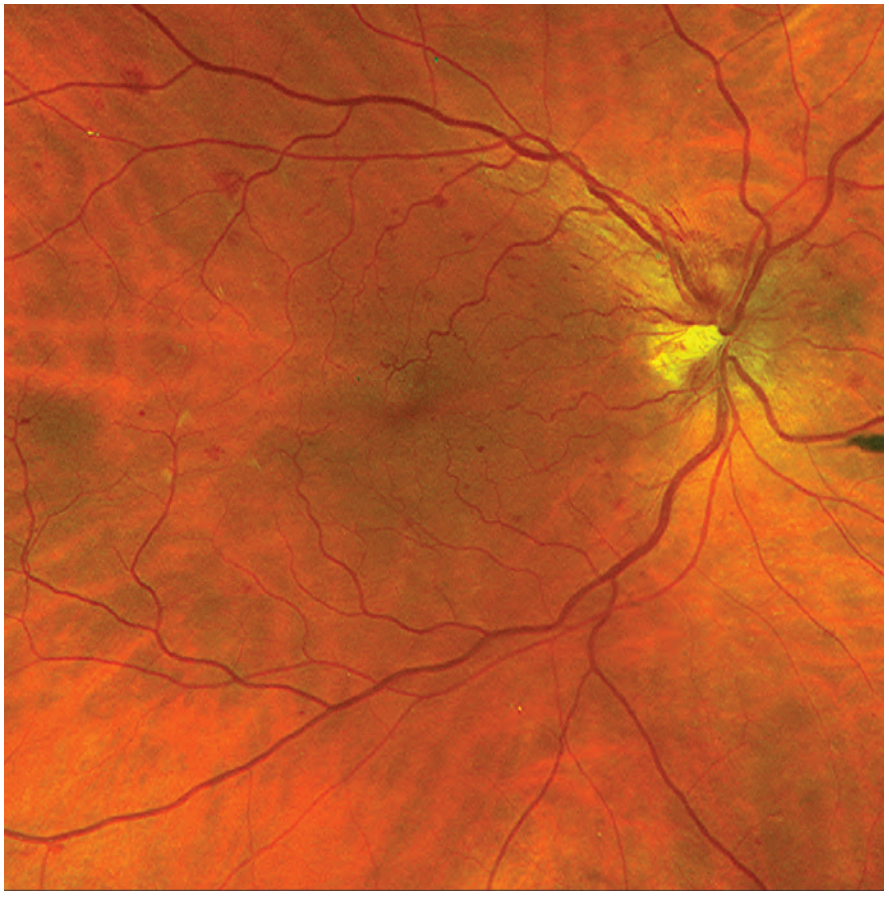

Figure 2. Magnified view of the macula shows disc edema, scattered dot and blot hemorrhages, and cotton-wool spots.

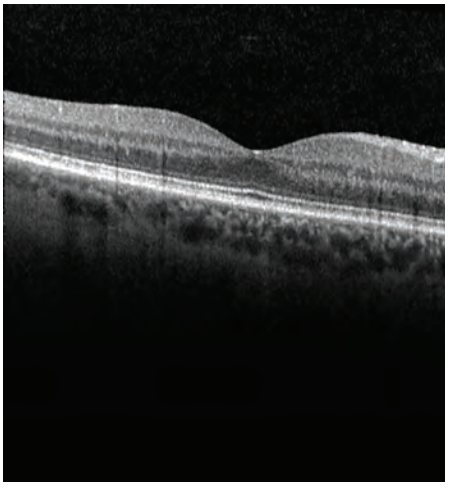

Figure 3. OCT of the right eye shows no macular edema or retinal opacities.

inducing a hypercoagulable state, which can lead to CRVO.

Clinicians should be aware that eyes of patients with COVID-19 infection are at risk for vascular occlusive events and that visual symptoms may occur even with milder forms of systemic viral infection. This may help distinguish COVID-19 from other common forms of upper respiratory illness not known to induce a hypercoagulable state. ■

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A Review of Clinical Trial Data for DME: BOULEVARD and MEAD


Dissecting the data from two studies provides perspective on the interaction of therapies with this disease.

BY CHRISTOPHER BARRON, MD, AND DAVID A. EICHENBAUM, MD

Advancement of commercially available therapy for diabetic macular edema (DME) has not evolved significantly for several years. Although approved therapeutic options for DME are adequate for many patients, concerns about durability and efficacy remain.

Here, we discuss two clinical trials—BOULEVARD and MEAD—and review the implications of the trials' findings. Reviewing these studies side by side provides perspective on the treatment of DME. The MEAD study is a foundational text in the modern era of DME treatment, and revisiting it refreshes our understanding of a seminal trial. BOULEVARD's importance may be that it has served as the foundation for phase 3 research, and it provides a glimpse into researchers' priorities and goals.

BOULEVARD Study

Sahni J, Patel SS, Dugel PU, et al

Simultaneous Inhibition of Angiopoietin-2 and Vascular Endothelial Growth Factor-A With Faricimab in Diabetic Macular Edema: BOULEVARD Phase 2 Randomized Trial[1]

Faricimab (Genentech/Roche) is the first bispecific antibody for intraocular use that binds and neutralizes both angiopoietin-2 (Ang-2) and VEGF-A. The BOULEVARD study was a phase 2 prospective, randomized, double-masked trial designed to assess the efficacy and safety of faricimab in patients with DME. Addressing the role of VEGF in DME (which is done by administration of anti-VEGF agents) may be only one component of treating this disease. Faricimab was designed to address the potential of affecting the additional angiopoietin pathway.

Ang-1 and Ang-2 are key cytokines in the angiopoietin pathway and interact with transmembrane receptor tyrosine kinase (Tie2). The activation of Tie2 by Ang-1 promotes

AT A GLANCE

- The phase 2 BOULEVARD trial evaluating the safety and efficacy of faricimab (Genentech/Roche) for the treatment of DME met its primary endpoint.
- Revisiting data from the phase 3 MEAD study reinforces the safety and efficacy of the 0.7 mg intravitreal dexamethasone implant (Ozurdex, Allergan).

vascular stability, pericyte recruitment, and the inhibition of vascular permeability factors. In proangiogenic states such as hypoxia, hyperglycemia, or oxidative stress, Ang-2 is upregulated and competitively binds to Tie2, competing with Ang-1. This binding of Ang-2 to the Tie2 receptor has been shown in multiple basic science settings to lead to endothelial destabilization, inflammation, and breakdown of the blood-retina barrier. As a novel anti–Ang-2/anti-VEGF bispecific antibody, faricimab binds to VEGF-A and Ang-2. Blocking Ang-2 may stabilize vasculature structures in patients with DME.

Researchers in the phase 2 BOULEVARD trial enrolled 229 patients, 168 of whom were treatment-naïve and 61 of whom had been treated with anti-VEGF agents. Patients had center-involving DME, BCVA of 73 to 24 ETDRS letters, and central subfield thickness (CST) of at least 325 µm.

Treatment-naïve patients were randomly assigned 1:1:1 to 6.0 mg faricimab, 1.5 mg faricimab, or 0.3 mg ranibizumab (Lucentis, Genentech). Patients with a history of anti-VEGF therapy were randomly assigned 1:1 to 6.0 mg faricimab or 0.3 mg ranibizumab. Patients were dosed monthly for 20 weeks and then followed monthly for up to 36 weeks to assess durability.

In the treatment-naïve group, the primary efficacy outcome measure was mean change in BCVA from baseline to week 24. Secondary efficacy outcomes included the proportion of patients who gained 15 ETDRS letters from baseline and mean change in CST as evaluated by spectral-domain OCT at week 24.

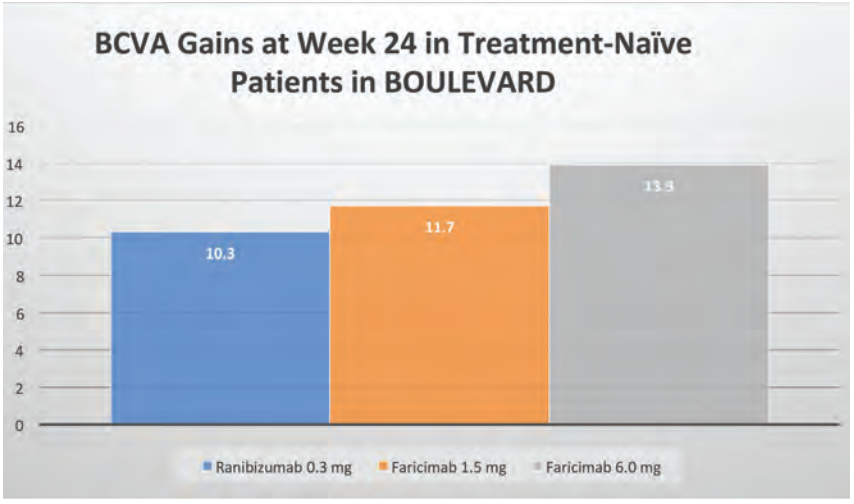

Figure 1. In BOULEVARD, at 24 weeks, treatment-naïve patients in the 6.0 mg faricimab group demonstrated a significantly greater gain in ETDRS letters compared with patients in the 0.3 mg ranibizumab group.

The trial met its primary efficacy endpoint. In treatment-naïve patients, BCVA gains in the faricimab group were higher than those in the ranibizumab group at week 24. Adjusted BCVA gains from baseline were 10.3 ETDRS letters for the 0.3 mg ranibizumab group, 11.7 letters for the 1.5 mg faricimab group, and 13.9 letters for the 6.0 mg faricimab group (Figure 1). The 3.6-letter difference between the ranibizumab group and the 6.0 mg faricimab group was statistically significant.

At week 24, a majority of patients in each arm gained at least 10 ETDRS letters (59.2% in the ranibizumab arm, 60.6% in the 1.5 mg faricimab arm, and 72.1% in the 6.0 mg faricimab arm). At week 24, adjusted mean change in CST was -204.7 µm, -217.0 µm, and -225.8 µm for those same groups, respectively. There was a greater probability for patients treated with 6.0 mg faricimab to exhibit a longer time to retreatment compared with patients treated with ranibizumab. Faricimab was well tolerated, with a safety profile similar to that of ranibizumab.

Data from BOULEVARD suggest a benefit of combined Ang-2/VEGF-A blockade over anti-VEGF monotherapy. This combined therapy may provide additional vascular stability and could be responsible for increased efficacy and durability. In patients with DME, faricimab therapy resulted in significantly higher BCVA gains compared with ranibizumab therapy and demonstrated reduction in CRT and extended durability.

MEAD Study

Boyer DS, Yoon YH, Belfort R Jr, et al; Ozurdex MEAD Study Group.

Three-Year, Randomized, Sham-Controlled Trial of Dexamethasone Intravitreal Implant in Patients With Diabetic Macular Edema (MEAD Study)[2]

MEAD, a pair of randomized, multicenter, masked, sham-controlled phase 3 clinical trials, evaluated the safety and efficacy of the intravitreal dexamethasone implant 0.7 mg (IDI; Ozurdex, Allergan) in patients with DME. A total of 1,048 patients with DME with BCVA between 20/50 and 20/200 and CRT of at least 300 µm on time-domain OCT were randomly assigned 1:1:1 to receive 0.7 mg IDI, 0.35 mg IDI, or a sham procedure. Patients were followed for 3 years, and the primary efficacy endpoint was BCVA gain of at least 15 letters.

At 3 years, 607 (57.9%) patients completed the study. On average, patients in the 0.7 mg IDI group had four treatments, patients in the 0.35 mg IDI group had five treatments, and patients in the sham group had three treatments. IDI at either dose demonstrated statistical superiority to sham in the primary efficacy endpoints, with BCVA improved at most timepoints.

Overall, BCVA was reduced in the IDI

THE BOULEVARD TRIAL PROVIDES A SIGNAL FOR HOPE—FOR REDUCED TREATMENT BURDEN, FOR A BETTER UNDERSTANDING OF A NEW MECHANISM OF ACTION, FOR A NEW OPTION FOR PATIENTS WITH DME WHOSE DISEASE RESPONSE HAS HIT A CEILING WITH ANTI-VEGF MONOTHERAPY.

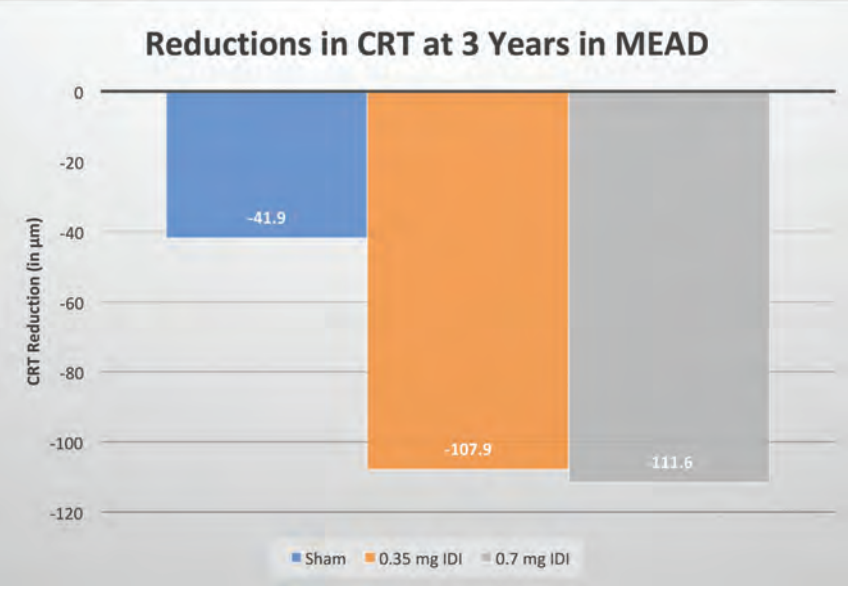

Figure 2. A dose-dependent response in CRT reduction was observed in patients with DME at 3 years in the MEAD study.

group at 15 months. Researchers attributed this to development of visually significant cataracts, which correlated with a reduced benefit of treatment. Vision improved after cataract extraction and remained improved in the IDI group through the end of the study.

The mean reduction in CRT was statistically significantly greater in the IDI groups than in the sham group (Figure 2). Increased CRT was observed after cataract surgery in the sham group but not in the IDI groups, suggesting a possible protective benefit of IDI therapy on macular edema in diabetic patients following cataract extraction. About one-third of patients in the IDI groups required treatment for increased IOP; this complication was generally managed with topical therapy. Vitreous hemorrhage was rarely noted with injection.

Since the FDA approved the 0.7 mg IDI in July 2014, the implant has served as a useful treatment for DME, especially in patients who do not have a good response to anti-VEGF treatment.

DISCUSSION: MEAD AND BOULEVARD

Data from the 2014 MEAD trial tell us what many of us in 2020 already know: that a 0.7 mg intravitreal dexamethasone implant is an effective tool for treating DME, especially in patients who are suboptimal anti-VEGF responders. Still, parsing the data reminds us that other factors that may mitigate visual gains (ie, cataract formation) or IOP medication burden (ie, treated steroid-associated IOP increased with topical therapies) are factors to weigh when considering DME therapy.

The BOULEVARD trial provides a signal for hope—hope for reduced treatment burden, for a better understanding of a new mechanism of action, for a new option for patients with DME whose disease response has hit a ceiling with our existing anti-VEGF medications. The coming years will reveal a future for DME therapy in which hopefully we can provide greater benefit for patients with less interference in their daily lives. ■

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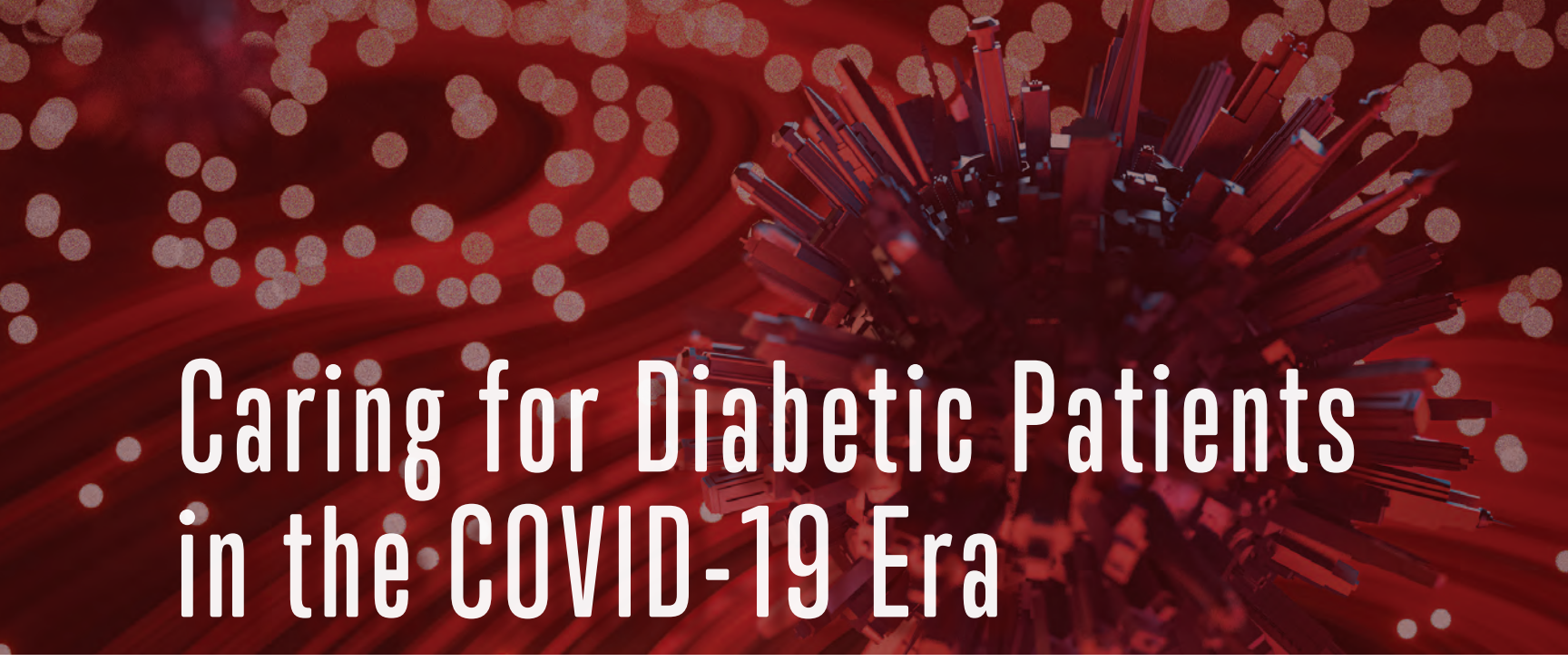

Caring for Diabetic Patients in the COVID-19 Era

Considerations for serving this vulnerable population during an evolving crisis.

BY JOHN W. KITCHENS, MD

Retina specialists face the unique challenge of caring almost exclusively for patient populations that are at high risk for severe illness from COVID-19. One such population at risk is our patients with diabetes.[1] Kentucky, where I practice, has one of the highest rates of diabetes in the country.[2]

Although our patient volume was reduced by up to 60% during the early days of the COVID-19 lockdown, when we were seeing only urgent and emergent cases, we have since met and exceeded our pre-COVID volume. This precipitous increase is due not only to the backlog created by delayed or cancelled appointments, but also to an influx of new patients who were unable to see their optometrist or general ophthalmologist during the lockdown and are now being referred for a variety of pathologies, including diabetes-related eye disease.

Pandemic-related concerns can affect our diabetic patients' diets and lifestyles, and even their ability to access medication and routine medical care. Unfortunately, the impact is greatest on the most marginalized patients. I have had patients present with significantly elevated A1C levels, and consequently exacerbated eye disease, who explained that they did not buy their insulin that month because they could not afford the copay.

Our practice has adopted several key strategies to help ensure that patients in this vulnerable population receive the care they need regardless of the difficult and ever-evolving circumstances of this global pandemic.

COMMUNICATING WITH PATIENTS

Because diabetes puts patients at greater risk for COVID-related complications and mortality, it is understandable that people living with the disease may be hesitant to leave home, whether it be to go to a grocery store or to the doctor's office. Communicating to patients all the precautions our practice has taken to ensure their safety has been a critical component of our efforts to ease patients' fears.

As a first step, our practice posted a video to our Facebook page and website in which we explained all of the measures we'd put into place, including social distancing, face mask requirements, and asking patients' family members to wait in the car. We also posted our complete COVID-19 policies and procedures. The feedback we received for this was extremely positive, as patients were

AT A GLANCE

- Communicating to patients the precautions your practice has taken to ensure their safety can be a critical component in easing patients' fears.
- Providing guidelines to referring doctors can help clarify which pathologies constitute urgent cases and which can wait 1 to 2 months for treatment.
- Greater reliance on imaging technology can minimize face-to-face interactions and decrease the amount of time patients spend in the clinic.

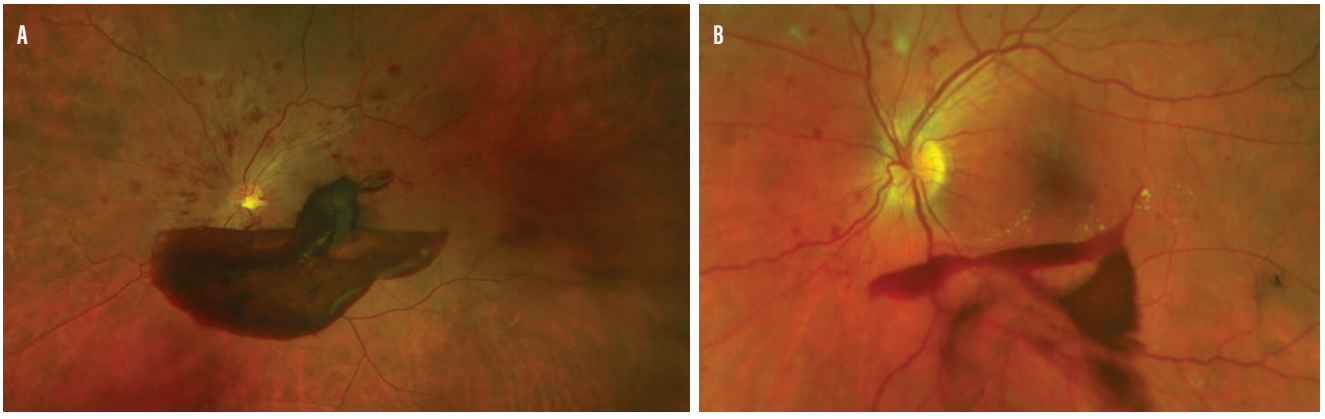

Figure. UWF imaging performed by referring physicians helps offices prioritize patients by pathology. UWF imaging depicting a subhyaloid hemorrhage secondary to proliferative diabetic retinopathy (A) and a diabetic vitreous hemorrhage (B) are seen here.

grateful that we made the information easily available.

In addition to this type of mass communication, we reached out by phone to patients who were scheduled for treatments to confirm appointments and explain the new protocols. For those in need of routine follow-up care, we contacted them proactively to schedule it.

COORDINATING WITH REFERRING PHYSICIANS

To ensure that we triage patients appropriately, we are actively coordinating with our referring doctors. This means distributing communications to help clarify which pathologies constitute urgent cases and which can wait 1 to 2 months for treatment. We also encourage referring physicians to capture and share with us ultra-widefield (UWF) images of patients about whom they are concerned (Figure). Reviewing the UWF images helps us determine how urgently these patients need to be seen, or if they can instead be managed by the referring doctor.

IMPROVING CLINIC EFFICIENCY

It would be impossible to serve our diabetic patients effectively while maintaining the new social distancing and cleaning protocols without increasing patient flow over pre-COVID levels. We have accomplished this in several ways.

First, we identified strategies for expediting appointments. In pre-COVID times, I would meet with and examine a patient prior to ordering imaging or tests. Now, if a patient arrives with a referral for significant diabetic retinopathy, diabetic macular edema (DME), or proliferative disease, our staff immediately captures UWF and OCT imaging, after I have reviewed the referring doctor's note to confirm that this is indeed the referring doctor's diagnosis. Having access to these tests before meeting with the patient allows me to assess the situation before I even enter the room. This new process also keeps the patient in the same room throughout the visit, minimizing patient movement throughout the practice.

We have also adopted a new injection protocol, recommending five monthly injections before the next full exam. Although this is more aggressive than our previous routine of performing examination after three treatments, the new protocol is more in line with that of most DME clinical trials, and it decreases overall exam times and patient time spent in the practice. We have always recommended bilateral same-day injections to patients, and we are finding that this, along with performing same-day injections and laser (panretinal photocoagulation), increases our ability to deliver care more efficiently.

Finally, we are relying more on UWF imaging and OCT to assess retinal status. Our practice's Optos device quickly captures high-resolution Optomap images of virtually the entire retina. These images are useful for identification and documentation of pathology. Under the current circumstances, this technology not only allows us to accurately and reproducibly grade a patient's retinopathy, it also minimizes face-to-face interactions and decreases the amount of time patients spend in the clinic.

LOOKING FORWARD

These strategies have played an invaluable role in maintaining our practice volume and patient flow during the past 6 months, and I believe they will continue to do so for the foreseeable future. The new processes have helped us to see and care for many diabetic patients, but we know there are still unserved patients who are taking a pass on potentially vital care due to health or financial concerns. We physicians must continue to do everything we can to expand our capacity and reach out to these patients so that they get the care they need. ■

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Expanding Access to Diabetic Retinopathy and Depression Screening

Telemedicine can help during the COVID pandemic.

BY RAJIKA JINDANI, MS; JACLYN PERREAULT, BA; RAQUEL GOLDHARDT, MD, FACS; JORGE CUADROS, OD, PHD; AND DELIA CABRERA DEBUC, PHD

A significant association has been identified between diabetic retinopathy (DR) and depression, two common comorbidities of diabetes. Both conditions greatly affect quality of life and management of this chronic systemic disease.[1]

Individuals with diabetes in low-resource settings have historically faced barriers to care, and these have been further aggravated by the COVID-19 pandemic, causing greater disruption to their eye care and mental health care. The increased use of technology to reach these populations could provide a solution to this health care gap.

The role of telemedicine in providing DR screening has been validated, but fewer than 50% of individuals with diabetes receive annual DR screening examinations.[2,3] This article presents one way in which telemedicine can play a role in screening for both DR and depression, potentially improving diabetes care in low-resource settings.

COMMON COMORBIDITIES

The prevalence of depression in individuals with DR ranges from 35.7% to 50%.[1,4] Studies have found that patients with any level of DR are more likely to experience depression compared with other diabetic patients.[5,6] Conversely, patients with diabetes with higher scores on depression screening have an increased risk for DR.[7,8]

DR and depression are each associated with socioeconomic risk factors that increase the likelihood of developing the other condition. DR and depression may also be biologically linked through mechanisms including circulating inflammatory cytokines, insulin deficiency,

AT A GLANCE

- DR and depression are common comorbidities of diabetes.
- DR and depression are each associated with socioeconomic risk factors that increase the likelihood of developing the other condition.
- A pilot program assessed the ability of a telemedicine-based screening model to detect DR and depression in a low-resource setting.

WITH THE EMERGENCE OF COVID-19, THE USE OF TELEMEDICINE HAS BECOME NOT ONLY MORE WIDESPREAD IN GENERAL BUT ALSO CRUCIAL FOR REACHING PATIENTS IN AREAS OF LIMITED ACCESS.

chronic hypo- or hyperglycemia, hypothalamus-pituitary-adrenal axis hyperactivity, and others.[1]

SCREENING TOOLS AND IMAGE TRANSMISSION

With the emergence of COVID-19, the use of telemedicine has become not only more widespread in general but also crucial for reaching patients in areas of limited access.[9,10] Telemedicine is valuable for its ability to reduce the number of in-person appointments for diabetic patients, who are at high risk for complications of COVID-19.[11]

The use of telemedicine allows clinic staff to conduct DR screening during a general primary care appointment, which can help to reduce the number of in-person appointments without sacrificing important assessments.

Depression screening using a validated questionnaire, such as the Patient Health Questionnaire (PHQ), can also be conducted during primary care appointments to identify patients who may require urgent referral to a psychiatrist. As social isolation and symptoms of depression may intensify during pandemic situations, depression screening for at-risk diabetic patients should be included during telemedicine or in-person appointments.

PILOT PROGRAM

Students from the University of Miami Miller School of Medicine initiated a pilot screening program for DR as a part of their MPH Capstone project at a secondary care outpatient center in Juiz de Fora, Brazil. Fifty patients with established type 1 or 2 diabetes were screened at the clinic by these students in collaboration with faculty and students from Universidade Federal de Juiz de Fora.

A telemedicine and artificial intelligence (AI)–based model was used to identify DR. Images were captured by a Fundus on Phone (FOP; Remidio) portable camera donated by the retina screening service EyePACS.[12] The fundus camera uploaded the retinal images onto the online EyePACS platform, which used an AI algorithm to identify referable cases (ie, DR/no DR) to an ophthalmologist within minutes without having to dilate the patient's eyes.

Ophthalmologists from the EyePACS system reviewed the images and provided final recommendations. Cases identified as referable through AI interpretation of retinal images were expedited for urgent evaluation by an ophthalmologist. A validated questionnaire for depression screening was also administered at the time of the primary care visit.

Preliminary results showed that, among the 50 patients screened, 22 (44%) were identified with signs of DR, and, of these, 13 (26%) required urgent referral to an ophthalmologist. All 50 patients were counseled on signs and symptoms of DR as well as preventive measures. One patient was scheduled for urgent surgery following the screening.

Among those who completed the depression screening questionnaire including the PHQ-2, 13 individuals (26%) had scores indicating a high risk of depression. Of the 13 individuals who had positive PHQ-2 results, eight were also identified as having signs of DR.

ULTIMATE VISION

We encourage providers in low-resource settings to implement telemedicine-based screening for DR and depression into their routine appointments for patients with diabetes mellitus. Our pilot program in Juiz de Fora, Brazil, demonstrated the feasibility of a medical student–run model to implement these screening measures during patients' primary care appointments, leading to expedited specialist referrals for high-risk individuals. The preliminary results demonstrated a need for retinopathy and depression screening in this patient population.

Benefits of this program can include improved outreach to patients in low-resource settings or rural locations lacking access to specialists, as well as potential improvement in compliance. Combining DR and depression screening with a routine care appointment decreases barriers to care by reducing the number of days patients take off from work, the money lost in wages, and expenditures for travel to appointments.[13,14]

It is anticipated that findings may be similar in other low-resource settings in which appointments with specialists are not readily accessible. In addition, this model may prove useful in reducing the number of in-person visits for patients with diabetes mellitus during the COVID-19 pandemic without sacrificing important comorbidity screening and may allow users to provide further assistance through an internet-based mental health program. ■

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(Continued on page 49)

A STROKE OF SERENDIPITY

A summary of the Retina Fellows Forum keynote lecture from Baruch Kuppermann, MD, PhD.

BY DAVID XU, MD

In January at the Retina Fellows Forum, Baruch Kuppermann, MD, PhD, told the audience of second-year retina fellows about his journey into and through retina. The retina landscape has been shaped by a handful of influential researchers and clinicians, Dr. Kuppermann among them. It was a privilege to join my peers at the Fellows Forum and to hear Dr. Kuppermann share details from his life.

It is difficult to communicate the inspiration one feels after hearing a leader from our field speak humbly and candidly about his journey. I hope I am able to do so here.

—David Xu, MD

Dr. Kuppermann began his talk by briefly describing his childhood. He idolized his father, a chemist, and decided to initially study biophysics and pursue an academic career. Dr. Kuppermann received his PhD in neuroscience studying synaptic plasticity at the California Institute of Technology in 1983. This led him to a career in visual sciences. He earned his medical degree from the University of Miami in 1985.

Although academics were always important to him, Dr. Kuppermann "enjoyed the process, not the product" of his academic career. "This led to my career as a retina specialist—without realizing it at the time," he told the audience. This mantra led him on a journey with, in his words, serendipitous encounters, that allowed him to forge rewarding collaborations in drug delivery and medical device research.

THERE AND BACK AGAIN

After completing his undergraduate work, Dr. Kuppermann joined his father in Israel and then Brazil, where he reconnected with his Brazilian heritage. He still keeps in touch with friends he made during those trips and maintains a close connection with several.

"One of my friends from Brazil spent a week with me and my family over the holidays," he said.

Dr. Kuppermann traveled frequently during his academic training, a trait he learned from his father. He took time off between graduate school and medical school, as well as during intern year and residency, which were formative years for his early career.

Taking a job at UC Irvine was an easy decision for Dr. Kuppermann—it came down to family. During his time abroad, he had limited communication with his family, so after training he returned to Southern California to be close to his parents, who lived in Pasadena. This way, his children could see their grandparents on a regular basis.

"To be close to family was a nice thing," he said. "It was my main motivating factor for returning home."

EARLY COLLABORATIONS

Dr. Kuppermann recounted his first year as an ophthalmology resident at USC, which coincided with the start of the HIV/AIDS epidemic.

"There was this group of young men who were exactly my age, with all the same interests in music, art, literature, as I had," Dr. Kuppermann recalled, "Except they were HIV positive and I wasn't. They were dying and going blind, and I was there to try to help them."

Dr. Kuppermann's tenure at UC Irvine took place at the height of the AIDS crisis. When Dr. Kuppermann arrived in 1992, most retina specialists had little collaborative experience with pharmaceutical companies. However, one area of crossover emerged: AIDS and cyto-

AT A GLANCE

- The keynote lecture at the Retina Fellows Forum was delivered by Baruch Kuppermann, MD, PhD.
- Dr. Kuppermann, responsible for shaping much of retina as we know it today, used his life story to advise second-year fellows to follow their passions and remain open to all the opportunities life presents.
- His experience as an early researcher in cytomegalovirus retinitis therapy opened a number of professional doors.

HIS TIME AS AN INVESTIGATOR WAS NOT SPENT ENTIRELY IN THE LAB. HIS WORK IN THE CLINIC LEFT A LASTING IMPRESSION. DR. KUPPERMANN DESCRIBED THE EXPERIENCE OF TREATING AIDS PATIENTS IN THEIR FINAL YEAR OF LIFE AS "A POWERFUL REMINDER OF HOW IMPORTANT VISION IS TO OUR PATIENTS."

megalovirus retinitis. Dr. Kuppermann's collaboration with industry allowed him to serve as an investigator for clinical trials earlier than some of his colleagues may have.

His time as an investigator was not spent entirely in the lab. His work in the clinic left a lasting impression. Dr. Kuppermann described the experience of treating AIDS patients in their final year of life as "a powerful reminder of how important vision is to our patients."

Drawing from his experience with industry, Dr. Kuppermann eventually developed his own ideas regarding drug delivery. He collaborated with Allergan on an intraocular implant, that has since evolved into the intravitreal dexamethasone implant (Ozurdex, Allergan).

FOLLOW YOUR HEART

Dr. Kuppermann concluded his talk with a simple piece of advice: Follow your heart and follow your passions.

Traveling gave Dr. Kuppermann experiences he wouldn't otherwise have encountered. He stayed open to new ideas and opportunities. All of these were important in shaping who he would become as a scientist.

"Although there are uncertainties in life and in your career, we are so lucky, in the scope of life and time, that we're alive here now in this amazing world," he concluded. ■

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REDUCED TEMPORAL RETINAL VASCULAR DENSITY AS AN EARLY FINDING IN SICKLE CELL RETINOPATHY

A small study may suggest a way to screen for early disease in patients with sickle cell disease.

BY TOMÁS LOUREIRO, MD; DIOGO LOPES, MD; ANA RITA CARREIRA, MD; SANDRA RODRIGUES-BARROS, MD; ANA VIDE-ESCADA, MD; AND NUNO CAMPOS, MD

Sickle cell disease (SCD) is the most prevalent structural hemoglobinopathy in the world. It is associated with multisystemic vascular occlusive events that can affect the retinal microvasculature.

Sickle cell retinopathy (SCR) is the most severe ocular complication of SCD. It is classified either as nonproliferative (NPSCR), with features including peripheral venous tortuosity, salmon-patch hemorrhages, iridescent spots and black sunbursts, or as proliferative (PSCR). Goldberg proposed a five-stage grading system for PSCR.[1] Without early detection and treatment, SCR can lead to irreversible vision loss.[2]

Macular thinning and lower vascular density have been proposed as preclinical alterations preceding SCR development.[3] Because these abnormalities are not detected in routine observations, imaging exams are crucial for SCR screening.

We performed a study to analyze the characteristics of the macula and temporal retina in children with SCD.

MATERIALS AND METHODS

This single-center, retrospective study included children less than 18 years old with SCD. Exclusion criteria were high refractive errors (> 6.00 D), media opacities, and retinopathy other than SCR. Approval was obtained from the relevant institutional research committee.

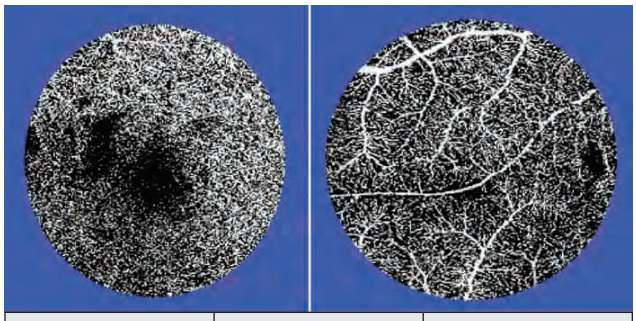
We collected clinical and laboratory data and performed ophthalmologic evaluation including BCVA, slit-lamp observation, and fundoscopy.

Macular OCT and OCT angiography (OCTA) imaging with the Cirrus HD-OCT 5000 with Angioplex (Carl Zeiss Meditec) was performed. Scan protocols included collecting 6x6–mm images centered at the fovea and 3x3–mm images through the temporal macula. Macular thickness, foveal avascular zone (FAZ), and superficial vessel density (SVD) were automatically generated.

Deep vascular density (DVD) was calculated with ImageJ using the method described by Parodi et al.[4] Vascular density (VD) was expressed as the ratio between vessel pixels and total area (Figure).

AT A GLANCE

- A small retrospective study found that the temporal region is the area of the retina most susceptible to damage in sickle cell disease (SCD).
- The study suggests that temporal retinal thinning and reduced vascular density may predict the presence of retinopathy in children with SCD.
- The study authors suggest that temporal centered OCT angiography should be a part of screening for children with SCD.



Total pixels	Vessels	Density
1048576	409231	0.390

Figure. A deep vascular density (DVD) image generated by ImageJ. On the left is the fovea-centered image; on the right, the temporal retina. At bottom, the output calculated by ImageJ (here, for deep foveal capillary density).

Statistical analysis was performed using SPSS Statistics 23.0 (IBM). Mann-Whitney tests were used to compare eyes with and without SCR. Statistical significance was defined as $P < .05$.

RESULTS

Our study included 15 children with SCD; eight had SCR and seven had no SCR. For two children, information could be retrieved from only one eye due to lack of cooperation. Hence, data for 28 eyes were included in the study.

Patients' mean age was 12 ±4 years. Demographic and laboratory data are presented in Tables 1 and 2, respectively. BCVA was 6/7.5 bilaterally in both the SCR and the no-SCR groups.

Fourteen of 28 eyes (50%) were classified as having NPSCR, and none had PSCR.

OCT data are shown in Table 3. There were no differences regarding foveal thickness between the SCR and no-SCR groups.

The temporal retina tended to be thinner than the fovea, with a thickness of 196.5 ±18.1 µm at 6 mm temporal to the macula. Mean temporal thickness was lower in eyes with retinopathy (185.3 ±16.2 µm vs 205.2 ±13.2 µm, respectively, $P < .01$). This difference was more pronounced in the temporal subfield of the displaced scan in the temporal retina (184.3 ±16.3 µm vs 196.4 ±10.7 µm, $P = .04$).

OCTA results are presented in Table 4. Mean FAZ appeared to be larger in the SCR group (0.36 ±0.11 vs 0.30 ±0.1 mm^2, $P = .46$).

Mean foveal VD values were lower in the SCR group than in the no-SCR group, both SVD (37.1 ±1.4% vs 43.3 ±1.7%, $P = .01$) and DVD (39.1 ±1.2% vs 44.3 ±2.2%, respectively, $P = .01$). In SCR eyes, the temporal SVD (27.6 ±3.7% vs 37.1 ±2.3, $P<0.01$) and DVD (32.3 ±2.6% vs 38.3 ±2.1%, $P < .01$) mean values were also lower.

DISCUSSION

SCR can lead to serious visual impairment if not recognized and treated early. Recent work has led to the detection of certain retinal alterations that can predict

TABLE 1. DEMOGRAPHIC INFORMATION

	No SCR (n = 7)	SCR (n = 8)
Age, years (range)	11 ±2 (9-15)	12 ±3.6 (8-17)
Sex		
Male	3	3
Female	5	4
Race		
Black	7	8
SCD Genotype		
HbSS	4	4
HbSC	2	2
HbS/ß-thalassemia	1	2
Medication		
Folic Acid	6	7
Hydroxyurea	2	4
Transfusion		
Yes	1	2
No	6	6
Other Manifestations		
Yes · Vaso-occlusive crisis · Dactilitis · Aplastic crisis · Femoral head avascular necrosis	5 2 2 1 0	6 2 2 1 1
No	2	2

Abbreviations: SCD, sickle cell disease; SCR, sickle cell retinopathy.

TABLE 2. GENERAL OPHTHALMIC EVALUATION FINDINGS (N = 28)

	No SCR (n = 14)	SCR (n = 14)
Spherical Equivalent		
OD	+0.50	+0.50
OS	+0.50	+0.90
BCVA		
	6/7.5	6/7.5
Anterior Segment		
No alternations	11	11
Sclerotic jaundice	3	3
Retinopathy		
Nonproliferative	-	14
Proliferative	-	0

Abbreviations: OD, right eye; OS, left eye; SCR, sickle cell retinopathy.

TABLE 3. OCT DATA: MACULAR AND TEMPORAL RETINA THICKNESS

	No SCR (n = 14)	SCR (n = 14)	*P* Value
Macular Thickness (µm)			
Fovea	232.4 ±13.7	221.5 ±15.4	.12
Temporal	303.5 ±26.7	305.4 ±8.2	.76
Nasal	322.7 ±18.1	323.2 ±9.3	.90
Inferior	325.4 ±10.9	315.6 ±14.3	.06
Superior	326.9 ±17.3	329.2 ±7.8	.8
Temporal Retina (µm)			
6 mm	205.2 ±13.4	185.3 ±16.2	**< .01**
Temporal	196.4 ±10.7	184.3 ±16.3	**.04**
Inferior	215.3 ±9.2	211.4 ±12.8	.473
Superior	214.7 ±15.2	208.7 ±15.8	.341

Abbreviations: SCR, sickle cell retinopathy.

TABLE 4. OCTA DATA: VESSEL DENSITY AND FOVEAL AVASCULAR ZONE

	No SCR (n = 14)	SCR (n = 14)	*P* Value
Fovea			
Superficial Capillary Plexus (%)	43.3. ±1.7	37.1 ±1.4	**.01**
Deep Capillary Plexus (%)	44.3 ±2.2	39.1 ±1.2	**.01**
6 mm Temporal			
Superficial Capillary Plexus (%)	37.1 ±2.3	27.6 ±3.7	**< .01**
Deep Capillary Plexus (%)	38.3 ±2.1	32.3 ±2.6	**< .01**
Foveal Avascular Zone (mm^2)			
	0.30 ±.01	0.36 ±.01	.46

Abbreviations: SCR, sickle cell retinopathy.

the development of proliferative disease, improving early diagnosis and treatment.[5-7]

In this study in children with SCD, mean foveal SVD and DVD values were lower in eyes with SCR than in eyes with no SCR. However, no difference was seen between the groups regarding foveal thickness. Mean temporal retinal thickness and VD in both plexuses were also lower in eyes with SCR, adding information to previous reports.[8]

This finding suggests that the temporal macula may be more susceptible to damage due to the small caliber of terminal arterioles. The authors believe that reduced VD could be reliable markers of early retinal damage.

Because these alterations are commonly asymptomatic and most often undetectable in routine ophthalmologic examination, OCTA could be helpful in screening for SCR. It is important to highlight that screening should start early, but there is also a need to establish parameters for OCTA data in healthy children to further help in identifying those at risk for SCR. We propose that temporal retina scans should be part of regular evaluation of children with SCD.

Our results are encouraging and, despite the small sample size, may provide a basis for prospective clinical trials to define the role of OCTA in SCR screening. ■

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LIGHTS, CAMERA, VIRTUAL!

Elevate your online presentations by following these 12 steps.

BY LISA M. NIJM, MD, JD

At the end of 2019, my dance card for 2020 was full. I was eagerly planning presentations for a busy 2020 ophthalmology meeting schedule. Little did I know that this year was not going to go exactly as planned. Ophthalmology meetings around the globe have been canceled, postponed, or retooled as virtual events. Like the rest of the world's population, we ophthalmologists have been expected to adapt to a new normal, which for many of us requires learning how to effectively teach and engage with colleagues online.

Although most of the skills that we typically use for in-person presentations transfer well to webinars, several unique aspects of virtual talks warrant careful consideration. For instance, online presentations lack a standard podium, and no audiovisual team is present in the room. Moreover, there may be few or no visible cues that the audience is actively focused on the material being presented. Although I have delivered numerous online webinars in the past, the transition of practically every ophthalmology meeting to a virtual format became an opportunity to customize my presentations and hone my skills to ensure success at these events.

With these thoughts in mind, here are my top 12 tips for elevating the quality of your online presentations.

1 WARM UP

In concert, professional musicians do not take their places on the rostrum and immediately commence performing. They tune up first. Follow their example. Your voice is an instrument. Warm up, whether by performing some vocal training exercises or, if you are going to be giving a presentation, by rehearsing it out loud.

2 BE A SAVVY SET DESIGNER

When deciding where to sit, look behind you. Whatever will be in the background of the shot should not be distracting, messy, or potentially offensive. I recommend starting with a screen test. Something that you did not notice initially may be an eyesore on a full-screen view. Early on when I was filming presentations in my condo, I realized that the bookshelf behind me was cluttered, so I removed a lot of the contents.

3 DRESS FOR SUCCESS

Avoid busy patterns. Wear solid colors that contrast with your background. This is not the time to see how well your shirt can serve as camouflage against the wall behind you.

4 OPTIMIZE YOUR LIGHTING

The lighting where you will be filming should allow viewers to see your face clearly and eliminate harsh shadows. Test out locations and ensure that the light is facing you. Webcams automatically adjust to the brightest source of light, so you may need to adjust the distance of your light source. (Pro tip: In a pinch, if you need an external light source, set your laptop or tablet to a white screen and place it in front of you.) Bear in mind that natural light shifts throughout the day, so the ideal spots for filming in the morning and evening may differ.

5 SET UP THE SHOT

Ideally, you should be located approximately 3 feet away from the camera on your computer because it is at a fixed point and typically uses a wide-angle lens. Sitting too close to a wide-angle lens can produce optical distortion of your face, in which some features appear to be overly large. Generally, the most flattering lens angle is achieved by positioning the camera at or slightly above your seated height so that you are visible from the chest up. This setup may require placing a few books or magazines beneath the computer.

6 KNOW YOUR BANDWIDTH

Video footage can be an excellent addition to a presentation—but not if it does not play well. Determine in advance if your internet bandwidth and the online platform you will be using can support the video(s) you wish to show.

Also test your sound capabilities. Your internet bandwidth may be able to support your video or your audio needs individually but not together. If that is the case, consider separating your audio

feed by calling in and placing your phone on speaker directly in front of you. I should also note that many computer microphones are not sufficiently high-tech or in tune for a webinar. If you are going to be speaking at many online events, you may want to consider investing in a USB microphone.

7 PAY ATTENTION TO BODY LANGUAGE

Be cognizant of how you are seated. It is normal to sit back in a chair, but doing so can make you appear to be slouching. Sit instead on the forward half of the chair. Keep your back and neck straight and relax your shoulders. Try not to touch your face while on camera because viewers can find it distracting.

8 ACT NATURALLY

Speak as you would if you were physically with your audience. Maintain a reasonable pace. Smile when appropriate and show enthusiasm for your topic. These areas seem to become most problematic with prerecorded sessions in which presenters rely heavily on notes; some speakers lose their usual vocal inflections and speak at an abnormal pace. I recently reviewed a video for a colleague in which the material was incredible, but, instead of delivering a dynamic presentation, the presenter sounded like he was reading from a book.

Be who you are in real life. It is okay to gesture while speaking if, like me, you talk with your hands; just be careful to avoid broad or wild movements. Use humor when appropriate. You can and should laugh at your own jokes (I do). The best online presentations I have seen are those in which it felt like the speaker was truly present.

9 LOOK AT THE CAMERA

Looking at the camera when you are speaking can feel particularly odd if the person or people to whom you are speaking are visible onscreen, but those people will experience the illusion of eye contact only if you look directly at the camera rather than at them. This strategy can increase their level of interest in both you and your material.

10 ENCOURAGE ENGAGEMENT

Audience engagement is the best measure of the success of any presentation. Most of the platforms being used for online meetings and presentations offer a variety of interactive tools such as audience polling, chat boards, and direct audience questions. At the beginning of a presentation or session, lay out the expectations for the audience on how you plan to engage them. For example, prepare them to participate in a poll, alert them that you will be directing questions to viewers or fellow panelists, or invite them to raise their hands.

Also keep in mind that those watching your presentation online may not be able to see what is going on in front of you. If you are going to pause to call up a visual aid, to resolve a technical difficulty, or to allow someone to pose or answer a question, verbalize what is occurring. (As an aside, showing a little humor about a technical problem can go a long way with your audience.)

11 BE SELECTIVE

Online viewers are often watching you and your visual aids simultaneously. At times, they may not be able to absorb both the words that you are saying and slides that are full of text, tiny graphs, and tables crammed with data. Minimize the number of words on your slides in favor of showing more photographs and videos. This will allow the audience to focus on what you are saying instead of trying to decipher what is on a slide.

12 REVIEW YOUR PERFORMANCE

If you watched the television series, "The Last Dance," you saw that Michael Jordan and the Chicago Bulls spent hours reviewing game footage to identify areas for improvement and to figure out what it would take for them to win that final championship. Consider reviewing your own performances. As tedious as it was, watching some of my early webinars gave me insight into where I needed to focus to improve my online delivery.

Moreover, if I am going to be presenting something new or trying a new technology, I take some extra time to record a demo in order to analyze the content and familiarize myself with the technology before the event.

Logging on at least 15 minutes early to ensure that the sound and video are working properly can allow you to relax and feel confident during your presentation. ■

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INDEX OF ADVERTISERS

CONVENTION UPDATES

Some ophthalmology meetings in 2020/2021 have changed direction. Others are staying the course—for now. This list is accurate as of *Retina Today's* press date in early September.

GOING VIRTUAL

RETINA SOCIETY 2020 VR
Three Sessions:
- August 25, 2020: New Member Spotlight
- September 8, 2020: Clinical Trials—The Cutting Edge
- September 21-22, 2020: RS2020 VR Live

More Information at: RetinaSociety.org

DUKE FELLOWS ADVANCED VITREOUS SURGERY COURSE
Duke Eye Center
Three Streaming Dates:
- September 24, 2020: Session 1 — How to Maximize My Fellowship Experience
- October 8, 2020: Session 2 — Retina Practice Pearls During COVID-19
- October 22, 2020: Session 3 — Life Beyond Fellowship

More Information at: MedConfs.com

EURETINA
October 2-4, 2020
More Information at: euretina.org

AAO ANNUAL MEETING: RETINA SUBSPECIALTY DAY
November 13, 2020
More Information at: aao.org/annual-meeting

AAO ANNUAL MEETING: UVEITIS SUBSPECIALTY DAY
November 13, 2020
More Information at: aao.org/annual-meeting

AAO ANNUAL MEETING
November 13-15, 2020
More Information at: aao.org/annual-meeting

CANCELED

MILANO RETINA MEETING 20/20
Milan, Italy

AMERICAN UVEITIS SOCIETY WINTER SYMPOSIUM
Park City, Utah

ANNUAL ADVANCED VITREORETINAL TECHNIQUES AND TECHNOLOGY (AVTT) SYMPOSIUM
Chicago, Illinois

PROCEEDING AS PLANNED

ASPEN RETINAL DETACHMENT SOCIETY
Snowmass, Colorado
March 6-10, 2021
More Information at: MedConfs.com

VIT-BUCKLE SOCIETY ANNUAL MEETING
Las Vegas, Nevada
April 8-10, 2021
More Information at: MedConfs.com

RESCHEDULED

EURETINA WINTER MEETING
Original Date:: March 20-21, 2020
New Date: February 26-27, 2021
More Information at: euretina.org/vilnius2020

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Visit **RetinaToday.com/event/submit** to post the details of your upcoming meeting to our events page.

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:
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A Member of the Roche Group
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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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