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Spotlight on IRDs and Gene Therapy

COVID-19: GLOBAL RETINA RESPONDS

BRILLIANT BLUE G AND THE FDA: ACCESS IN THE UNITED STATES

PEDIATRIC RETINAL IMAGING AND TREATMENT DURING COVID-19

HOW WILL THE PANDEMIC AFFECT FELLOWSHIP AND TRAINING?

THIS IS PRECISION

This is

FINESSE™ SHARKSKIN™ ILM Forceps

Laser-ablated micro-surface is designed to support atraumatic ILM peel initiation[1]

Optimized grasping platform and angled tip closure to help mitigate membrane shredding[2]

GRIESHABER® DSP IMPORTANT PRODUCT INFORMATION

Caution: Federal (USA) law restricts this device to sale by, or on the order of, a physician. **Indications for Use:** GRIESHABER® DSP instruments are a line of single-use vitreoretinal microinstruments which are used in ophthalmic surgery, for cases either in the anterior or the posterior segment. The GRIESHABER® Advanced Backflush Handles DSP are a family of instruments for fluid and gas handling in vitreoretinal surgery. **Warnings and Precautions:** • Potential risk from reuse or reprocessing GRIESHABER® DSP instruments include: foreign particle introduction to the eye; reduced cutting or grasping performance; path leaks or obstruction resulting in reduced fluidics performance. • Verify correct tip attachment, function and tip actuation before placing it into the eye for surgery. • For light fiber instruments: Minimize light intensity and duration of exposure to the retina to reduce risk of retinal photic injury. The light fiber instruments are designed for use with an ALCON® illumination source. • Good clinical practice dictates the testing for adequate irrigation and aspiration flow prior to entering the eye. If stream of fluid is weak or absent, good fluidics response will be jeopardized. • Use appropriate pressure supply to ensure a stable IOP. • If unwanted tissue gets engaged to the aspiration port, it should be released by interrupting aspiration before moving the instrument. **Attention:** Please refer to the product labeling for a complete listing of indications, warnings, and precautions.

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

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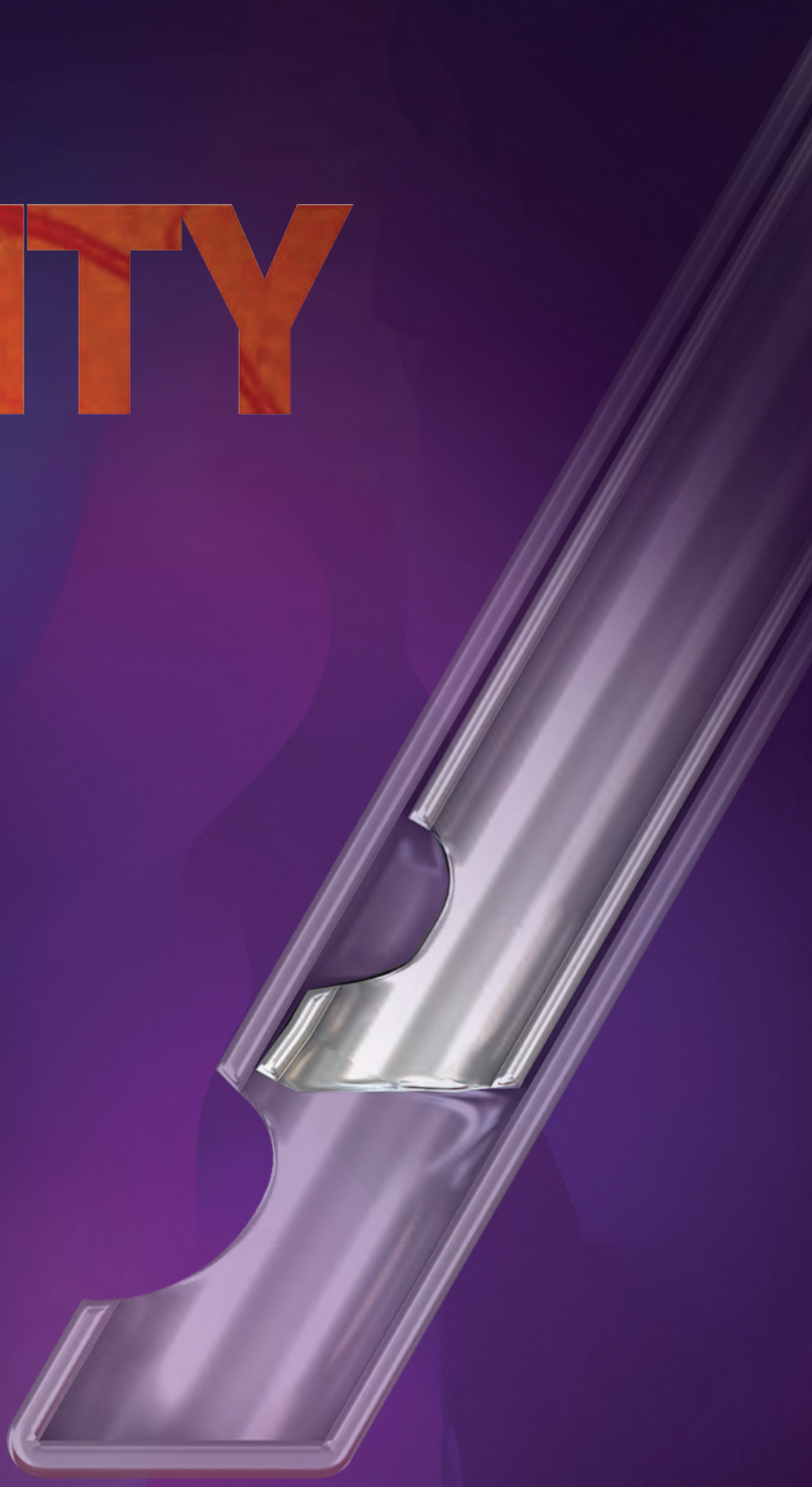
THIS IS STABILITY

This is HYPERVIT™

DUAL BLADE VITRECTOMY PROBE



Designed to:

- Enhance stability with a continuously open port and CONSTELLATION® Vision System's IOP compensation[1]
- Reduce pulsatile traction with **20 000 cuts per minute** using 25+® and 27+® gauge probes*, [2,3]
- Improve vitreous flow[4]
- Enable closer access to tissue plane with beveled tip[5]

*At similar single-blade flow rates

MIVS IMPORTANT PRODUCT INFORMATION

Caution: Federal law restricts this device to sale by, or on the order of, a physician. Indications for Use: The CONSTELLATION® Vision System is an ophthalmic microsurgical system that is indicated for both anterior segment (i.e., phacoemulsification and removal of cataracts) and posterior segment (i.e., vitreoretinal) ophthalmic surgery. The ULTRAVIT® Vitrectomy Probe is indicated for vitreous cutting and aspiration, membrane cutting and aspiration, dissection of tissue and lens removal. The valved entry system is indicated for scleral incision, canulae for posterior instrument access and venting of valved cannulae. The infusion cannula is indicated for posterior segment infusion of liquid or gas. **Warnings and Precautions:** • The infusion cannula is contraindicated for use of oil infusion. • Attach only Alcon supplied products to console and cassette luer fittings. Improper usage or assembly could result in a potentially hazardous condition for the patient. Mismatch of surgical components and use of settings not specifically adjusted for a particular combination of surgical components may affect system performance and create a patient hazard. Do not connect surgical components to the patient's intravenous connections. • Each surgical equipment/component combination may require specific surgical setting adjustments. Ensure that appropriate system settings are used with each product combination. Prior to initial use, contact your Alcon sales representative for in-service information. • Care should be taken when inserting sharp instruments through the valve of the Valved Trocar Cannula. Cutting instrument such as vitreous cutters should not be actuated during insertion or removal to avoid cutting the valve membrane. Use the Valved Cannula Vent to vent fluids or gases as needed during injection of viscous oils or heavy liquids. • Visually confirm that adequate air and liquid infusion flow occurs prior to attachment of infusion cannula to the eye. • Ensure proper placement of trocar cannulas to prevent sub-retinal infusion. • Leaking sclerotomies may lead to post operative hypotony. • Vitreous traction has been known to create retinal tears and retinal detachments. • Minimize light intensity and duration of exposure to the retina to reduce the risk of retinal photic injury. **ATTENTION:** Please refer to the CONSTELLATION® Vision System Operators Manual for a complete listing of indications, warnings and precautions.

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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Discover continuous calm in uveitis

YUTIQ® (fluocinolone acetonide intravitreal implant) 0.18 mg:

- **Proven to reduce uveitis recurrence at 6 and 12 months[1]***
  [At 6 months–18% for YUTIQ and 79% for sham for study 1 and 22% for YUTIQ and 54% for sham for study 2 (*P*<.01). At 12 months–28% for YUTIQ and 86% for sham for study 1 and 33% for YUTIQ and 60% for sham for study 2.]
- **Innovative Durasert® technology is designed for a sustained release of fluocinolone acetonide for up to 36 months with just 1 YUTIQ implant[2]**

For more information, visit **YUTIQ.com**

J code: J7314

*Study design: The efficacy of YUTIQ was assessed in 2 randomized, multicenter, sham-controlled, double-masked, phase 3 studies in adult patients (N=282) with noninfectious uveitis affecting the posterior segment of the eye. The primary endpoint in both studies was the proportion of patients who experienced recurrence of uveitis in the study eye within 6 months of follow-up; recurrence was also assessed at 12 months. Recurrence was defined as either deterioration in visual acuity, vitreous haze attributable to noninfectious uveitis, or the use of prohibited medications.[1,3]

INDICATIONS AND USAGE

YUTIQ® (fluocinolone acetonide intravitreal implant) 0.18 mg is indicated for the treatment of chronic noninfectious uveitis affecting the posterior segment of the eye.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

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

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

WARNINGS AND PRECAUTIONS

Intravitreal Injection-related Effects: Intravitreal injections, including those with YUTIQ, have been associated with endophthalmitis, eye inflammation, increased or decreased intraocular pressure, and choroidal or retinal detachments. Hypotony has been observed within 24 hours of injection and has resolved within 2 weeks. Patients should be monitored following the intravitreal injection.

Steroid-related Effects: Use of corticosteroids including YUTIQ may produce posterior subcapsular cataracts, increased intraocular pressure and glaucoma. Use of corticosteroids may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses. Corticosteroids are not recommended to be used in patients with a history of ocular herpes simplex because of the potential for reactivation of the viral infection.

Risk of Implant Migration: Patients in whom the posterior capsule of the lens is absent or has a tear are at risk of implant migration into the anterior chamber.

ADVERSE REACTIONS

In controlled studies, the most common adverse reactions reported were cataract development and increases in intraocular pressure.

References: 1. YUTIQ® (fluocinolone acetonide intravitreal implant) 0.18 mg full U.S. Prescribing Information. EyePoint Pharmaceuticals, Inc. October 2018. **2.** EyePoint Pharmaceuticals Receives FDA Approval of YUTIQ™ (fluocinolone acetonide intravitreal implant) 0.18 mg. Global Newswire. https://www.globenewswire.com/news-release/2018/10/15/1621023/0/en/EyePoint-Pharmaceuticals-Receives-FDA-Approval-of-YUTIQ-fluocinolone-acetonide-intravitreal-implant-0-18-mg.html. Accessed February 7, 2020. **3.** Data on file.

Please see next page for Brief Summary of full Prescribing Information.

EyePoint PHARMACEUTICALS

480 Pleasant Street, Suite B300, Watertown, MA 02472

2/2020
US-YUT-2000020

YUTIQ™ (fluocinolone acetonide intravitreal implant) 0.18 mg, for intravitreal injection
Initial U.S. Approval: 1963

BRIEF SUMMARY: Please see package insert for full prescribing information.

1. INDICATIONS AND USAGE. YUTIQ™ (fluocinolone acetonide intravitreal implant) 0.18 mg is indicated for the treatment of chronic non-infectious uveitis affecting the posterior segment of the eye.

4. CONTRAINDICATIONS. 4.1. Ocular or Periocular Infections. YUTIQ is contraindicated in patients with active or suspected ocular or periocular infections including most viral disease of the cornea and conjunctiva including active epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections and fungal diseases. **4.2. Hypersensitivity.** YUTIQ is contraindicated in patients with known hypersensitivity to any components of this product.

5. WARNINGS AND PRECAUTIONS. 5.1. Intravitreal Injection-related Effects. Intravitreal injections, including those with YUTIQ, have been associated with endophthalmitis, eye inflammation, increased or decreased intraocular pressure, and choroidal or retinal detachments. Hypotony has been observed within 24 hours of injection and has resolved within 2 weeks. Patients should be monitored following the intravitreal injection *[see Patient Counseling Information (17) in the full prescribing information]*. **5.2. Steroid-related Effects.** Use of corticosteroids including YUTIQ may produce posterior subcapsular cataracts, increased intraocular pressure and glaucoma. Use of corticosteroids may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses. Corticosteroids are not recommended to be used in patients with a history of ocular herpes simplex because of the potential for reactivation of the viral infection. **5.3. Risk of Implant Migration.** Patients in whom the posterior capsule of the lens is absent or has a tear are at risk of implant migration into the anterior chamber.

6. ADVERSE REACTIONS. 6.1. Clinical Studies Experience. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. Adverse reactions associated with ophthalmic steroids including YUTIQ include cataract formation and subsequent cataract surgery, elevated intraocular pressure, which may be associated with optic nerve damage, visual acuity and field defects, secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera. Studies 1 and 2 were multicenter, randomized, sham injection-controlled, masked trials in which patients with non-infectious uveitis affecting the posterior segment of the eye were treated once with either YUTIQ or sham injection, and then received standard care for the duration of the study. Study 3 was a multicenter, randomized, masked trial in which patients with non-infectious uveitis affecting the posterior segment of the eye were all treated once with YUTIQ, administered by one of two different applicators, and then received standard care for the duration of the study. Table 1 summarizes data available from studies 1, 2 and 3 through 12 months for study eyes treated with YUTIQ (n=226) or sham injection (n=94). The most common ocular (study eye) and non-ocular adverse reactions are shown in Table 1 and Table 2.

Table 1: Ocular Adverse Reactions Reported in ≥ 1% of Subject Eyes and Non-Ocular Adverse Reactions Reported in ≥ 2% of Patients

Ocular		
ADVERSE REACTIONS	**YUTIQ (N=226 Eyes) n (%)**	**Sham Injection (N=94 Eyes) n (%)**
Cataract[1]	63/113 (56%)	13/56 (23%)
Visual Acuity Reduced	33 (15%)	11 (12%)
Macular Edema	25 (11%)	33 (35%)
Uveitis	22 (10%)	33 (35%)
Conjunctival Hemorrhage	17 (8%)	5 (5%)
Eye Pain	17 (8%)	12 (13%)
Hypotony Of Eye	16 (7%)	1 (1%)
Anterior Chamber Inflammation	12 (5%)	6 (6%)
Dry Eye	10 (4%)	3 (3%)
Vitreous Opacities	9 (4%)	8 (9%)
Conjunctivitis	9 (4%)	5 (5%)
Posterior Capsule Opacification	8 (4%)	3 (3%)
Ocular Hyperemia	8 (4%)	7 (7%)
Vitreous Haze	7 (3%)	4 (4%)
Foreign Body Sensation In Eyes	7 (3%)	2 (2%)
Vitritis	6 (3%)	8 (9%)
Vitreous Floaters	6 (3%)	5 (5%)
Eye Pruritus	6 (3%)	5 (5%)
Conjunctival Hyperemia	5 (2%)	2 (2%)
Ocular Discomfort	5 (2%)	1 (1%)
Macular Fibrosis	5 (2%)	2 (2%)
Glaucoma	4 (2%)	1 (1%)
Photopsia	4 (2%)	2 (2%)

(continued)

Table 1: Ocular Adverse Reactions Reported in ≥ 1% of Subject Eyes and Non-Ocular Adverse Reactions Reported in ≥ 2% of Patients

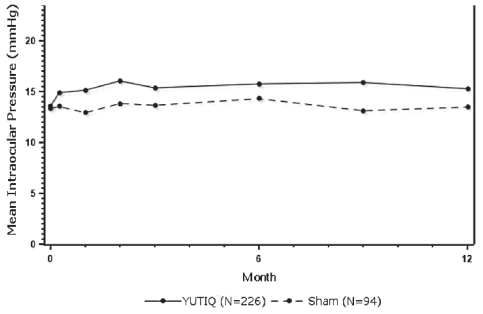
Ocular		
ADVERSE REACTIONS	**YUTIQ (N=226 Eyes) n (%)**	**Sham Injection (N=94 Eyes) n (%)**
Vitreous Hemorrhage	4 (2%)	0
Iridocyclitis	3 (1%)	7 (7%)
Eye Inflammation	3 (1%)	2 (2%)
Choroiditis	3 (1%)	1 (1%)
Eye Irritation	3 (1%)	1 (1%)
Visual Field Defect	3 (1%)	0
Lacrimation Increased	3 (1%)	0
Non-ocular		
ADVERSE REACTIONS	**YUTIQ (N=214 Patients) n (%)**	**Sham Injection (N=94 Patients) n (%)**
Nasopharyngitis	10 (5%)	5 (5%)
Hypertension	6 (3%)	1 (1%)
Arthralgia	5 (2%)	1 (1%)

1. Includes cataract, cataract subcapsular and lenticular opacities in study eyes that were phakic at baseline. 113 of the 226 YUTIQ study eyes were phakic at baseline; 56 of 94 sham-controlled study eyes were phakic at baseline.

Table 2: Summary of Elevated IOP Related Adverse Reactions

ADVERSE REACTIONS	YUTIQ (N=226 Eyes) n (%)	Sham (N=94 Eyes) n (%)
IOP elevation ≥ 10 mmHg from Baseline	50 (22%)	11 (12%)
IOP elevation > 30 mmHg	28 (12%)	3 (3%)
Any IOP-lowering medication	98 (43%)	39 (41%)
Any surgical intervention for elevated IOP	5 (2%)	2 (2%)

Figure 1: Mean IOP During the Studies



8. USE IN SPECIFIC POPULATIONS. 8.1 Pregnancy. Risk Summary. Adequate and well-controlled studies with YUTIQ have not been conducted in pregnant women to inform drug associated risk. Animal reproduction studies have not been conducted with YUTIQ. It is not known whether YUTIQ can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. YUTIQ should be given to a pregnant woman only if the potential benefit justifies the potential risk to the fetus. All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the United States general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. **8.2 Lactation.** Risk Summary. Systemically administered corticosteroids are present in human milk and can suppress growth, interfere with endogenous corticosteroid production. Clinical or nonclinical lactation studies have not been conducted with YUTIQ. It is not known whether intravitreal treatment with YUTIQ could result in sufficient systemic absorption to produce detectable quantities of fluocinolone acetonide in human milk, or affect breastfed infants or milk production. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for YUTIQ and any potential adverse effects on the breastfed child from YUTIQ. **8.4 Pediatric Use.** Safety and effectiveness of YUTIQ in pediatric patients have not been established. **8.5 Geriatric Use.** No overall differences in safety or effectiveness have been observed between elderly and younger patients.

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

IT TAKES A PLANET


Retina specialists tend to think of themselves as part of a global community. We see this reflected in the (soon-to-return, we hope) meeting circuit. Access to annual meetings for national or continent-wide organizations (eg, American Academy of Ophthalmology, Euretina) are not restricted to residents of the meeting's respective country or geographic region. Further, international meetings (eg, Retina World Congress, World Ophthalmology Congress) are growing in numbers and influence.

International problem solving is an outgrowth of that model, and that has not slowed during the COVID-19 era. That's why this issue of *Retina Today* features a collection of global authors.

Medicine has spent plenty of time communicating effective safety measures when managing disease in patients at risk of COVID-19 complications. This is particularly useful in our field, where we often see patients who have systemic disease or are of advanced age. But what do we do when treating children? María A. Martínez-Castellanos, MD (Mexico); Judith A. Espinoza-Navarro, MD (Mexico); Lisseth Chinchilla, MD (Venezuela); Heber Galarza, MD (Mexico); and Paulina Ramirez-Neria, MD (Mexico), offer direction for safely navigating pediatric patient care, relying on the latest data to drive their protocols.

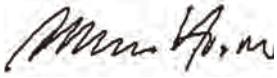
Sometimes, however, the latest data simply take to long to reach the clinician. That is where clinical decision-making becomes key. By relying on the guidance from various ophthalmic societies, a panel of retina specialists—Ashish Sharma, MD (India); Nilesh Kumar, MD (India); Nikulaa Parachuri, MD (India); Rohini Sharma, MDS (India); Barbara Parolini, MD (Italy); Sengul Ozdek, MD, FEBO (Turkey); Baruch D. Kuppermann, MD, PhD (United States); Francesco Bandello, MD, FEBO (Italy); and Anat Loewenstein, MD, MHA (Israel)—offer their protocol for intravitreal injection.

Continuing that conversation, Fred Y. Chien, MD (United States), and Theodore Leng, MD, MS (United States), explore methods for keeping patients and physicians safe during intravitreal injections—particularly in those patients who might be positive for COVID-19. In their estimation, the data suggest that mere masking is not enough.

The disruption that COVID-19 has caused in the professional aspects of our field are coming into focus. In his contribution to this issue, Ravi R. Pandit, MD, MPH (United States), urges his colleagues to begin thinking more completely about the relationship retina has to medicine as a whole. As the crisis pushes us toward thinking more purposefully about the complete patient (rather than just their eyes), Dr. Pandit suggests that we reconsider interspecialty communication methods and our narrow clinical concerns.

Rounding out the discussion of the pandemic's lasting consequences, Michael Venincasa, MD (United States), and Jayanth Sridhar, MD (United States), propose a future in which interviews for residencies and fellowships rely on digital platforms rather than in-person interactions, perhaps saving time and money for applicants and institutions. Erol Eri Verter, MD, MS (United States); Patrick Coady, MD, MBA (United States); Deven Huang (United States); and John J. Huang, MD, MBA, CPE (United States), break down recent data from a survey sent to members of the American Society of Retina Specialists that may help us assess to what degree patients and practices have been set back during this crisis.

Thanks for being with *Retina Today* through all of this. We appreciate you. ■

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GLOBAL RETINA RESPONDS TO COVID-19

SPOTLIGHT COVERAGE ON GENE THERAPY AND IRDs

DEPARTMENTS

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FDA ISSUES COMPLETE RESPONSE LETTER FOR ABICIPAR PEGOL

The US FDA has issued a complete response letter to the biologics license application for abicipar pegol, a novel biologic candidate in development for treatment of wet age-related macular degeneration (AMD) by Allergan, the company's parent AbbVie announced in June. The issue was safety, according to a company press release.

"The letter from the FDA indicates that the rate of intraocular inflammation observed following administration of abicipar pegol 2 mg/0.05 mL results in an unfavorable benefit-risk ratio" in the treatment of wet AMD, the release stated. AbbVie, which finalized its $63 billion acquisition of Allergan in May, plans to meet with the FDA to discuss the comments raised in the letter and determine next steps, according to the release.

In May, two phase 3 studies, CEDAR and SEQUOIA, met their primary endpoints showing abicipar pegol noninferior to ranibizumab (Lucentis, Genentech) for achieving stable vision in individuals with wet AMD. At 1 year, abicipar demonstrated similar efficacy with six or eight injections, compared with 13 injections of ranibizumab.[1]

However, the trials also showed that medication-related adverse events (AEs) were more frequent in the groups receiving abicipar (16.8% in a group receiving abicipar 2 mg every 8 weeks and 20.4% in a group receiving abicipar 2 mg every 12 weeks) than in the group receiving ranibizumab 0.5 mg every 4 weeks (4.5%). In particular, the incidence of intraocular inflammation AEs was 15.4% and 15.3% in the two abicipar groups, respectively, and 0.3% in the ranibizumab group.[1]

1. Kunimoto D, Yoon YH, Wykoff CC, et al. Efficacy and safety of abicipar in neovascular age-related macular degeneration: 52-week results of phase 3 randomized controlled study. *Ophthalmology*. 2020;S0161-6420(20)30320-1.

COMPLEMENT INHIBITOR ADDS 18-MONTH DATA IN DRY AMD TRIAL

In patients with geographic atrophy (GA) secondary to AMD, a complement C5 inhibitor showed continued efficacy and safety at 18 months, according to Iveric Bio. Avacincaptad pegol (Zimura) had already demonstrated statistical significance in the primary efficacy endpoint of the trial, change in GA at 12 months as measured by fundus autofluorescence.

The reduction in the mean rate of GA growth over 18 months was 28.11% for the 2 mg treatment group compared to a sham control group and 29.97% for the 4 mg treatment group as compared to its corresponding sham control group. The prespecified efficacy analysis for the primary endpoint was performed at month 12 using all of the power in the trial to detect a statistically significant difference. Therefore, the probability values for the 18-month statistical analyses are descriptive in nature. The descriptive values for the treatment effects at month 18 were $P = .0014$ for the 2 mg group and $P = .0021$ for the 4 mg group.

In this trial, OPH2003, the treatment effect was observed as early as 6 months, with an increase in the absolute difference of the mean change in GA growth for treatment with either avacincaptad pegol 2 mg or 4 mg, as compared with sham, at each subsequent time point. This suggests a progressive benefit of continuous treatment with avacincaptad pegol, the company stated. The therapy maintained a favorable safety profile at 18 months with no reported treatment-related AEs, no endophthalmitis, and a lower rate of choroidal neovascularization than has been reported for C3 inhibition.

PHASE 3 ENROLLMENT COMPLETE FOR COMPLEMENT INHIBITOR IN DRY AMD

Apellis Pharmaceuticals announced in July that enrollment has been completed in two phase 3 studies, DERBY and OAKS, investigating its drug candidate intravitreal pegcetacoplan (APL-2) for the treatment of GA secondary to AMD.

Pegcatacoplan is a targeted C3 therapy, designed to control excessive complement activation, according to a press release from Apellis. GA is a progressive, complement-driven disease with no approved therapies.

A total of 1,259 patients are enrolled in the two pivotal randomized phase 3 trials, which are designed to compare the efficacy and safety of intravitreal pegcetacoplan with sham treatment in patients with GA secondary to AMD. The primary objective of the studies is reduction in growth of GA lesion size, as measured by fundus autofluorescence, at month 12 compared to baseline. ■

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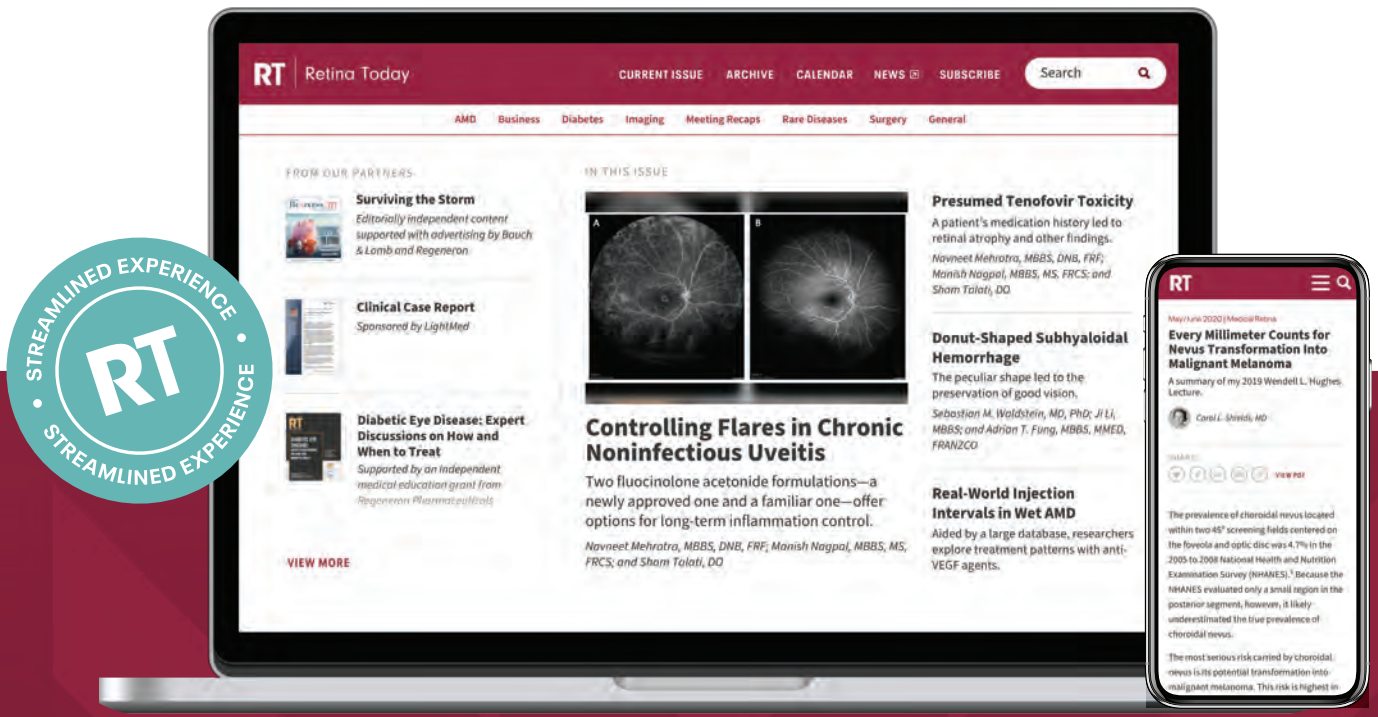

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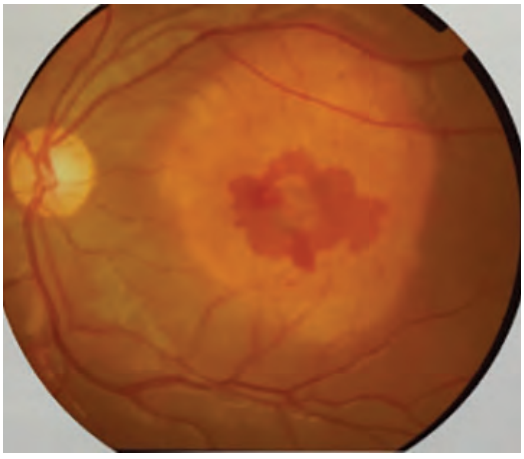
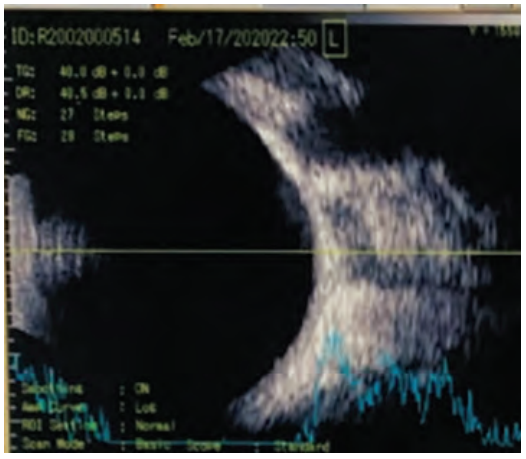
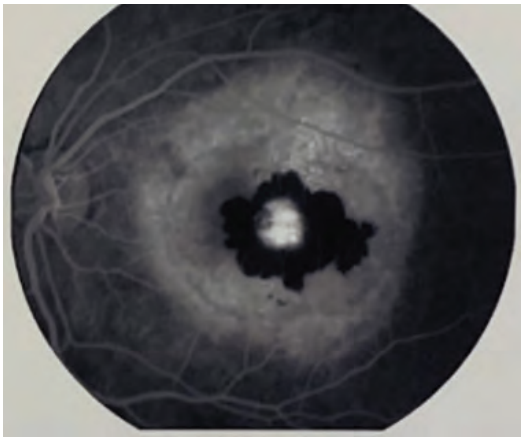
MACULAR CHOROIDAL OSTEOMA

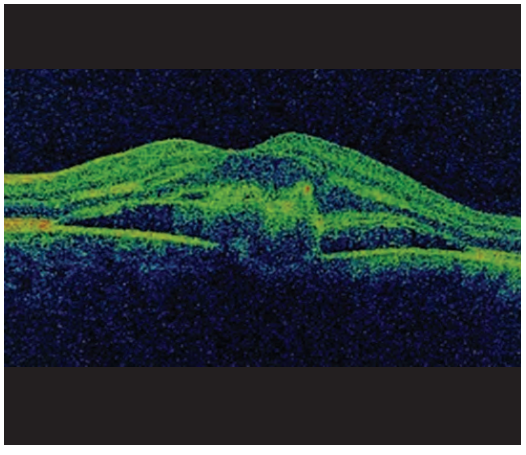
A pediatric patient's blurred vision resulted in a diagnosis of choroidal osteoma.

BY DIPAK KUMAR NAG, FCPS, MSC









A 12-year-old boy visited our clinic for sudden, painless blurred vision and metamorphopsia in his left eye (OS) starting 7 days back. His BCVA was 6/60 OS and 6/6 in right eye (OD). Anterior segment examination was unremarkable in each eye. On fundus examination OS, a yellow-white lesion was seen at the macula with a well-defined geographic border and diffuse, mottled depigmentation of the overlying retinal pigment epithelium (RPE). An elevated gray-green area could be seen at the center of the yellow-white area, with subretinal hemorrhage surrounding it (Top Left). The fundus OD was normal.

B-scan ultrasonography showed a slightly elevated, highly reflective choroidal mass with acoustic shadowing of a "pseudo–optic nerve" (Top Right). The mass persisted even at lower gain. A-scan ultrasonography showed a high-intensity spike. Fluorescein angiography showed early patchy hyperfluorescence with late diffuse staining of the lesion, block fluorescence at the hemorrhage, and leakage at the center—suggestive of a choroidal neovascular membrane (CNVM; Bottom Left). OCT showed a subretinal CNVM with fluid exudation; the RPE was not visible due to backscattering from subretinal blood (Bottom Right).

The patient was diagnosed with choroidal osteoma with active CNVM OS. Anti-VEGF injections were advised.

DISCUSSION

Choroidal osteoma is a benign tumor of the choroid composed of mature bone. It is typically found in healthy young females in the second or third decades of life,[1] usually as a juxtapapillary lesion that may extend into the macular region.[2] Asymptomatic or stable choroidal osteoma can be observed. Long-term poor visual acuity in patients with choroidal osteoma is associated with subretinal fluid, RPE alterations, and subretinal hemorrhage from CNVM[3] and decalcification.[4]

At 10 years of age, 56% to 58% of patients with choroidal osteoma have VA of 20/200 or worse. CNVM occurs in 31% to 47% of patients by 10 years of age,[5] and decalcification in 46%.[4]

The case presented here is a rare one, in that choroidal

To improve vision in DME,* macular edema following RVO,† or noninfectious posterior segment uveitis

- Achieves clinically significant 3-line gains in BCVA[2,‡]
- Significantly reduces vitreous haze vs sham in noninfectious posterior segment uveitis[2]
- Suppresses inflammation by inhibiting multiple inflammatory cytokines[2]

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

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

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

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

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.

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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.

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osteoma was found at an early age in a male patient with marked reduction of vision at his first presentation. Only the macula was involved, with all complications presenting in that compact space: CNVM, subretinal and intraretinal hemorrhage, and serous and hemorrhagic retinal detachment.

Recently, successful treatment of subretinal neovascularization with intravitreal injections of an anti-VEGF agent has been described.[6] ■

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To share an image, contact Manish Nagpal, MS, DO, FRCS(Edin), at drmanishnagpal@yahoo.com.
Note: Images should be 400 dpi or higher and at least 10 inches wide.

WAARDENBURG SYNDROME

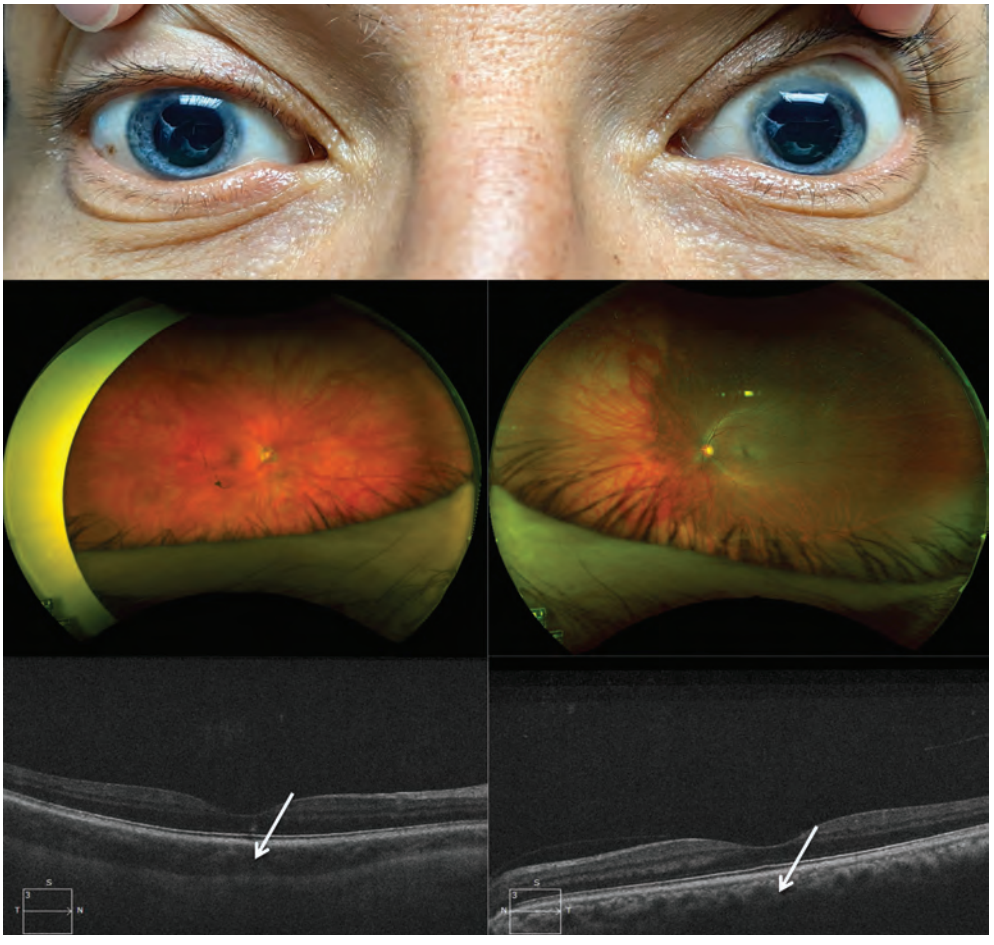
A unique presentation leads to a rare diagnosis.

BY KUNYONG XU, MD, MHSC; DAVID R.P. ALMEIDA, MD, MBA, PHD; AND ERIC K. CHIN, MD

A 47- year-old Hispanic man presented with congenital iris heterochromia, white forelock, and bilateral hearing loss. VA was 20/25 in both eyes.

The patient has blue eyes, and iris hypopigmentation was noted in both eyes with focal areas of pigmentation superotemporally in the left eye (Figure, top). Hypopigmentation of the retina and choroid in both eyes was observed, and relative temporal hyperpigmentation was observed in the left eye only (Figure, middle). OCT of the macula showed relative choroidal thinning in the right eye compared with the left eye (Figure, bottom, white arrows).

There was no history of malformation of upper extremities or Hirschsprung disease. External examination revealed no telecanthus, synophrys, or patches of skin depigmentation. There was no tubular nose and no small nasal alae. The patient was diagnosed with Waardenburg syndrome based on the findings and history. ■



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GEL AND GENES: NOVEL WAYS TO INTERVENE!


Dressed as Gregor Clegane (aka The Mountain) from *Game of Thrones*, Robert Avery, MD, reported on novel therapies that may reduce the burden of intravitreal injections.

BY DAVID XU, MD; AND LUV G. PATEL, MD

The Vit-Buckle Society (VBS) held an exciting *Game of Thrones*-themed online conference with many interesting talks (Figure). To start, Royce Chen, MD, shared his personal reflections on managing patients with COVID-19 in New York City. We also heard an excellent presentation by James Vander, MD, on navigating the COVID-19 world from a practice management standpoint. This article summarizes surgical talks by Rajeev Muni, MD; Ninel Gregori, MD; Gaurav Shah, MD; Caroline Baumal, MD; and Robert Avery, MD.

RAJEEV MUNI, MD - PNEUMATIC RETINOPEXY

Dr. Muni's talk expanded on the movement from traditionally held criteria for pneumatic retinopexy (PnR) to the newly defined criteria described in the Pneumatic Retinopexy Versus Vitrectomy for the Management of Primary Rhegmatogenous Retinal Detachment Outcomes Randomized Trial (PIVOT). PIVOT broadened the indications for PnR to include extensive lattice; any number, location, and size of breaks within attached retina; and breaks in attached retina that are in more than one quadrant or present inferiorly. In his practice, Dr. Muni performs the procedure in the following steps:

1. Laser retinopexy of lattice or breaks in attached retina
2. Subconjunctival anesthesia
3. Anterior chamber paracentesis
4. SF_6 gas injection
5. Use of the steamroller technique to gradually express subretinal fluid from the retinal break followed by positioning to the break
6. Staged laser retinopexy or cryopexy prior to anterior chamber paracentesis

He introduced the terms *low-* and *high-integrity retinal reattachment* (LIRA and HIRA) in the context of PnR versus pars plana vitrectomy (PPV). His studies have found that, compared with PPV, PnR favors high-integrity retinal reattachment with less retinal displacement, which is detected using fundus autofluorescence imaging. The PIVOT has also demonstrated that patients undergoing PnR have less frequent and less severe vertical metamorphopsia.

NINEL GREGORI, MD - GENE THERAPY SURGERY

Dr. Gregori shared surgical pearls for subretinal gene therapy. This technique has been used for the subretinal delivery of voretigene neparvovec-rzyl (Luxturna, Spark Therapeutics) as well as in clinical trials for choroideremia, X-linked retinitis pigmentosa, achromatopsia, and other conditions. Adeno-associated viral vectors are largely impermeable to the retina, so a subretinal injection via a retinotomy and successful creation of a bleb are important for treatment efficacy. Ideally, the viral vector is delivered to the intended retinal loci with minimal reflux into the vitreous space.

One tip from Dr. Gregori for performing the novel procedure addressed how to efficiently lift the posterior hyaloid membrane—which can be anomalous in patients with retinal dystrophy—while using triamcinolone acetonide staining and a backflush or a Finesse Flex Loop (Alcon). She also described her technique for loading the injection syringe without air bubbles, creating a balanced salt solution before the bleb is created, and using a pedal-controlled MicroDose injector (MedOne Surgical). The tip of the cannula can be beveled by the surgeon. Dr. Gregori discussed the avoidance of complications such as inadvertent suprachoroidal injection or reflux and macular hole formation, and she

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Reference: 1. Nash BM, Wright DC, Grigg JR, Bennetts B, Jamieson RV. Retinal dystrophies, genomic applications in diagnosis and prospects for therapy. *Transl Pediatr*. 2015;4(2):139-163.

N-UNBD-US-690001-2 5/20

advocated the use of microscope-integrated OCT to guide the surgeon and monitor progression of the bleb and foveal configuration during injection.

GAURAV SHAH, MD; AND CAROLINE BAUMAL, MD - INTERNAL LIMITING MEMBRANE PEELING DURING RETINAL DETACHMENT REPAIR

The conference included an interesting and vigorous debate between Drs. Shah and Baumal on the benefits of internal limiting membrane (ILM) peeling for routine rhegmatogenous retinal detachment repair. Dr. Shah took the pro position and cited clinical and pathophysiologic evidence: Patients who received ILM peeling have lower rates of postoperative epiretinal membrane formation and may have better visual acuity.

Dr. Baumal countered by stating that performing an ILM peel on a detached retina can be technically challenging, which increases the risk and complexity of surgery. Moreover, she stated, it can be argued that peeling the macula is separate from the primary aim of rhegmatogenous retinal detachment repair and is often unnecessary for surgical success.

Both physicians made important points. It is to be hoped that debates such as this one advance specialists' understanding of surgical techniques and spur more research in the field.

DR. GREGORI SHARED SURGICAL PEARLS FOR SUBRETINAL GENE THERAPY. THIS TECHNIQUE HAS BEEN USED FOR THE SUBRETINAL DELIVERY OF VORETIGENE NEPARVOVEC-RZYL ... AS WELL AS IN CLINICAL TRIALS FOR CHOROIDEREMIA, X-LINKED RETINITIS PIGMENTOSA, ACHROMATOPSIA, AND OTHER CONDITIONS.

ROBERT AVERY, MD - REDUCING THE BURDEN OF INTRAVITREAL INJECTIONS

Dr. Avery delivered a pair of talks at this VBS meeting. In his first talk, he described tyrosine kinase inhibitors (TKIs) as an exciting novel therapeutic class for the treatment of wet age-related macular degeneration (AMD). As with the larger biological anti-VEGF agents, these small molecules were originally studied as cancer therapeutics because of their antiangiogenic effects. The major drawbacks of these molecules are their limited bioavailability and short intraocular half-life, which are overcome by intravitreal injection designed for sustained release over 3 to 6 months.

Dr. Avery's presentation was the first to report data from a phase 1 trial of a TKI. He discussed data from 12 patients with AMD-related subfoveal neovascular membrane who were divided into two dose-dependent cohorts, each receiving an implant that dissolved over 6 to 9 months. The safety profile was generally favorable. Although three patients developed pigmented keratic precipitates, no patient to date has experienced iritis, vitritis, or retinitis. One patient had vitreous opacities at 6 months that were thought to be related to a breakdown of the implant, and another patient had inert fiber and reflective material in the vitreous thought to be related to the injection procedure. Some patients showed a decrease in fluid by 2 months, suggesting possible biologic activity. The durability of therapy was as long as 4.5 months in the higher-dose cohort. Dr. Avery stated that research is ongoing to determine the durability of treatment, maximum tolerated dose, and utility of the treatment in combination with existing anti-VEGF therapies.

(Continued on page 28)

Figure. VBS panelists donned *Game of Thrones* costumes during a recent virtual event.

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An Exciting Journey in SubLiminal Laser Treatment Therapy for DME

BY ALEJANDRO FILLOY-RIUS, MD, PHD, FEBO

DME is one of the most common causes of sight-threatening retinopathy for people with diabetes, which currently affects more than 30 million people worldwide.[1] As the prevalence of diabetes and vision diseases related to diabetes continues to rise, so does the burden it creates on health care systems.

Treatment options for DME vary as we continue to learn more about its pathogenesis and molecular pathways. These new insights have led to innovative clinical trials where we've learned a significant amount about different treatment protocols. Results offered from the Early Treatment Diabetic Retinopathy Study (ETDRS) research group led to laser photocoagulation becoming the initial mainstay treatment for DME.[2] Since then, the industry has introduced corticosteroids, anti-VEGF therapy injections, laser therapies, and several combinations thereof to treat DME. While all these are important tools when developing an appropriate treatment response, laser therapy is becoming increasingly relevant, including SubLiminal laser therapy (Quantel Medical).

SubLiminal laser therapy is a modern subthreshold laser that employs a customizable pattern grid selection and delivers treatment through a succession of short, microsecond-long pulses of laser instead of the usual "continuous" beam of conventional laser. This allows for cooling of the retinal pigment epithelium (RPE) between pulses, preventing a critical amount of heat from accumulating in the tissue and the consequential RPE and retinal scarring which we know to be unnecessary to attain a therapeutic response[3] and to limit the possibilities for future retreatments. Repeatability and safety are the two leading advantages of treating DME with subthreshold SubLiminal laser therapy versus conventional laser.

SubLiminal laser therapy also provides an option for making physicians less dependent on intravitreal therapy. SubLiminal laser therapy is a strong option for patients with a mild to moderate exudative/inflammatory edema, saving injections and associated risks and costs, as well as decreasing the number of visits.[4] Concerning the application technique, the learning curve is relatively flat compared to conventional macular laser. Particular considerations involve the treatment of large areas to stimulate a significant response from the targeted RPE cells. To treat these areas densely and avoid leaving "blank spaces," the goal is to recruit every cell in the treatment area to "work for you." It is important to note that insufficient spots have been identified as the number one cause for treatment failure.[5]

When treating DME with SubLiminal laser therapy the OCT thickness map should guide your treatment area. The power to use in each patient should be individually titrated for efficacy and safety purposes. We titrate at one-third of the minimum energy to cause a barely visible burn in the peripheral healthy macula. The rest of the parameters can be universalized (spot size 160 µm, 5% duty cycle). Also, we like to avoid transfoveal treatment. The fovea represents a small area, so leaving it out of the treatment plan will not affect your outcomes and will add an extra safety step especially when you begin delivering these treatments. Evaluate your results using OCT (pay attention to the thickness map) as well as autofluorescence to check for any disturbance of the RPE indicating too much power was employed ("suprathreshold" treatment).

RATIONALE OF SUBLIMINAL LASER TREATMENT FOR DME

Steroids are the most powerful tool available for local treatment of DME, but they also cost the most both in terms of raw costs and intraocular complications. Anti-VEGF is less powerful than steroids and at a lesser cost comes with fewer intraocular complications including a very mild (but nevertheless present) risk of endophthalmitis. Continuous-wave (conventional) laser photocoagulation while way more affordable (and weaker) than the aforementioned alternatives comes with potentially dangerous side effects including epiretinal fibrosis, choroidal neovascularization, and enlargement of laser scars which as mentioned will limit your chances of retreatment.[6] Subthreshold lasers offer a safer, more efficient treatment profile than continuous-wave laser photocoagulation while remaining in the lower-cost scale. The question then becomes, regardless of its cost why would we choose SubLiminal laser therapy, which offers less "antiedema" power over intravitreal treatment options? The answer is that DME manifests itself in many different degrees, and a significant number of our patients present with mild to moderate edema with potential for deterioration. SubLiminal laser therapy might be all you need to treat DME safely, effectively, and efficiently in these cases, both to achieve improvement and to prevent them from advancing to more severe phases. When considering SubLiminal laser therapy, good patient selection is key. Inflammatory/exudative edema without relevant ischemia is a strong patient selection target. Predominantly ischemic edema will not respond well to the stimulation targeted by SubLiminal laser therapy. The following are the scenarios most likely to benefit from SubLiminal laser treatment in DME.

CLINICALLY SIGNIFICANT EXTRAFOVEAL EDEMA

The edema, in these cases, is distant enough from the fovea to keep the central vision safe. The benefit of using SubLiminal laser therapy in cases like this is the durability and repeatability of the laser treatment since there is no damage to the RPE as well as to prevent further central threatening deterioration (Figure 1).

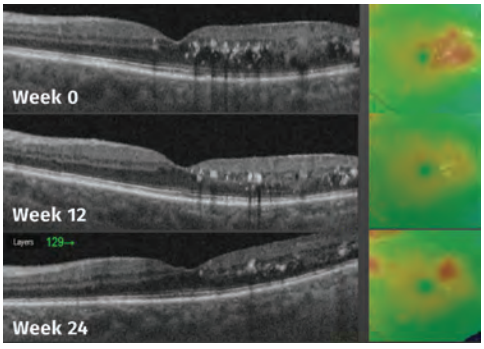

Figure 1. Clinically significant extrafoveal edema (weeks 0, 12, 24).

COMBINATION TREATMENT IN THICKER FOVEAE/DECREASED VISUAL ACUITY

Combination therapy is an interesting scenario for SubLiminal laser therapy. When the fovea is deeply involved and the vision is damaged, you do not want to lose time. My recommended course of therapy is to "dry" the fovea as quickly as possible. This involves using intravitreal therapy as first-line treatment and once the fovea has been restored then you can move forward with SubLiminal laser therapy as a consolidation therapy. It is difficult to know how many injections the patient may need; every case must be assessed individually (Figure 2).

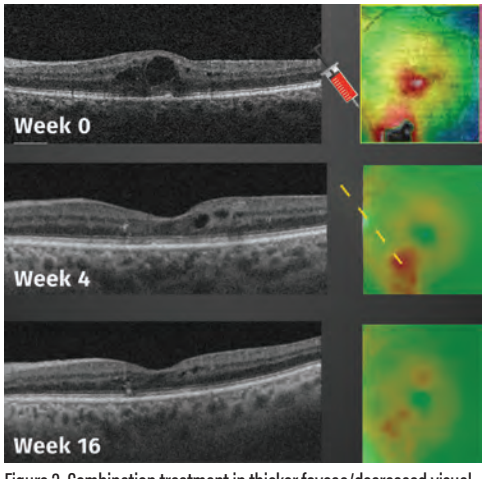

Figure 2. Combination treatment in thicker foveae/decreased visual acuity: weeks 0 (injection day), 4 (laser day), and 16.

FOVEA-INVOLVING MILD EDEMA

Patients with a fovea-involving mild edema are my favorite for SubLiminal laser because it offers a game-changing alternative. These patients are at risk. The vision is still good at this point and the use of anti-VEGF won't be too cost-effective (not to mention that an endophthalmitis in a 20/20 eye, although rare, is a disaster). Using conventional laser so close to the fovea is unadvisable, but SubLiminal laser can work very close to the fovea. SubLiminal laser makes a significant difference in the growing severity of the edema and potentially reduces the need for future intravitreal injections. We conducted a short case study series (publication pending) of patients with fovea involved and good vision with successful results both in terms of effectiveness and safety. From week 1 to 12, the central retinal thickness decreased an average of 16 µm (P = .001), and from week 1 to the end of follow-up we saw an average decrease of 22 µm (P = .0003). OCT showed the edema had completely resolved in 30% of the cases after the first SubLiminal laser therapy treatment and significantly improved for 50% of the cases. At the end of the follow-up, a total of 56% of cases were resolved. Not one of the treated patients experienced deterioration requiring intravitreal treatment (Figure 3). This must be compared to the DRCR protocol V results,[7] where 34% of the patients with foveal edema and good vision who were in the observation arm eventually deteriorated and required intravitreal therapy.

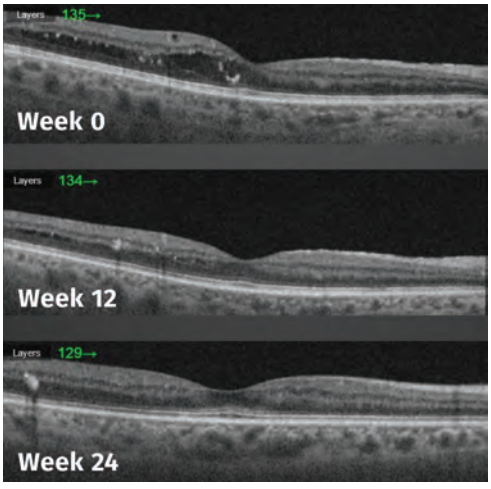

Figure 3. Fovea-involving mild edema with good vision (weeks 0, 12, 24).

CONCLUSION

I have been using the Easyret 577-nm SubLiminal laser (Quantel Medical) for nearly 3 years, and it has been an exciting journey. SubLiminal laser therapy is an advanced technology and therapeutic tool to treat DME patients and decrease the burden of monthly visits and costly injections. In my experience, the more I utilize SubLiminal laser therapy for DME, the more encouraging the outcomes are. DME is a complex disease that requires careful examination, monitoring, and treatment to gain a good response. SubLiminal, as with any subthreshold laser therapy, is more surgical than medical retina therapy, so your personal experience is vital, and you must face the learning curve. It is key to understand the laser parameters and adhere to the treatment guidelines. I can assure you, it is a voyage worth the cost. ■

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CONTINUED FUNCTION OF AN ARGUS II RETINAL PROSTHESIS IN THE SETTING OF RETINAL DETACHMENT

Despite a complex postoperative course, a patient continues to benefit from the implant after almost 4 years.

BY NOY ASHKENAZY, MD; KASEY ZANN, OD, FAAO; AND NINEL Z. GREGORI, MD

The Argus II Retinal Prosthesis System (Second Sight Medical Products) was approved by the US FDA in 2013 for use in patients with retinitis pigmentosa (RP) with bare light perception or no light perception vision in both eyes.[1] A metal case and receiving coil on the temporal sclera connect through a cable with an epimacular array of 60 electrodes, pinned with a tack over the central macula. Real-time video is sent from a camera located on eyeglasses to a visual processing unit worn on a belt. Interpretation of the artificial patterns of light must be learned through rehabilitation training.[1-3]

Complications remain a reality after implantation.[4] Here, we present a case of a patient who continues to experience useful visual stimulation almost 4 years after implantation despite a complex postoperative course.

CASE REPORT

A 44-year-old man with end-stage RP and bilateral bare light perception vision underwent an uncomplicated Argus II implantation in his left eye. The implant was well positioned over the macula at postoperative weeks 1 and 3 (Figure, A). At week 3, the device fitting and visual rehabilitation processes were initiated (Figure, B). At week 7, the patient presented with a tractional membrane under the electrode array with surrounding retinal detachment (Figure, C and D). This resulted in rotation of the array so that the first row of electrodes overlapped the optic disc, necessitating repair.

The patient underwent 23-gauge pars plana vitrectomy, membrane peeling, endolaser application, air-fluid exchange, and injection of 5,000 cs silicone oil. The array was rotated away from the optic nerve with a 23-gauge pick. Subretinal fluid was drained through stretch holes located immediately inferior to the macula. Endolaser was applied in the periphery, sparing the area of the stretch holes to avoid damaging the electrodes.

After 1 week of prone positioning, examination revealed proper positioning of the array over the macula. No visible residual preretinal membranes were seen. However, shallow subretinal fluid was observed inferior and temporal to the array (Figure, E and F). Over the next 3.5 years, the retina remained shallowly detached under oil with progressively increased fibrosis around the array (Figure, G). The macula was pinned flat by the array (Figure, H). The patient continued to undergo visual rehabilitation, and he developed the ability to interpret simple, high-contrast targets and to apply these skills to his daily activities.

At month 44 after implantation, the patient presented with rubeosis iridis and a 1-mm hyphema. The rubeosis was controlled with two intravitreal injections of bevacizumab (Avastin, Genentech) at 4-week intervals and then intravitreal aflibercept (Eylea, Regeneron) every 6 weeks. All injections are administered through the inferonasal quadrant to avoid implant components sutured to the sclera in the superotemporal and inferotemporal quadrants. The patient remains minimally symptomatic for artificial vision changes, reporting that the stimuli appear only 10% fainter than before the onset of the rubeosis. He continues daily use of his device.

DISCUSSION

The availability of new technologies such as Argus II for visual rehabilitation has improved quality of life for many patients living with irreversible damage due to end-stage RP.[5-7]

Complications such as retinal detachment, vitreous hemorrhage, tack

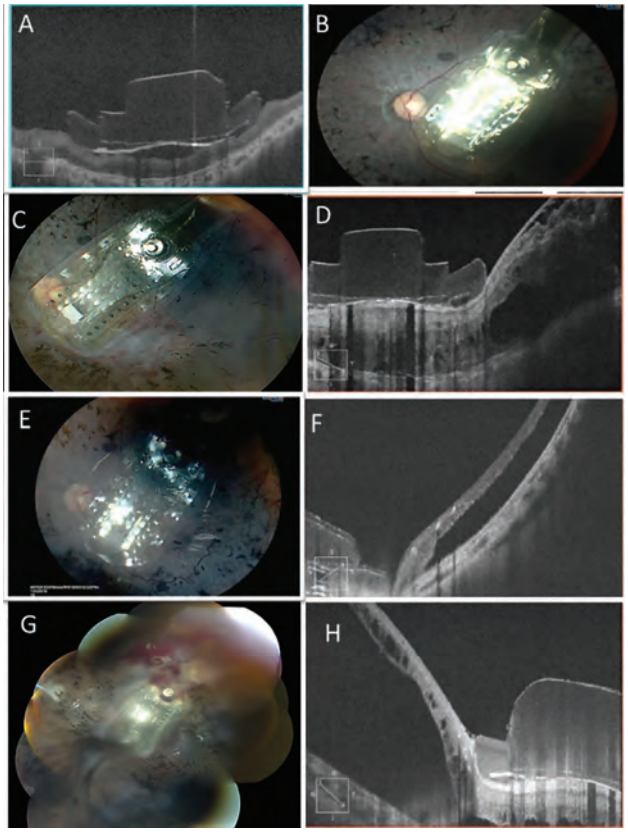

Figure. OCT through the fovea at postoperative day 4 after Argus II implantation shows a well-positioned electrode array over the inner retina (A). Fundus photograph at postoperative week 3 shows that the Argus II array is well-centered over the macula without electrodes overlapping the optic nerve (B). At this visit, adjustment of the electrodes' settings (fitting of the prosthesis) and rehabilitation were initiated. Fundus photograph at week 7 shows a preretinal fibrotic membrane temporal to the electrode array causing rotation of the array toward the optic nerve (C). OCT B-scan shows a preretinal membrane with traction on the underlying retina and macular edema (D). Fundus photograph at 1 week after vitrectomy, membrane peeling, and silicone oil injection shows rotation of the electrodes away from the optic nerve (E). OCT B-scan temporal to the array shows a shallow retinal detachment at 1 week after silicone oil injection (F). Fundus photograph montage at 3.5 years after implantation demonstrates an intraretinal hemorrhage and significant fibrosis around the array and the cable (G). OCT B-scan through the nasal portion of the electrode array shows a retinal detachment but complete apposition of the array to the macula at 3.5 years after implantation (H).

loosening, sterile anterior or posterior uveitis, endophthalmitis, and macular edema have been reported after Argus II implantation. Chronic hypotony and conjunctival erosion occur in approximately 13% of cases by 5 years.[1-4]

The longest prospective cohort, by da Cruz and colleagues, reported 5-year efficacy and safety data from 30 patients treated across 10 centers. The authors reported a total of 24 serious adverse events among 12 patients, most of which occurred within the first year after implantation. By 3 years, there was one rhegmatogenous retinal detachment and one tractional retinal detachment. By 4.5 years, another patient developed a rhegmatogenous retinal detachment followed by neovascular glaucoma the following year, treated by vitrectomy and silicone oil. Two device failures due to loss of signal transmission were identified by 4 years.[4]

When complications arise, patients are eager to hear about their artificial vision prognosis, and surgeons seek guidance on how to surgically manage these patients, avoid damage to the implant, and manage patients' expectations. The case presented here illustrates several important points.

First, the electrode array can continue to function in silicone oil and after laser application to the peripheral retina. Second, because it is not recommended to apply laser close to the array—laser may damage electrodes—and the retina is significantly degenerated in eyes with advanced RP, retinal detachment repair may be challenging in these cases. Retinal breaks may have to be left untreated. Third, rubeosis in the setting of chronic retinal detachment may be managed with anti-VEGF injections given via the nasal scleral quadrants. It is recommended to avoid passing needles in the temporal quadrants where the external components of the implant are located.

Familiarity with the Argus II device and the location of the implant components around the eye is essential for safe management of complications that may arise after implantation. We stress the importance of providing long-term follow-up, visual rehabilitation, and emotional support to the patients to encourage continued use of the prosthesis and a sense of psychological wellbeing. ■

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FOUNDATION FIGHTING BLINDNESS AND THE RETINAL DEGENERATION FUND

An update on some pipeline candidates that received Foundation funding.

BY BEN SHABERMAN, MA, MS

The most challenging aspect of therapy development for the eye is advancing a treatment into a clinical trial. Crossing the threshold from the lab into the clinic requires significant investment as well as regulatory expertise, knowledge of good manufacturing processes, and risk tolerance.

In 2018, the Foundation Fighting Blindness launched a venture philanthropy investment arm called the Retinal Degeneration (RD) Fund to help companies and researchers advance promising treatments for inherited retinal diseases (IRDs) into and through early-stage human studies. The targeted IRDs include retinitis pigmentosa (RP), Usher syndrome, and Stargardt disease. As a global leader in driving research for IRD treatments and cures, the nonprofit brings unparalleled scientific expertise and credibility to the projects that it funds.

"The Foundation has been a research-funding leader in the IRD space for nearly 50 years, which is very attractive to potential investors," Benjamin Yerxa, PhD, chief executive officer at the Foundation, told me in an interview. "Our investment in a project often serves as a seal of approval for our potential partners. We also bring clinical development expertise to the efforts, which is valuable to small R&D teams in start-up companies emerging from academic settings."

The goal of the RD Fund is to demonstrate early proofs of concept for emerging therapies to attract much larger investments from biotech and pharmaceutical companies for later-stage human studies, which hopefully lead to regulatory approval.

"If through our RD Fund investment we can show safety and evidence of efficacy in a phase 1/2 trial and reduce risk, then large companies are more inclined to take on the development effort and, ultimately, the commercialization process," Dr. Yerxa said.

Currently, the RD Fund has allocated about 75% of its $72 million fund to eight investments. A few examples are outlined below.

ProQR Therapeutics: RNA Therapies

Based in the Netherlands, ProQR develops RNA therapies for rare diseases. The company has three emerging therapies, all of which are antisense oligonucleotides (AONs) in clinical trials for the treatment of IRDs. AONs are small, single-stranded DNA fragments designed to mask or correct mutations in RNA. They are administered via intravitreal injection.

The Foundation is investing $7.5 million in development of the candidate QR-421a, an AON therapy that is being evaluated in the STELLAR trial, a phase 1/2 dose-escalation clinical trial for patients with mutations in exon 13 of the *USH2A* gene, which can cause Usher syndrome type 2A and nonsyndromic RP. In an interim report on the QR-421a clinical trial, ProQR said that two of eight participants had improvements in functional and structural measures.[1]

The company also has a phase 2/3 clinical trial under way to evaluate sepofarsen, an AON therapy that targets a mutation (c.2991+1655A>G in Intron 26) in the gene *CEP290*, which causes Leber congenital amaurosis 10 (LCA 10). In the phase 1/2 clinical trial evaluating sepofarsen, four of six participants demonstrated vision improvements.[2]

In late 2019, ProQR launched an AON clinical trial for people with RP caused by the *P23H* mutation in the gene *RHO*, but no results have been reported.

Nacuity Pharmaceuticals: Antioxidative Treatment

Based in Fort Worth, Texas, Nacuity Pharmaceuticals is developing an oral antioxidant candidate known as NPI-001, which is designed to slow vision loss in patients with IRDs such as RP and Usher syndrome. In May 2020, the company launched a phase 1/2 clinical trial in Australia to evaluate the safety of NPI-001. Researchers in

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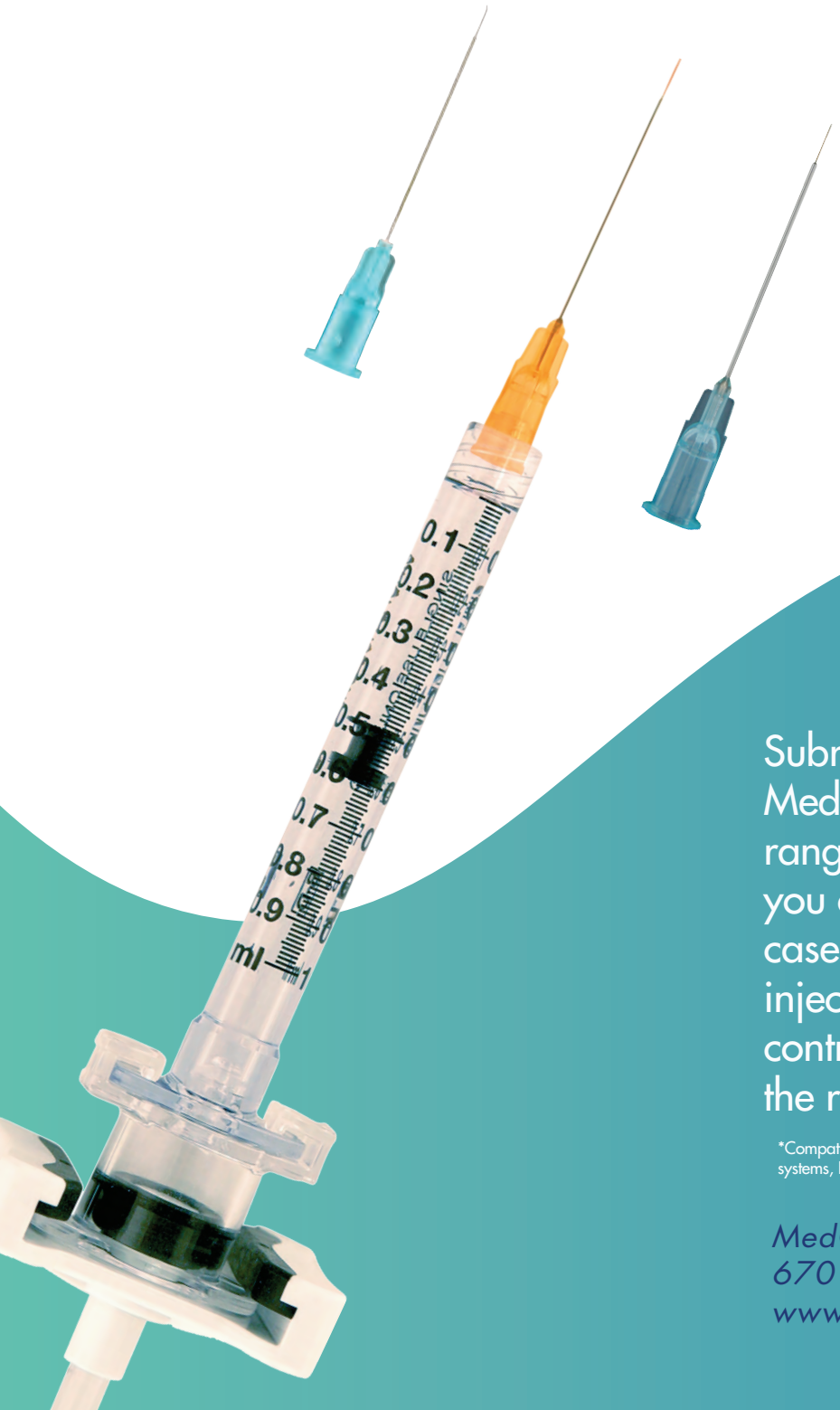

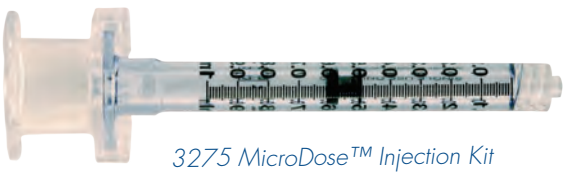

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the study SLO-RP, will enroll at least 48 patients with Usher syndrome and follow them for 2 years. If results for SLO-RP are favorable, Nacuity plans to launch clinical trials in 2021 to evaluate NPI-001 in patients with RP in the United States and Australia.

The Foundation is investing $7.5 million in NPI-001 development and providing scientific consulting for the clinical trial and therapy development. Dr. Yerxa is on Nacuity's board of directors.

SparingVision: Neuroprotection for RP

In most patients with RP, vision loss begins in rod cells. As a result, night and peripheral vision are affected first. However, over time, central vision and visual acuity are often affected due to loss of cone cells. Researchers from the Institut de la Vision in Paris identified a protein produced by rod cells that preserves cone cells. Researchers have begun to develop a gene therapy to express this protein, aptly named rod-derived cone viability factor, or RdCVF. The goal of the treatment is to preserve cone cells in patients with RP, Usher syndrome, and other related conditions. This therapy is designed to work independently of the mutated gene that underlies the IRD in question. The company plans to launch a clinical trial of the RdCVF gene therapy in 2021.

The Foundation is investing $7.9 million (€7 million) in development of this gene therapy. ■

1. Interim Findings of QR-421a Phase 1/2 Clinical Trial for Usher Syndrome and nsRP [press release]. ProQR Therapeutics; Leiden, Netherlands, and Cambridge, Massachusetts; March 2020.
2. ProQR Announces Positive Top-Line Results from the Phase 1/2 Study of Sepofarsen in LCA10 Patients [press release]. ProQR Therapeutics; Leiden, Netherlands, and Cambridge, Massachusetts; October 10, 2019.

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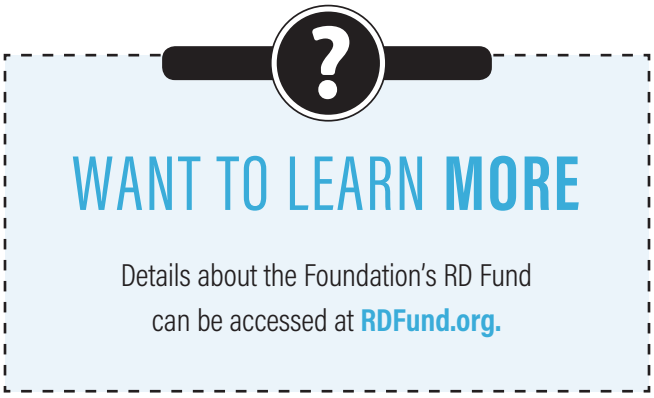

(Continued from page 20)

His second talk covered another weapon in the arsenal to reduce the burden of intravitreal injections: gene therapy. Dr. Avery presented the initial results of the OPTIC trial in wet AMD patients. This 2-year phase 1 study is assessing the safety and tolerability of a single intravitreal injection of the ADVM-022 (Adverum Biotechnologies) vector encompassing a gene expressing the aflibercept protein. Secondary outcomes include BCVA, anatomic outcomes, and patients' need for rescue injections of aflibercept (Eylea, Regeneron). Two dose-dependent cohorts of six patients each are receiving oral steroid prophylaxis for intraocular inflammation.

According to Dr. Avery, although there have been no significant adverse events, low-grade inflammation is common among the patients. Both cohorts have shown an early anatomic response, more prevalent in the higher-dose group. All six patients in the higher-dose cohort have thus far not required rescue therapy, whereas two patients in the lower-dose cohort have required rescue aflibercept injections. Two additional cohorts of this study will receive a similar dose of intravitreal vector and will use topical steroids for inflammation prophylaxis.

The second half of this presentation addressed data regarding RGX-314 (RegenxBio), an adenovirus vector delivering a gene for the ranibizumab protein. Dr. Avery explained how this vector is delivered into the subretinal space via PPV, and noted that suprachoroidal delivery systems are in development. A phase 1/2a trial is under way, with 42 patients divided into five dose cohorts. Treatment has been well tolerated thus far without significant medication-related intraocular inflammation, but Dr. Avery cautioned that two patients experienced procedure-related complications (one retinal detachment and one endophthalmitis following anterior chamber tap for protein determination). Patients enrolled in the study have so far shown a possibly dose-dependent response with respect to anatomic outcomes, visual outcomes, and injection-free follow-up. A phase 2 trial is planned, and the application of this form of therapy to additional disease processes such as diabetic retinopathy will be explored.

Most important, Dr. Avery won the coveted buckle prize for best costume! ■

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A RARE PRESENTATION OF MULTIFOCAL CHOROIDAL MELANOMA

The multifocal lesions, themselves rare, were even more unexpected in the absence of ocular melanocytosis and germline *BAP-1* mutation.

BY ERIN JENNINGS, BS; MICHAEL CHANG, MD; AND CAROL L. SHIELDS, MD

Uveal melanoma is a rare tumor with an incidence of 4.3 per million people in the general population.[1] This malignancy is typically solitary and unilateral, rarely manifesting as multifocal unilateral or bilateral tumor.[2] In an analysis of 8,033 eyes with uveal melanoma by Shields et al, less than 1% of patients (11 of 8,022) presented with either multifocal or bilateral tumors.[2]

Predisposing factors associated with the development of uveal melanoma include preexisting choroidal nevus; ocular melanocytosis; breast cancer type 1 (*BRCA1*)–associated protein (*BAP-1*) cancer predisposition syndrome; and, rarely, neurofibromatosis and myotonic dystrophy.[1,3-5]

Ocular melanocytosis, a congenital pigmentary abnormality, promotes a 1 in 400 risk for uveal melanoma (compared with 1 in 13,000 in the general white population).[6] In a study of 507 patients with uveal melanoma who underwent germline *BAP-1* sequencing, Gupta et al identified 25 patients (4.9%) harboring an underlying *BAP-1* mutation, and this can promote multifocal melanoma.[7]

Here we report a unique case of multifocal uveal melanoma in a patient with no evidence of ocular melanocytosis or *BAP-1* cancer predisposition syndrome.

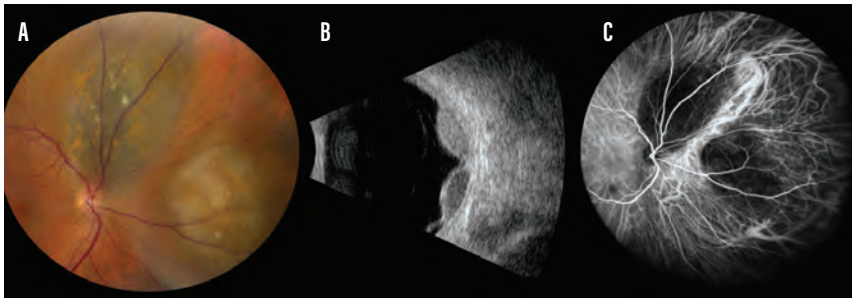

Figure. Multifocal choroidal melanoma in the right eye of a 56-year-old woman (A). B-scan ultrasonography showed two distinct hollow, dome-shaped lesions with subretinal fluid (B). Evaluation with indocyanine green angiography documented hypocyanescence at the two tumor sites with normal choroidal flow in between, implying two distinct tumors (C).

CASE REPORT

A 56-year-old white woman with a history of two choroidal nevi in the right eye (OD) reported experiencing photopsia for 3 weeks. She related a family history of leukemia, prostate cancer, and breast cancer, but reported no previous personal history of cancer.

On our examination, VA was 20/25 OD and 20/20 in the left eye (OS). IOP was 13 mm Hg in each eye. On anterior segment examination, there was no ocular melanocytosis on either eye. However, two iris freckles were noted OS. Fundoscopic examination of the left eye was unremarkable. Funduscopic examination of the right eye showed two independent small choroidal melanomas located superonasal to the optic disc and nasal to the optic disc (Figure, A).

B-scan ultrasonography documented two distinct echolucent tumors, with No. 1 (superonasal) measuring 9.0 mm in base and 4.6 mm in thickness and No. 2 (nasal) measuring 9.0 mm in base and 4.3 mm in thickness (Figure, B). There was no extrascleral extension, and the two tumors were distinct.

Fluorescein angiography revealed patchy areas of hyperfluorescence in both tumors during the arteriovenous phase. Indocyanine green angiography displayed the tumors as hypocyanes-

cent and with no evident connection between the two independent melanomas (Figure, C). Autofluorescence revealed prominent orange pigmentation over both tumors.

OCT revealed macula-sparing subretinal fluid extending from 2 o'clock to 8 o'clock at the ora serrata in the right eye. Additional fluid was noted between the two tumors, and no connection between the two tumors was seen on OCT.

Fine needle aspiration biopsy for cytogenetic analysis was performed, and tumor No. 1 showed chromosome 3 monosomy, partial loss in chromosome 1, chromosome 6 disomy, and chromosome 8q gain and 8p loss, suggestive of high risk for metastasis and correlating with The Cancer Genome Atlas (TCGA) classification of group C.[8] Cytogenetics of tumor No. 2 showed chromosome 3 partial monosomy as well as chromosomes 1, 6, and 8 disomy, suggestive of TCGA group A. The patient was negative for germline *BAP-1* mutation.

The melanomas were treated simultaneously with plaque radiotherapy using a single 22-mm notched radioactive iodine-125 device. At 24-month follow-up, both tumors demonstrated regression, with tumor No. 1 decreasing in thickness from 4.6 mm originally to 2.4 mm and tumor No. 2 from 4.3 mm originally to 2.1 mm. Systemic evaluation at 2 years confirmed absence of metastatic disease.

DISCUSSION

Multifocal melanoma is an extremely rare condition. Based on the reported risk of developing uveal melanoma in patients with ocular melanocytosis, Honavar et al estimated a lifetime risk of 1 in 160,000 for developing two uveal melanomas in the same eye.[6,9]

From a genetic perspective, *BAP-1* is a recognized predisposing factor associated with multifocal uveal melanoma, but other gene mutations, some as yet unrecognized, could contribute to this condition.[1] Guanine nucleotide-binding protein G (*GNAQ/GNA11*) mutations, which are present in 85% of all uveal melanomas, are involved in regulation of the mitogen-activated protein kinase pathway; it has been speculated that this pathway is involved in the malignant transformation of melanocytes.[10]

Other genes, such as eukaryotic translation initiation factor 1A (*EIF1AX*), splicing factor 3B subunit 1 (*SF3B1*), and preferentially expressed antigen in melanoma (*PRAME*), have also been identified as having an influence on patient outcomes.[1] Several of these genes—*BAP-1*, *EIF1AX*, and *SF3B1*—have been found to be mutually exclusive of one another, illustrating the complexity involved in tumor development.[10] There may be other as yet undiscovered germline or somatic mutations that contribute to the development of multifocal uveal melanoma.

The *BAP-1* gene, located on the short arm of chromosome 3, expresses a tumor-suppressor protein that works with a variety of recombination proteins (most notably *BRCA-1*) to enhance regulation of DNA repair, cell cycle mechanisms, cellular differentiation, and genomic stability.[1] Rao et al reported the first case of multifocal uveal melanoma with presence of germline *BAP-1* mutation, suggesting the importance of germline testing in uveal melanoma, especially in multifocal cases.[4]

In addition to uveal melanoma, patients with an autosomal dominant germline mutation of this gene are at risk for other heritable cancers described as *BAP-1* tumor predisposition syndrome (*BAP1*-TPDS).[1] In a review of the literature of 246 patients with underlying *BAP-1* mutation, Masoomian et al observed that 63% of patients (156 of 246) developed one or more tumors, including mesothelioma (20%), cutaneous melanoma (10%), renal cell carcinoma (8%), atypical Spitz tumor (AST), breast cancer, and prostate cancer, among others.[1]

BAP-1 mutations have also been associated with a strong family history of cancer. Gupta et al studied 507 patients with uveal melanoma who underwent germline *BAP-1* sequencing.[7] They found that those with germline *BAP-1* mutations (versus those without mutation) had a higher frequency of family history of any cancer (100% vs 65.9%, $P = .06$), family history of ocular melanoma (25.0% vs 1.9%, $P = .01$), and personal history of cutaneous melanoma (62.5% vs 9.9%, $P = .001$).[7]

Given an increased risk of systemic cancer in patients with *BAP1*-TPDS, Masoomian et al advised genetic testing of patients with early onset of uveal melanoma (< 30 years old) or one or more of the following: family history with two or more uveal melanoma cases, uveal melanoma with another primary neoplasm, two or more primary tumors in first- or second-degree relatives, and bilateral or multifocal tumors.[1]

The presence of multiple lesions with a strong family history of cancer in this case raised suspicion for an underlying mutation, despite the patient's having no detectable pathologic *BAP-1* variants.

In addition to germline *BAP-1*, somatic *BAP-1* can be a prognostic biomarker for uveal melanoma metastasis. Located on chromosome 3p21.1, *BAP-1* is strongly correlated with monosomy 3.[1] However, tumor studies have expanded beyond single chromosome 3 analysis, now including chromosomes 1, 6, and 8, highlighting the polygenic influence on uveal melanoma prognosis.[8,10]

Shields et al studied 1,059 patients with somatic genetic testing of uveal melanoma and identified the highest metastatic risk in those with complete monosomy 3 combined with disomy 6, 8q gain, and 8p loss (hazard ratio, 31.6).[10]

TCGA describes the genetic influence on uveal melanoma prognosis by categorizing tumors into four classes based on somatic karyotype: classes A (disomy 3, normal 8q), B (disomy 3, 8q gain), C (monosomy 3, 8q gain), and D (monosomy 3, multiple 8q gains). This system was examined by Vichitvejpaisal et al in a study of 658 patients, and these authors confirmed the reliability of the TCGA classification for prediction of metastasis and death.[8] A comparison (class

(Continued on page 45)

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FOVEA PLANA IN A 6-MONTH-OLD INFANT

This may be the youngest patient in which this abnormality has been noted.

BY KEVIN GEORGE, BS; ANTONIO YAGHY, MD; AND CAROL L. SHIELDS, MD

The term *fovea plana* refers to the anatomic absence of a foveal pit.[1] An estimated 3% of children with clinically normal eyes have an underdeveloped foveal pit on OCT.[2]

A foveal pit is not necessarily required for foveal cone specialization.[1] On its own, a diagnosis of fovea plana does not automatically portend functional disability. It is certainly possible to maintain adequate visual acuity in an eye with fovea plana.[1,3]

By contrast, *foveal hypoplasia* refers to an underdeveloped fovea with associated vision loss.[4] Foveal hypoplasia has been seen with conditions such as aniridia, albinism, achromatopsia, nanophthalmos, incontinentia pigmenti, and retinopathy of prematurity.[1,2,5]

Fovea plana is generally discovered in younger or older adults during routine OCT evaluation, but it has also been reported in children as young as 4 years.[2] Fovea plana is typically a bilateral process with symmetric structural findings on spectral-domain OCT, suggesting a developmental process that results in arrested foveal maturation.[6] Rare cases of unilateral fovea plana have been reported, however, suggesting that independent factors such as genetic mosaicism or local tissue environment might play a role in the development of fovea plana.[6,7]

We recently cared for a 6-month-old boy with unilateral advanced retinoblastoma necessitating enucleation. At the time of evaluation, he was noted to have fovea plana in his uninvolved eye on OCT. To the best of our knowledge, this is the earliest reported case of fovea plana, with clear microstructural loss of the foveal pit in this 6-month-old infant.

CASE REPORT

A 6-month-old white boy with left esotropia for 4 months was referred to the Ocular Oncology Service at Wills Eye Hospital for possible retinoblastoma. On examination, visual acuity was fix-and-follow in the right eye and no fix-and-follow in the left eye. Finger tension pressures were normal in both eyes.

The anterior segment and fundus in the right eye were normal with no evidence of tumor and with minimally pigmented choroid, subtle foveal ring-shaped light reflex, and minimal foveolar central light reflex. The left eye demonstrated 30–prism diopter left esotropia and leukocoria. Funduscopically, there was a multinodular, exophytic retinoblastoma (group D) measuring 22.0 mm in diameter and 8.3 mm in thickness, extending through the macula, overhanging the optic nerve, and with viable subretinal seeds. Magnetic resonance imaging demonstrated the enhancing mass with possible distal optic nerve invasion.

Enucleation of the left eye was performed, and retinoblastoma was confirmed with no evidence of uveal or optic nerve invasion histopathologically. The foveal anatomy was altered due to the massive tumor. Genetic testing revealed germline mutation in the *RB1* gene.

On follow-up, the right eye remained stable, with stable fovea plana (Figure). There was no evidence of aniridia, albinism, nanophthalmos, or other diseases. At 3-year follow-up, VA was 20/60 in the right eye and the fovea plana was unchanged.

DISCUSSION

Foveal development begins to occur in week 25 of gestation and continues into the postnatal period.[3] Due to specialized "midget" circuitry in the foveal region, where each cone connects to a single bipolar cell and a single ganglion cell, fewer lateral connections form between neurons in the foveal avascular zone than elsewhere in the retina.[3] This makes the foveal avascular zone susceptible to displacement of cone photoreceptors and inner retinal layer cells, forming a complete foveal pit.[3] Importantly, even when this pit is absent, cones in the central retina can still morphologically elongate and narrow, enabling them to align compactly with greater numbers for high-resolution visual acuity.[3]

In 2008, Marmor et al introduced

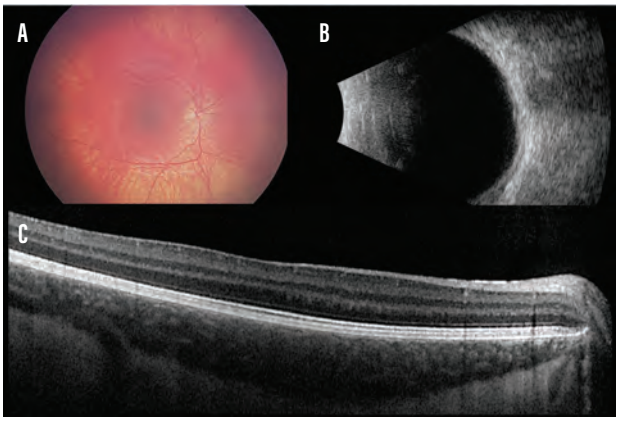

Figure. Funduscopy of the right eye showing blonde fundus and prominent choroidal vessels (A), with flat retina on ultrasonography and axial length of 22.3 mm (B). On OCT, there was minimal foveal pit, consistent with fovea plana, and the retinal layers appeared intact (C).

the term *fovea plana* in a description of four patients, ages 10 to 26 years, with OCT-evident fovea plana. These patients had VA of 20/20 to 20/50 and no evidence of nystagmus or abnormalities on multifocal electroretinogram. The authors concluded that foveal cone specialization can be preserved independently from foveal contour.[1] They proposed that the term *fovea plana* is anatomically descriptive, based on OCT, and that it can appear in patients with related conditions such as aniridia, albinism, and achromatopsia, or might appear in patients with no underlying disease.

Thus, the clinician should not infer that the lack of a foveal pit on OCT signifies poor visual potential. However, any child or adult with poor pit morphology should be evaluated clinically for underlying related conditions.

Since that initial description, several studies of this entity have been published. In 2014, Noval et al reviewed the OCTs of 286 normal children and found an absent foveal pit in nine patients (3%).[2] All nine children with fovea plana had bilateral findings and VA of 20/20 in both eyes, with normal stereoacuity.[2] The measured mean foveal thickness was greater in eyes with fovea plana (294.5 µm) compared with age-matched controls (219.8 µm, $P = .029$).[2] In 2016, Dolz-Marco et al noted both the loss of the foveal avascular zone and preserved fusion of the superficial and deep capillary plexuses around the foveal center in three patients with fovea plana.[8]

In 2018, Villegas et al noted that fovea plana presented as a bilateral disease in five of six patients, all of whom maintained 20/40 or better BCVA.[6] In the one patient with asymmetric manifestation, an 8-year-old girl, her right eye with 20/25 VA showed obvious fovea plana, whereas her left eye with 20/25 VA showed a normal foveal contour. Both eyes showed exactly the same refraction, +1.00 +1.50 X 90°. The authors noted that astigmatism of +1.50 D or greater was present in 45% of eyes, suggesting that astigmatism may be more prevalent in patients with fovea plana than initially suspected.[6]

On evaluation, fovea plana can be associated with aniridia, albinism, nanophthalmos, incontinentia pigmenti, retinopathy of prematurity, and achromatopsia, or can be seen in an otherwise healthy eye. In the case presented here, there was initial suspicion for albinism due to a blunted foveal contour, noticeable reduction in uveal pigmentation, and prominent choroidal vessels. However, there was no nystagmus or iris transillumination defect. Thus, this case is likely fovea plana in an otherwise healthy eye, and a good visual outcome is anticipated.

CONCLUSION

Fovea plana is typically a bilateral fundus finding on OCT imaging. It can occur in patients with excellent visual acuity. This rare presentation of fovea plana diagnosed in an eye of a 6-month-old child could represent the youngest patient to be recognized with this abnormality. ■

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THE EFFECT OF PPV WITH 1,000 CST SILICONE OIL ON IOP

A study assessed low-viscosity silicone oil tamponade in retinal detachment repair.

BY JITENDER PHOGAT, MS; MANISHA RATHI, MS; SUMIT SACHDEVA, MS; DIXIT SONI, MBBS; LATIKA PANDEY, MBBS; AND RITESH VERMA, MS, FICO, MRCSED

Retinal detachment (RD) is an ocular emergency for which, generally, pars plana vitrectomy (PPV) is performed, along with intraocular tamponade using gas or silicone oil. The viscosity of silicone oil ranges from 1,000 to 10,000 centistokes (cSt).

We performed a study to examine the effect of low-viscosity silicone oil (1,000 cSt) on IOP elevation and the effectiveness of medical and surgical treatment in controlling IOP. This low-viscosity product is one-fifth as expensive as 5,000 cSt silicone oil—a vital factor in developing countries such as India.

MATERIALS AND METHODS

A total of 60 patients with RD were included in this study. Patients had no history of glaucoma, uveitis, or ocular hypertension. After informed consent, a three-port PPV was performed by a single surgeon, and 1,000 cSt silicone oil was injected at the end of the surgical procedure as a tamponade.

IOP was measured 1 week, 1 month, and 4 months postoperatively by Goldmann applanation tomometry. Any patient with an IOP of greater than 21 mm Hg was considered to have silicone oil–induced ocular hypertension, and antiglaucoma treatment was started.

RESULTS

Sixty patients with RD underwent PPV with 1,000 cSt silicone oil tamponade. The age of the patients ranged from 20 to 81 years (mean age, 60 years), and 35 were men. Mean preoperative IOP was 13.6 ±4.8 mm Hg.

At 1 week postoperative, mean IOP was 17.8 ±4.2 mm Hg. Ten patients had IOP greater than 21 mm Hg and were started on antiglaucoma medication.

At 1 month postoperative, the mean IOP was 16.2 ±3.9 mm Hg. At 1 month, there were three new patients with IOP of greater than 21 mm Hg. These patients were also started on antiglaucoma treatment. At 4 months, mean IOP was 15.8 ±3.6 mm Hg and there were six more new patients with IOP greater than 21 mm Hg (Figure). These patients were also started on antiglaucoma drugs.

Thus, during 4 months, 19 of the 60 patients (31.6%) showed an increase in IOP to greater than 21 mm Hg. More than half of these cases (10/19; 53%), were observed during the first postoperative week. After 1 month, there were 13 patients, and after 4 months, there were 19 patients with an IOP of greater than 21 mm Hg, all of whom were started on antiglaucoma therapy.

Seventeen of the total 19 patients (89.5%) who developed elevated postoperative IOP were controlled with antiglaucoma treatment. Timolol with brimonidine twice daily was effective

AT A GLANCE

- In a study, 60 patients with retinal detachment were injected with 1,000 cSt silicone oil after three-port vitrectomy.
- Most patients who developed postoperative IOP of greater than 21 mm Hg were controlled with antiglaucoma treatment.
- In this study, 1,000 cSt silicone oil was equivalent to 5,000 cSt silicone oil in efficacy and safety.

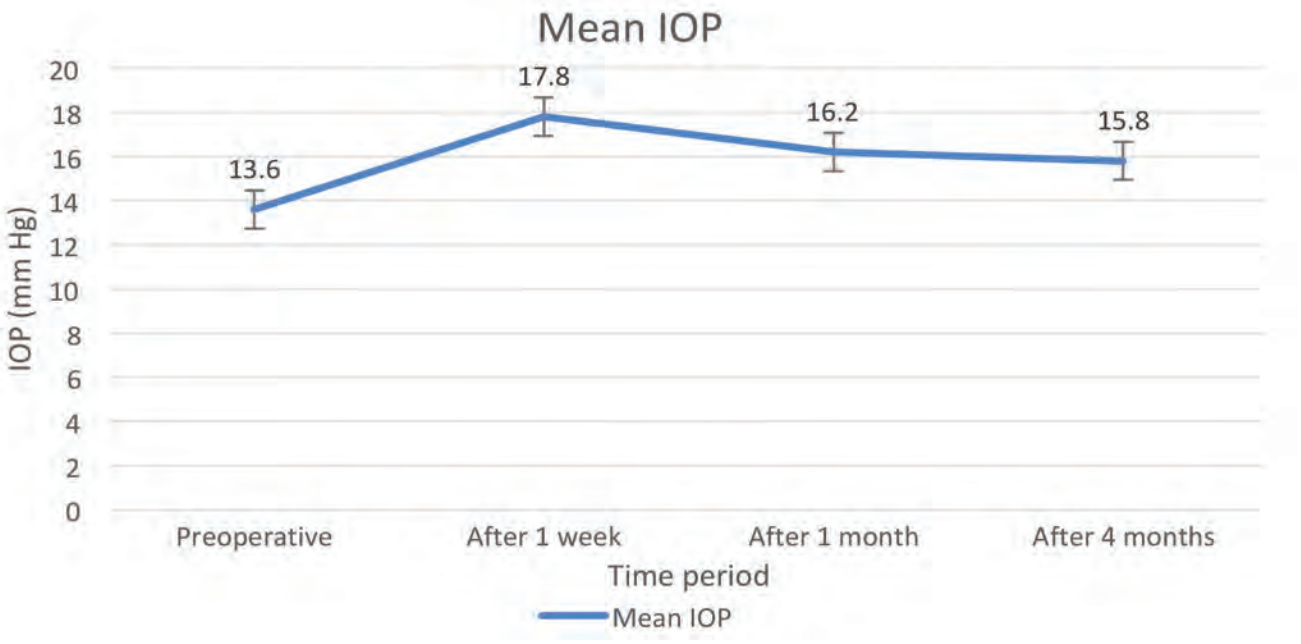

Figure. Postoperative mean IOP in patients who were treated with silicone oil 1,000 cSt tamponade.

in 15 of the 19 (78.9%) patients. A third drug (dorzolamide twice daily) was added in the remaining four patients, of which two responded well in terms of IOP control. Two patients were unresponsive and required surgical intervention in the form of silicone oil removal. One of the two patients who required surgical intervention was aphakic with pupillary block.

WHAT WE LEARNED

Silicone oil is preferred after PPV for surgical tamponade and vitreous substitute. Complications such as IOP elevation in the first few weeks postoperative are not uncommon. Studies have reported an incidence of postoperative rise in IOP after silicone oil in 21% to 48% of eyes.[1-4]

In our study, over a period of 4 months, 89.5% of patients (17/19) with elevated IOP were controlled medically. In 10.5% of patients (2 of 19), silicone oil removal was needed before 4 months postoperative to control IOP. The results of our study are comparable to those of other published studies. The main drawback of our study is its short follow-up period.

Affordability is an important factor in the use of silicone oil. In most published studies, silicone oil with a viscosity of 5,000 cSt has been used, whereas we used 1,000 cSt silicone oil.

India is a developing nation, where the cost of 5,000 cSt silicone oil (approximately $100 USD) is prohibitively expensive compared to the cost of 1,000 cSt silicone oil (approximately $20 USD). In our experience, as shown in this study, 1,000 cSt silicone oil is as effective and safe as 5,000 cSt silicone oil for RD repair. ■

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US RETINA SURGEONS CAN STOP SINGING THE BLUES

TissueBlue has arrived.

BY BRIAN C. JOONDEPH, MD, MPS

Vital dyes are an essential tool of retina surgeons who perform macular surgery, specifically peeling of epiretinal membranes (ERM) or the internal limiting membrane (ILM). According to Market Scope, ILM peeling is performed in about a quarter of all vitrectomies.[1]

Goals for membrane staining include reliable and adequate staining, good contrast with surrounding tissue, easy application, and safety of underlying retinal tissue.

In 2011 and 2015, I reviewed membrane staining options available in the United States at the time, including indocyanine green (ICG) (IC-Green, Akorn), triamcinolone, and compounded brilliant blue G (BBG).[2,3] Although a commercially available brilliant blue product known as ILMBlue (DORC) has been an option for surgeons outside of the United States, not until recently has a US FDA–approved product been available in the United States.

Let's briefly summarize these vital dyes (Table).

ICG

ICG is used off-label for ILM staining. Contrast is dependent on ICG concentration, which involves a trade-off between safety and efficacy: A more concentrated solution, while providing more robust staining, risks toxicity to the exposed RPE during macular hole surgery.[4]

TRIAMCINOLONE

Triamcinolone, also used off-label, isn't an actual stain. Microparticles settling on the membrane surface provide a demarcation of peeled and unpeeled membrane.

COMPOUNDED BBG

Compounded BBG, also off-label in the United States, must be supplied via a compounding pharmacy and may vary in preparation and safety. It has been reported that under limited FDA guidance, compounding pharmacies, if not vigilant, may provide contaminated product.[5]

TISSUEBLUE

In December 2019, the FDA approved TissueBlue (0.025% brilliant

TABLE. SUMMARY OF VITAL DYES AVAILABLE TO US SURGEONS

Stain	Approved by FDA for Selective Stain of ILM	Stains ILM	High Specific Gravity	High Viscosity	Low Osmolarity	Stable / Prefilled Syringe	Absence of Reported Toxicity
ICG	x	✓	x	x	x	x	x
BBG	x	✓	x	x	x	x	✓
Trypan Blue	x	x	x	x	✓	x	x
Triamcinolone	x	x	x	x	✓	x	✓
ICG / BBG + D20	x	✓	✓	x	✓	x	x
TissueBlue	✓	✓	✓	✓	✓	✓	✓

Abbreviations: BBG, brilliant blue G; FDA, US Food and Drug Administration; ICG, indocyanine green; ILM, internal limiting membrane.

AT A GLANCE

- Brilliant blue G is a vital dye that was recently approved by the US FDA under the name TissueBlue (Dutch Ophthalmic USA).
- US retina surgeons may now access an on-label vital dye for ILM staining.
- Among the conveniences of TissueBlue are its prefilled syringe, sharp contrast on the ILM, and elimination of the need to inject the dye under air or with infusion turned off.

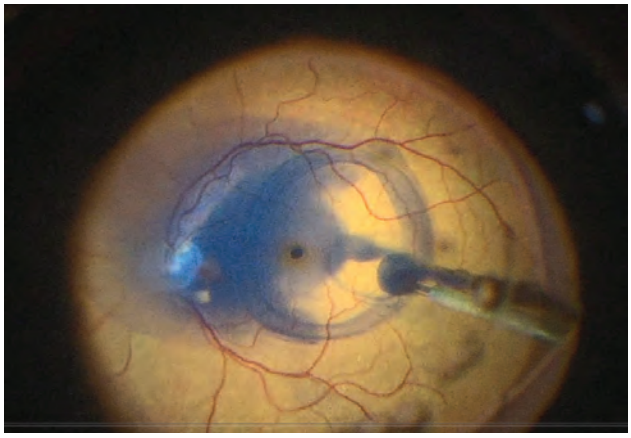

Figure 1. Pooling of dye over the posterior pole.

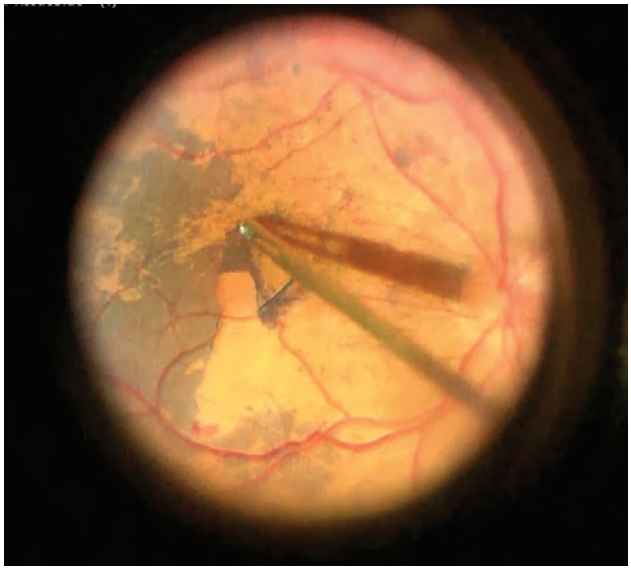

Figure 2. Contrast between stained ILM and underlying retina.

Figure 3. TissueBlue in a prefilled syringe.

blue G, Dutch Ophthalmic USA) for selective ILM staining. This approval finally provides access to a product that colleagues in Europe and globally have used for more than 350,000 cases since its launch in 2010.

As an FDA-approved product, TissueBlue meets active pharmaceutical ingredient standards, assuring levels of purity and consistency in manufacture. Outside of the United States, TissueBlue is marketed under the brand ILMBlue, which has a proven track record for safety and high-performance staining. The patented formulation of TissueBlue is unique in containing 4% polyethylene glycol (PEG). PEG is the carrier that is used to ensure that the staining agent maintains a tight, cohesive ball of dye as it falls to the back of the eye, due to its higher specific gravity compared with balanced salt solution, thereby avoiding the need for a fluid-air exchange during surgery.

WHAT I'VE LEARNED

In my experience, the density of TissueBlue provides a pooling effect on the posterior pole with robust ILM visualization 30 to 40 seconds after initial infusion. The PEG is critical to provide both higher density and higher specific gravity so that the dye settles through gravity to the back of the eye and also spreads in a flat wave across the macula without dispersing in the vitreous cavity.

Because TissueBlue settles over the posterior pole, it is not necessary to turn off infusion to the eye or inject the dye under air—measures often needed to keep a dye over the macula and avoid dispersal after injection (Figure 1).

The dark blue color of the stained ILM stands in sharp contrast to the underlying retina when peeling commences (Figure 2). Additionally, because the stain is selective to the ILM, any areas covered by ERM are clearly visible via negative staining in contrast to the stained areas of ILM. With its proven safety profile in more than 300,000 cases, I have no concerns regarding restaining to confirm complete removal of the ILM if there is any doubt about the completeness of the peel. Finally, for the surgical staff, the availability of TissueBlue in a prefilled syringe is a major advantage: It is convenient and obviates the need to prepare or mix the dye prior to use (Figure 3).

For many years, I have advocated for the use of BBG in vitreoretinal surgery for membrane staining, so the availability of a version that is approved by the FDA for staining the ILM and in a formulation that is designed specifically to meet the needs of vitreoretinal surgeons is a significant advance. I have no reservations in recommending TissueBlue for ILM staining. This will be a useful new tool for vitreoretinal surgeons in the United States, who no longer must *sing the blues* over the lack of brilliant blue in their ORs. ■

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UPDATES IN PEDIATRIC RETINAL IMAGING


Case studies illustrate the utility of new imaging technologies in children.

BY MICHAEL J. HEIFERMAN, MD; AND R.V. PAUL CHAN, MD, MSC, FACS

Imaging is an integral part of the evaluation of pediatric retina patients. Given the unique challenges in pediatrics, imaging is particularly helpful in augmenting patient histories and clinical examinations in this patient population. Imaging in pediatric patients can help clinicians to detect pathology not seen on clinical examination and to monitor disease activity, provide guidance for treatment decisions, and serve as a tool for educating patients and their families.

The cases we describe in this article demonstrate some of the practical uses of retinal imaging in pediatric patients.

CASE No. 1

A 3-year-old boy was referred for leukocoria with no light perception vision in his right eye (Figure 1). Examination revealed an exudative retinal detachment, and fluorescein angiography (FA) showed multiple light-bulb aneurysms. OCT demonstrated intraretinal and subretinal fluid and exudates, as well as disruption of the ellipsoid zone and the external limiting membrane.

Recent studies have demonstrated the utility of OCT in the management of Coats disease.[1,2] Gupta et al found that microstructural retinal abnormalities in Coats disease, such as intraretinal edema and subretinal fluid, may be identified more frequently with OCT than with clinical examination. These microstructural abnormalities seen on OCT correlated with visual acuity, visual prognosis, and clinical disease staging.[1]

Ong et al also documented the benefits of using OCT along with fundus photography and FA in Coats disease.[2] They found that exudates can form in all layers of the retina, particularly in the upper half of the outer nuclear layer in eyes with a macular star pattern of exudation. They also described extensive outer retinal atrophy above fibrotic nodules and the presence of small preretinal hyperreflective dots on OCT. These dots are of unclear etiology; however, the authors speculated that they may represent lipids, inflammatory cells, or red blood cells. This study also correlated OCT findings with histopathologic analysis, including hyperreflective linear structures that may represent cholesterol clefts, and hyperreflective dots in subretinal fluid that may be macrophages similar to those seen in central serous chorioretinopathy. Together, these studies demonstrate the benefit of using OCT in the evaluation of patients with Coats disease.

CASE No. 2

A girl born at 30 weeks and 5 days gestational age and weighing 1,560 g underwent examination under anesthesia (EUA) after screening for retinopathy of prematurity (ROP). Retinal examination revealed membranes overlying the optic disc and vascular arcades, causing retinal detachments in each eye, and anomalous retinal vasculature without plus disease in each eye. FA showed diffuse avascularity and neovascularization in each eye (Figure 2).

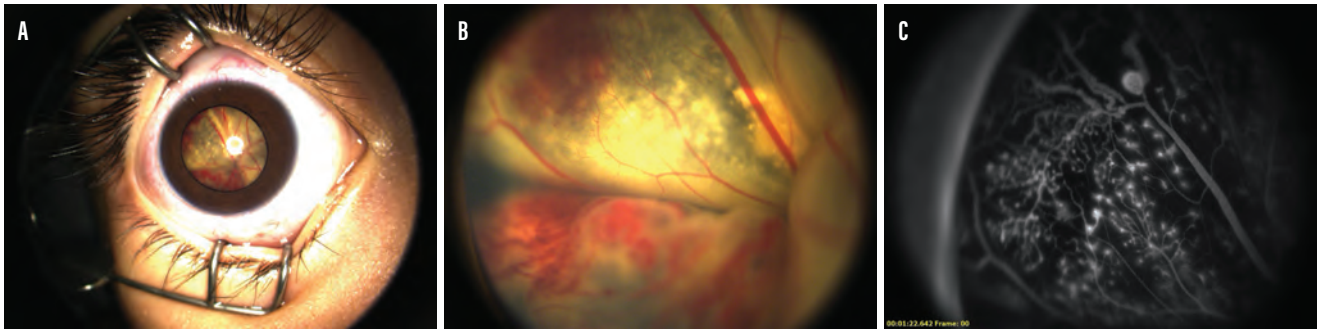

Figure 1. A 3-year-old patient presented to the clinic with no light perception in his right eye. External examination (A), fundus examination (B), and FA (C) helped clinicians identify a retinal detachment.

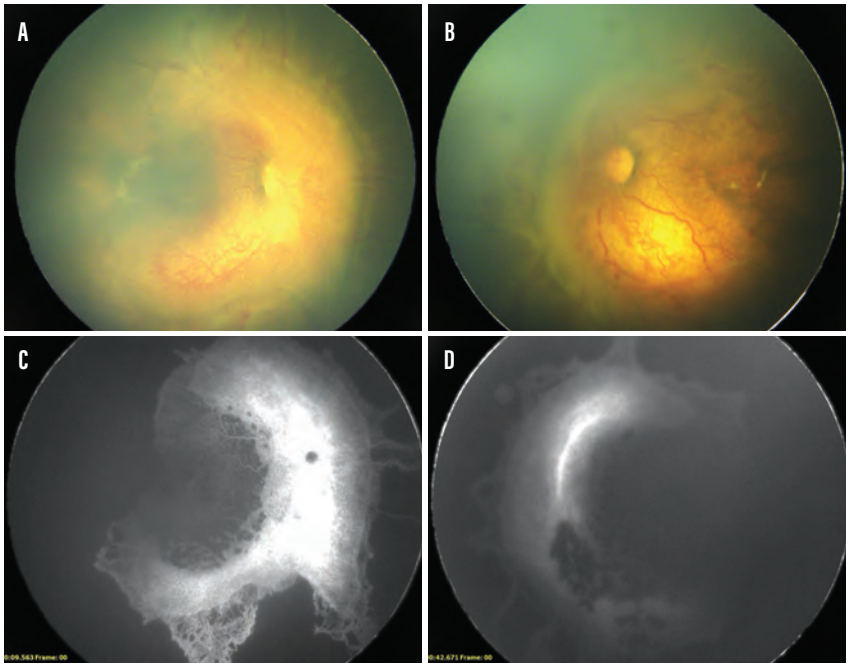

Figure 2. During examination for ROP, a patient was found to have retinal detachment in her right (A) and left eyes (B). Diffuse avascularity and neovascularization were noted in the patient's right (C) and left eyes (D).

Gupta et al reported a series of three moderately premature neonates with aggressive posterior vitreoretinopathy (APVR).[3] This entity, more consistent with familial exudative vitreoretinopathy (FEVR) than with ROP, is characterized by the presence of severe retinal pathology despite relatively older gestational age at birth and larger birth weight. APVR is characterized by an absence of prominent plus disease and is more aggressive than the entity known as *ROPER* (also called *ROP vs FEVR*).[4] EUA with FA should be considered early and can help distinguish this entity from ROP.

The role of FA in pediatric retina patients has been an area of recent investigation in other disorders. Abraham et al evaluated pediatric patients with posterior-involving uveitis on immunosuppressive therapy deemed quiescent on clinical examination.[5] They performed FA on these patients and found that 11 of 14 (79%) had persistent subclinical inflammation requiring a change in their immunosuppressive therapy. These authors emphasized the importance of FA for monitoring disease activity in pediatric patients. They also speculated that subclinical retinal vasculitis may contribute to the worse prognosis in pediatric posterior-involving uveitis.

Chee et al reported on the safety of FA specifically in the pediatric population.[6] These authors found no significant adverse events during 214 FAs and no change in 5-minute preinjection and postinjection physiologic parameters in the 27 FAs that were conducted during EUA. The most common inpatient diagnosis was ROP followed by Coats disease, FEVR, and nonaccidental trauma. The most common outpatient diagnosis was Coats disease, followed by FEVR and sickle cell retinopathy. They found that FAs were done as inpatient procedures more often for younger patients, given patient cooperation issues and the need to coordinate with intervention under anesthesia.

These studies, taken together, demonstrate the safety and importance of FA in managing pediatric retina patients.

CASE No. 3

A 9-year-old girl with an exophoria was found to have counting fingers VA in the right eye. The patient was born full-term with normal birth weight and had no history of ocular trauma, surgery, systemic illness, or similar family history. Examination revealed a large peripapillary subretinal lesion with associated retinal edema (Figure 3). OCT confirmed subretinal hyperreflective material with associated intraretinal and subretinal fluid. FA demonstrated vascularization of the lesion with leakage. OCT angiography (OCTA) was performed to show flow within the subretinal hyperreflective material. A diagnosis of choroidal neovascularization (CNV) was made, and serial anti-VEGF intravitreal injections were performed, with subsequent improvement in the intraretinal and subretinal fluid.

Ong et al reported eight patients with pediatric CNV evaluated with OCTA.[7] These authors compared active and quiescent CNV and demonstrated the presence of fine capillaries, anastomoses, and vessel loops in active cases. These findings may be helpful in monitoring for CNV recurrence and may indicate when repeat FA and treatment is appropriate.

Another potential role for OCTA is in screening for retinal pathology. Alam et al used machine learning–based artificial intelligence to differentiate and stage OCT angiograms of patients with nonproliferative diabetic retinopathy and sickle cell retinopathy.[8] Using their screening tool, they were able to quantify blood vessel tortuosity, caliber, density, and branch-point geometry, as well as the foveal avascular zone contour irregularity and area. Using these OCTA parameters, their screening tool achieved 94.84% sensitivity to identify retinopathy from the general pool of controls. These findings support the use of artificial intelligence in screening vulnerable groups without access to retinal specialists, including the pediatric population.

The role of OCTA in the management of pediatric retinal patients remains to be fully explored, but the studies noted here contribute to the limited volume of knowledge to date.

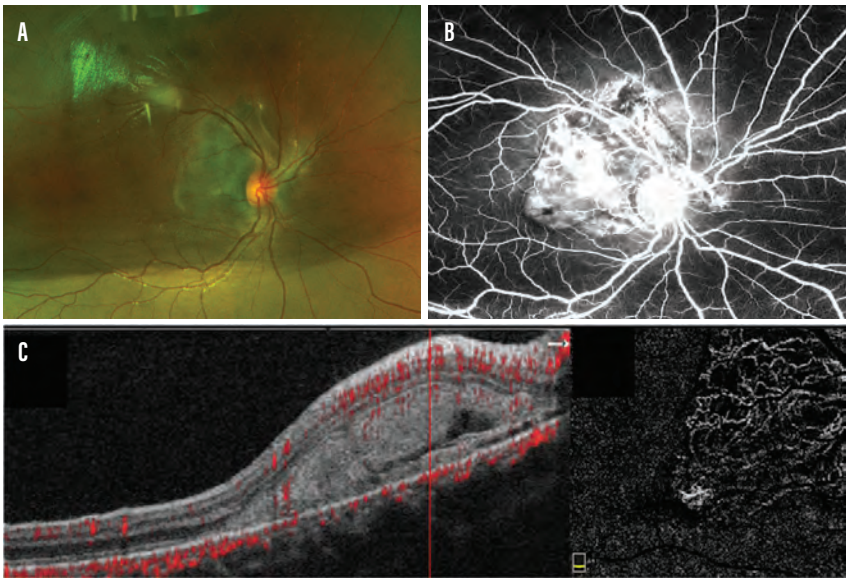

Figure 3. A large peripapillary subretinal lesion was detected in a 9-year-old patient with counting fingers vision (A). Vascularization of the lesion was noted on FA (B), and subretinal hyperreflective material was observed on OCTA (C).

CONCLUSION

Pediatric retinal imaging has become a focus of research with the development of new imaging modalities and clinical applications. Many pediatric retina specialists now have access to color fundus photography, FA, OCT, and new imaging techniques including OCTA. These novel imaging modalities have the potential to redefine pediatric retinal disease classifications and treatment algorithms and to improve patient care. ■

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CRYOTREQ: A NEW OPTION FOR RETINAL CRYOTHERAPY

According to early surgeon experience, this device could be a complete game-changer in vitreoretinal surgery.

Introduction

BY FRANK RUSELER

Cryogenic technologies in health care are not new. For many years now, cryotherapy—using extreme cold to perform cryocoagulation of human tissue—has been used in dermatology to treat skin conditions. More recently, cryotherapy techniques have been applied in general and thoracic surgery, oncology, proctology, and urology.

Cryotherapy was introduced in ophthalmology around 1933 to induce adhesive choroiditis. In the early 1960s, cryotherapy was used for intracapsular cataract removal and croypexy was used for treatment of retinal tears with or without retinal detachment.

CryoTreq (Vitreq, a BVI company), recently introduced to the market in Europe, is the first and only disposable, standalone, handheld instrument for ophthalmic cryosurgery. It does not rely on an external energy source or require maintenance, and it is not connected to a large-volume external gas cylinder. It is indicated for retinal detachment, glaucoma, cataract extraction, trichiasis, and retinopathy of prematurity.

HOW IT WORKS

Retinal indications for cryotherapy include tears and detachment where extreme cold applied on the episcleral tissues creates an adhesive scar that seals the retina against the wall of the eye. Cryotherapy, an alternative to laser photocoagulation, induces chorioretinal adhesion by using a cold metal probe rather than heat from a laser. The drawback to traditional cryotherapy is that it employs expensive and cumbersome equipment connected to a foot-controlled cryoprobe that requires time-consuming priming. Moreover, reusable cryoprobes are known to malfunction due to excess moisture accumulation after sterilization.

Cryopexy with CryoTreq is straightforward and effective. CryoTreq eliminates the complexities related to managing traditional ophthalmic cryosurgery equipment. The tip of the CryoTreq technology reaches cryogenic temperature within a few seconds of activation. Inside the handle, a sealed micro-tank holds liquid nitrous oxide. When the device is activated, the liquid evaporates and gas expands to create a tip at cryogenic temperatures. The device delivers a minimum of 15 freeze dots in the same patient.

ADVANTAGES

CryoTreq has obvious advantages over traditional cryotherapy techniques. It can be used in the OR for retinal tears and detachments and in the office for pneumatic retinopexy. Moreover, CryoTreq doesn't require any special training for handling and preparation, which is particularly advantageous in hospitals without specialized ophthalmic clinic staff. Finally, it does not require sterilization and can be disposed of at the end of the procedure.

In early experience with the device, surgeons have reported that it is reliable, and they appreciate its brief preparation and activation time. They also like that it provides an opportunity to enhance efficiency. CryoTreq is a standalone, hand-controlled, maneuverable device that does not rely on staff support to activate the footpedal.

Based on surgeons' feedback, we are convinced that CryoTreq will be a game-changer, helping ophthalmic surgeons take another step forward in patient care, especially in the vitreoretinal world. Commercialization of the device has begun in Europe, with future expansion to other major markets including the United States, Japan, Canada, and Australia.

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CryoTreq in the OR

BY STANISLAO RIZZO, MD

In certain fields of health care, standalone handheld cryoprobes have been successfully used for years. In ophthalmology, however, the lack of significant modernization in cryosurgery has made it an unattractive and inefficient procedure. About 2 years ago, I contacted Vitreq and proposed that the company look to replicate the functions of dermatological disposable standalone cryoprobes in vitreoretinal surgery, with the goal of providing patients with a better, more efficient surgery.

In my early experience with CryoTreq, I have enjoyed great function and reliability in the device, which requires only a few simple steps for use and offers the advantages of a disposable device, with higher standards in terms of hygiene and efficiency. In this article, I overview the differences between traditional cryotherapy and CryoTreq and outline the steps of the procedure.

COMPARISON

There are many differences between hand-controlled (CryoTreq) and foot-controlled (traditional) ophthalmology-specific cryotherapy devices. The new hand-controlled device is not only economically convenient, but it also decreases the organizational time

Figure 1. The CryoTreq is the first and only disposable handheld instrument for ophthalmic cryocoagulation (A,B).

Figure 2. The probe of the CryoTreq device.

and effort required of the OR staff to prepare the cryo equipment, connect the cryoprobe, ensure there is enough pressure in the gas bottle, and initiate the priming cycle. The latter step can take up to 90 seconds to complete, which negatively impacts OR efficiency.

Moreover, I have experienced malfunction of traditional cryoprobes due to blockage after resterilization. These traditional devices also take longer to defrost at the tip and have variable performance due to poor gas pressure. Foot-controlled equipment also has higher running costs for service, sterilization, and acquisition of the bottle than hand-controlled technology such as the CryoTreq. Additionally, with CryoTreq I have fewer wires on the floor and no longer need large-capacity gas cylinders in the OR.

All these considerations translate into more efficient patient flow and a safer environment when the CryoTreq is used.

ERGONOMIC DESIGN

The CryoTreq has an ergonomic design (Figure 1A). Once the button on the CryoTreq is pushed (see *Activation Procedure*), the blue activation lever is manually lifted and the micro-container is unsealed (Figure 1B). The device is now activated. As the liquid evaporates, the gas expansion creates a tip at cryogenic temperatures. The device is ready to be used in contact with the eye once the cryo-ball forms around the tip. The probe of the CryoTreq is placed on the exterior surface of the eye (Figure 2).

When the activation bottom is released, the expansion of the gas is interrupted, and the device defrosts. Any residual gas in the container is dispersed into the air.

PROCEDURAL BASICS AND SURGICAL TIPS

CryoTreq is approved for ab external procedures including retinal tear and detachment; scleral buckling with and without cryopexy or laser photocoagulation; and vitrectomy with laser photocoagulation, retinopexy, or cryopexy. It should not be used in patients who have undergone intraocular gas tamponades within the past 3 past months.

During treatment, freezing and unfreezing cycles are applied to the affected area to achieve tissue scarring and sealing. These cycles should be repeated until coagulation is visually successful. Several surgical tips can be helpful to maximize the benefits of the procedure.

Tip No. 1. Transitioning from a foot-controlled to a hand-controlled device requires patience. Familiarize yourself with the device to understand what finger is best to activate the device. This will depend on the position of the lesion you are treating.

Tip No. 2. When the activation button is pressed, the tip probe cools; when the button is released, the tip defrosts. The probe should be kept in contact with the sclera during freezing. Only when the tip is defrosted is it safe to pull it back and repeat the process if required. I always use a syringe filled with balanced saline solution to facilitate defrosting.

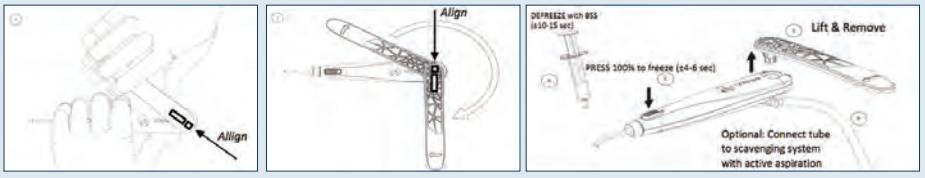
Tip No. 3. With experience, the surgeon can start to adjust the duration of each freezing cycle and the number of freezing cycles. This should coincide with the extension and location of the lesion. Complications, although rare, are typically due to inflammatory responses caused by over-freezing or freezing the nontarget tissue.

Tip No. 4. When managing retinal detachments, endolaser treatment is ineffective in the presence of subretinal fluid. Liquid perfluorocarbon (PFCL) is then used to drain the subretinal fluid, and the endolaser is applied to promote chorioretinal adhesion. In those cases, CryoTreq becomes an attractive alternative because it does not use PFCL. CryoTreq does not require chorioretinal approximation, is simple to perform, and is less expensive.

CONCLUSION

CryoTreq is a promising device that I expect to completely change the way I perform vitreoretinal surgery. It is the innovation in cryotherapy that ophthalmologists have been waiting for. ■

Activation Procedure



- Visually inspect packaging for possible damages and expiration date. Devices from previously opened or damaged packaging or devices past the expiration date must be deemed unsterile and discarded. Unpack the CryoTreq for introduction into a sterile environment *(see 1)*.
- The CryoTreq is intended to be used in a well-ventilated room with a downflow system; if unavailable, attach the hose to the exhaust of the CryoTreq and a scavenging system *(see 4)*.
- A syringe with sterile balanced saline solution at room temperature (22°C/72°F) may be used to speed up tip release after freezing *(see 6)*.
- Rotate the activation lever clockwise in a fluent motion by following the direction shown on the lever to prepare the CryoTreq; this may require a limited amount of force *(see 2)*.
- After rotating the lever over 270° and aligning stripes on the lever and the tool, the lever can be manually removed by pulling it upward *(see 3)*.
- Always check proper functioning of the CryoTreq without tissue contact to the tip of the probe. In less than 2 seconds, push the activation button while pointing the tip downward; the point of the tip should become white from the drop in temperature *(see 5)*.

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CryoTreq is currently not available in the United States

RETINAL MASSAGER: AN ADJUNCTIVE TOOL FOR MACULAR HOLE SURGERY


Its tip is used to massage the edges of the hole atraumatically to encourage closure.

BY MANISH NAGPAL, MS, DO, FRCS (EDIN), AND GAYATHRI MOHAN, MS

Macular hole surgery is one of the most common indications for vitrectomy. The gold standard procedure in the treatment of macular holes include pars plana vitrectomy, induction of posterior vitreous detachment, peeling of the internal limiting membrane (ILM), complete fluid-gas exchange, and facedown positioning postoperatively.

Reported anatomic success rates for macular hole surgery range from 93% to 98%.[1-4] By contrast, reported anatomic success rates for large macular holes range from 70% to 90%.[5,6]

Several adjuncts to the conventional procedure have been described to aid in the closure of large holes, including inverted ILM flap, free ILM flap, autologous lens capsular flap, and neurosensory retinal flap.[7-10]

In our own approach to macular hole surgery, we have been gently massaging the edges of the macular hole after ILM peeling using the tip of forceps or the edges of the vitreous cutter to help with approximation of the edges. Following fluid-air exchange, usually the holes would close or decrease in size on the table. However, forceps and cutter are not ideal instruments for this maneuver, as they have irregular edges that could be traumatic to the surface of the retina.

To facilitate our massaging technique, we have devised a new instrument, the Retinal Massager (RM, Epsilon).

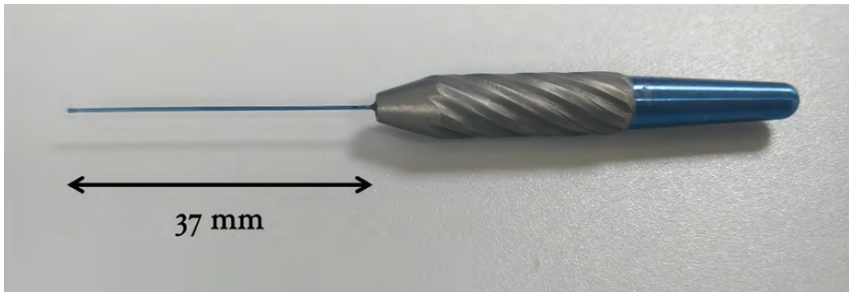


Figure 1. The Retinal Massager (RM) is a 25-gauge titanium instrument with a 37-mm shaft and a handle. The smooth bulbous tip at the end of the shaft is designed to be atraumatic to the retinal surface.

DESIGN

Designed for 25-gauge vitreous surgery, the RM has a 37-mm–long titanium shaft with a handle (Figure 1). The smooth bulbous tip at the end of the shaft is designed to be atraumatic to the retinal surface. Its shape resembles a miniature version of an external indenter. Its clinical application in macular hole surgery is to facilitate approximating the edges of the hole.

We have used the RM in treatment-naive patients with large full-thickness macular holes (>600 µm in diameter) as measured with the caliper function on OCT.

SURGICAL TECHNIQUE

The instrument is used during standard 25-gauge pars plana vitrectomy. A posterior vitreous detachment is induced using a vitreous cutter, with triamcinolone acetonide injection to enhance visualization. After the vitreous is cleared, brilliant blue G dye (Ocublue Plus, Aurolab) is injected over the macular area to stain the ILM. The stained ILM is pinched

AT A GLANCE

- The Retinal Massager (RM) is a tool for safely treating large full-thickness macular holes.
- After core vitrectomy and ILM peeling, the tool is used to massage the edges of the hole.
- The RM enhances the closure rate in large macular holes.

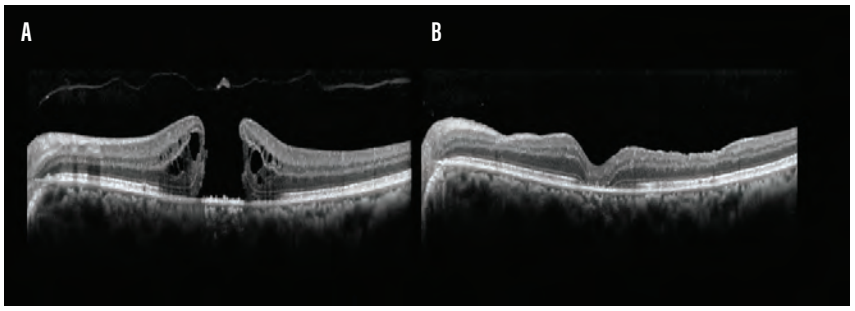


Figure 2. Idiopathic macular hole. Preoperative OCT of a 65-year-old woman shows a large full-thickness macular hole with cystoid spaces (A). At 1 month postoperative, OCT shows a type 1 closure (B).

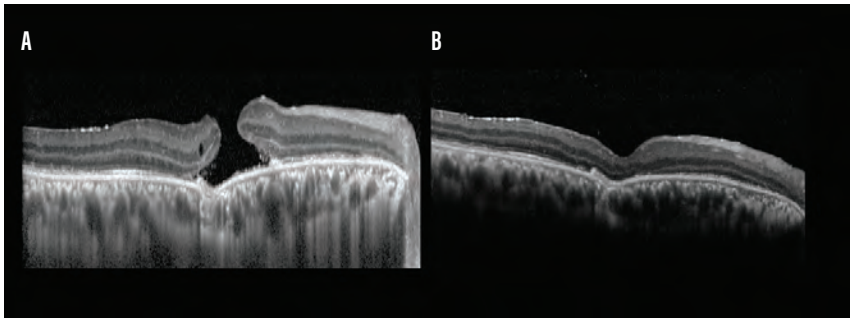
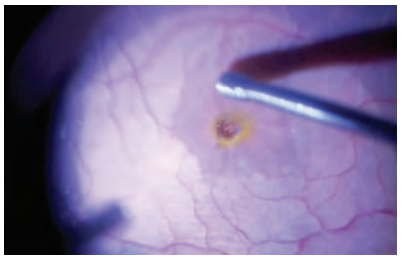


Figure 3. Traumatic macular hole. Preoperative OCT of a 40-year-old man shows a traumatic macular hole (A). At 1 month postoperative, OCT shows anatomic closure of the hole (B).

WATCH IT NOW



Macular hole surgery using the Retinal Massager.

BIT.LY/MOHAN0720

with 25-gauge end-gripping forceps (Grieshaber, Alcon) and peeled off in a circular fashion, using a pinch-and-peel technique, to approximately 2 disc diameters around the hole.

The RM is then used to gently massage the edges of the macular hole. The rounded tip of the instrument is massaged over the edges in an outside-in direction along the entire circumference of the hole. The surrounding edges of the macular hole tend to be relaxed by this maneuver, and the overall size of the hole becomes smaller.

Fluid-air exchange is performed, and the fluid is aspirated over the area of the macular hole. The hole is visibly smaller at this stage, almost a pinpoint. Peripheral retina is thoroughly screened for any residual vitreous or iatrogenic breaks. C_3F_8 gas is then injected followed by postoperative facedown positioning.

Preoperative and postoperative OCT are used to assess the anatomic outcomes of surgery, and BCVA and microperimetry are used to evaluate functional outcomes at 1 month follow-up. Anatomic closure on OCT is defined as the approximation of the edges of the hole with resolution of the subretinal cuff of fluid.

Because the maneuver involves contact with the retinal surface, we have used the MP-3 Microperimeter (Nidek) to assess changes in retinal sensitivity in areas where the massaging was done, looking for any reduction in sensitivity. Scans were obtained preoperatively and 1 month postoperatively.

SURGICAL OUTCOMES

At the time of this writing, we have used the RM 45 in patients with large full-thickness macular holes. Mean BCVA (logMAR) improved from 0.6 preoperatively to 0.4 postoperatively. Macular hole closure was observed in 93.3% (42 of 45) of patients. On OCT imaging, type 1 closure was observed at 1 month postoperative in all cases (Figures 2 and 3).

Comparing microperimetry scans, we observed that retinal sensitivity in the area of the macular hole improved following closure of the hole in all our

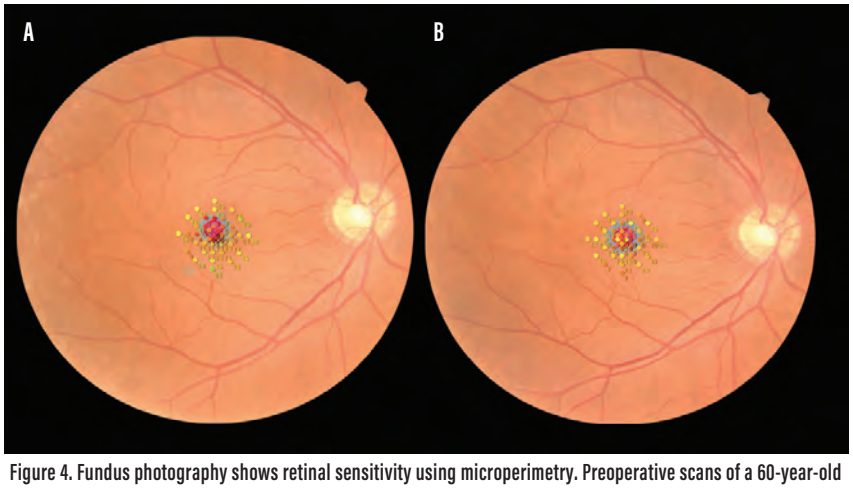


Figure 4. Fundus photography shows retinal sensitivity using microperimetry. Preoperative scans of a 60-year-old patient show reduced sensitivity in the foveal area corresponding to a macular hole. The retinal sensitivity in the parafoveal area where the RM would be used can be noted (A). At 1 month postoperative, scans show almost identical retinal sensitivity in the parafoveal area, indicating that the act of massaging did not cause detrimental effects on retinal sensitivity. Also, the retinal sensitivity in the foveal area has improved corresponding to hole closure (B).

patients. Our main focus was on the circumferential area around the hole where the RM was used, and we found that the retinal sensitivity in preoperative and postoperative scans was almost identical, indicating that the act of massaging did not have detrimental effects on retinal sensitivity (Figure 4).

CONCLUSION

Aside from macular hole surgeries, we have also used the RM in surgery for proliferative vitreoretinopathy. In these surgeries, the device aids in ironing out stiff retinal folds and helps unfold the stiff rolled-over edges of large tears (Video, bit.ly/Mohan0720).

The RM is an efficient adjunct to standard macular hole surgery to enhance anatomic and functional outcomes in surgeries for large macular holes. Postoperative retinal imaging with OCT and functional assessment with microperimetry can help to elucidate the efficacy and safety of this surgical tool and technique. ■

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(Continued from page 30)

A vs B vs C vs D) revealed that more advanced classifications had increasing 5-year risk of metastasis (3% vs 10% vs 25% vs 41%, $P < 0.001$).[8] This information highlights not only the utility of TCGA classification system, but also the influence that genetics has on tumor behavior.

CONCLUSION

Here we have presented a case of a patient with unilateral, multifocal uveal melanoma who lacked detectable mutation in *BAP-1* or presence of ocular melanocytosis. We speculate that there may be other as yet undiscovered germline or somatic mutations that could lead to multifocal uveal melanoma. ■

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ANTISEPSIS FOR INTRAVITREAL INJECTIONS DURING THE COVID-19 PANDEMIC


Application of povidone-iodine to the nares and oropharynx should be considered when high-risk patients are seen.

BY FRED Y. CHIEN, MD, AND THEODORE LENG, MD, MS

The COVID-19 pandemic has had an unprecedented impact on society, the economy, and medical practice. Medical and dental subspecialties were hit especially hard. More than 90% of dentists surveyed in the first week of April reported a reduction of 90% or more in patient volume compared to the week before.[1] Decreases in ambulatory practice visits were greater than 60% in cardiology, orthopedic surgery, gastroenterology, head and neck surgery, general surgery, urology, and pediatrics. Ophthalmology was one of the hardest hit specialties with, a 79% drop in outpatient visits.[2]

The negative impact is due directly to the highly contagious nature of the virus SARS-CoV-2. A large-scale meta-analysis of 172 observational studies including more than 25,000 patients found that physical distancing of 1 m or more and the use of masks and eye protection were associated with less infection.[3] High-contact businesses such as hotels, restaurants, airlines, and medical and dental offices that are unable to maintain 1 m or more physical distancing are the most greatly affected and will continue to be at the most financial and economic risk. Estimates from the St. Louis Federal Reserve project say that demand in these businesses could decline by 51%.[4]

A recent paper in *Cell* described at length the mode of transmission for SARS-CoV-2.[5] The nose is the dominant initial site of infection via aerosolized particles, facilitated by the high concentration of ACE2-expressing nasal ciliated cells. Microaerosol inhalation and microaspiration results in progression from the upper nasal airway to the oropharynx and finally to the alveolar cells in the lower lung surfaces. Patients at a higher risk for microaspiration and thus more severe complications from SARS-CoV-2 include the elderly, diabetic patients, and obese patients.

This model supports the widespread use of masks as a barrier to aerosol and large droplets. In the discussion in the *Cell* paper, the authors recommend complementary therapies such as nasal lavage, use of topical antivirals, and immune

AT A GLANCE

- The nose is the dominant initial site of infection with SARS-CoV-2 via aerosolized particles.
- A computational model showed transmission of respiratory droplets beyond 70 cm, even with the use of masks.
- During intravitreal injections, oropharyngeal droplet transmission poses a risk to the physician and to the patient receiving the injection.

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

MASKS ARE NOT ENOUGH. A MULTIPHASE COMPUTATIONAL FLUID DYNAMICS MODEL FOUND TRANSMISSION OF DROPLETS BEYOND 70 CM EVEN WITH THE USE OF MASKS.

modulation, in addition to the use of masks, to reduce the nasal viral load early in the disease as a means to decrease transmission.[5]

Use of nasal and oral decontamination with ethanol, chlorhexadine, and povidone-iodine (PVP-I) is receiving renewed interest during the COVID-19 pandemic.[6] Patients undergoing elective orthopedic surgery with hardware implantation who received a chlorhexidine oral rinse and nasal PVP-I as a decontamination protocol the night before surgery experienced a statistically significantly lower surgical site infection rate than those who did not.[7] Oral decontamination using oral PVP-I–based gargle is recommended by the Japanese Respiratory Society for the prevention of hospital-acquired pneumonia.

A study in 2006 showed PVP-I and ethanol to be effective in the inactivation of SARS-CoV after 2 minutes.[8] Recent trials have shown rapid inactivation times against SARS-CoV-2 of 15 seconds for PVP-I in concentrations as low as 0.5% and 30 seconds for 70% ethanol.[9] Hydrogen peroxide has not demonstrated virucidal activity against SARS-CoV-2, but it has been shown to be toxic to mucosal surfaces and oral keratinocytes.[10,11]

MASKS ARE NOT ENOUGH

One of the most common procedures in ophthalmology is the administration of intravitreal injections for conditions including wet age-related macular degeneration, proliferative diabetic retinopathy, diabetic macular edema, retinal vein occlusion, and uveitis. In 2016, approximately 5.9 million intravitreal injections were performed in the United States.

The COVID-19 pandemic provides a particularly difficult challenge to ophthalmology not only due to the close proximity required to examine the patient, but also because many of our patients are at the highest risk for severe illness from SARS-CoV-2 due to age, hypertension, diabetes, and other comorbidities.[12] Moreover, oropharyngeal droplet transmission is a factor during intravitreal injections, posing a risk not only to the physician performing the procedure but, more important, to the patient receiving the injection.

Masks are not enough. A multiphase computational fluid dynamics model found transmission of droplets beyond 70 cm even with the use of masks.[13]

Administration of 0.5% PVP-I to the nares and oropharynx should be considered in these high-risk patients. PVP-I concentrations in the range of 0.5% to 1.25% have been shown to be safe for intranasal or intraoral administration, with no adverse effects on the nasal or oral mucosa.[14] Within this PVP-I concentration range, clinical studies have demonstrated a persistent bacterial decontamination effect for at least 1.6 to 4.0 hours.[15,16]

MODIFY, ADAPT

The COVID-19 pandemic has forced many businesses to modify and adapt practices to minimize transmission of SARS-CoV-2. Dentists, dental assistants, and dental hygienists are considered at the highest risk for exposure among all professions.[17] Therefore, dental clinics are rapidly adapting to the use of oral decontamination protocols with PVP-I.[18]

Retina specialists should consider adopting similar practices. Before the COVID-19 pandemic, only 36% of retina specialists surveyed used masks during intravitreal injections.[19] Since the onset of the ongoing pandemic, the use of masks has been deemed necessary, as specified in practice guidelines from the AAO and the US Centers for Disease Control and Prevention.[20]

This practice pattern shift, with both physician and patient wearing a mask during intravitreal injections, along with the implementation of oral and nasal antisepsis as a means to reduce viral transmission, may have the additional benefit of further reducing bacterial endophthalmitis rates.

The retina specialty is one of the most innovative in medicine. We have the ability to rapidly adopt new practices and routines to optimize outcomes and minimize adverse events. Now is the time to reconsider our safety protocols for intravitreal injections. ■

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TECHNIQUES FOR SUCCESSFUL REATTACHMENT

Reconnecting ophthalmology to the larger medical world after COVID-19.

BY RAVI R. PANDIT, MD, MPH

As the national and international consequences of COVID-19 continue to unfold, ophthalmologists find themselves in a particularly unique position. Our daily work of reaffixing falling retinas, protecting ganglion cells, and salvaging traumatized eyes undoubtedly saves patients from irreversible blindness and its tragic social, economic, and physical consequences. Timely recognition of uveitis, retinal emboli, or orbital tumors may even save lives. As elective surgeries are put on hold, many ophthalmologists must continue to operate because, often, what requires our expertise simply cannot wait.

But we also now live in a world in which medical professionals and the general public alike know far more than they ever expected to know about N95 masks, ventilators, and acute respiratory distress syndrome. As the numbers of infected patients swell and health systems groan under the strain of critically ill patients, many physicians are assuming clinical responsibilities outside their usual scope of practice.[1] In areas heavily affected by the virus, ophthalmologists are being asked to work on medical floors and in emergency departments.[2] For many, that prospect is alarming.

We are primarily outpatient specialists who, in contrast to almost every other medical specialty, can provide faster and better care when we have access to office-based equipment, such as slit lamps, OCT platforms, and fundus cameras.[3] As surgical techniques have advanced, the need for inpatient surgery has diminished.[4] Accordingly, our cross-specialty collaborations have shifted from in-person interactions to templated letters autogenerated by our electronic health record systems. Ophthalmologists have gradually, perhaps inevitably, drifted away from the general medical milieu. Now, we have abruptly been yanked back into this unfamiliar world.

We now confront the reality that ophthalmologists cannot afford to be so detached from general medicine; fortunately, there are several strategies for reattaching ourselves to the medical family. (Puns absolutely intended.)

STRATEGY NO. 1. REMEMBER YOUR TRAINING

First, recognize that we are, in fact, medical doctors who went to medical school and learned about endometriosis, otitis media, and the coagulation cascade. This ethos should permeate ophthalmology training. There is a movement toward integrated ophthalmology residencies, wherein part of the intern year is dedicated to "getting up to speed" for the dedicated ophthalmology years to come.[5] After all, it is often rhetorically asked, "How many asthma exacerbations do you have to manage to be a good ophthalmologist?" In 2020, the answer may be "more than you think."

As we contemplate how to cram an ever-expanding ophthalmology knowledge base into 3 years of postgraduate training, we should remain mindful of the balance that we are physicians specializing in eyes, not simply "eye doctors." The purpose of the heart, it turns out, goes beyond perfusing the retina. With that in mind, a few seconds of extra attention to general examination of our patients might reveal a shuffling gait, psychomotor retardation, actinic keratosis, or any number of conditions amenable to early diagnosis and management.

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AS ELECTIVE SURGERIES ARE PUT ON HOLD, MANY OPHTHALMOLOGISTS MUST CONTINUE TO OPERATE BECAUSE, OFTEN, WHAT REQUIRES OUR EXPERTISE SIMPLY CANNOT WAIT.

STRATEGY NO. 2. COMMUNICATE BETTER WITH OTHER DISCIPLINES

We must also rethink how we interact with other medical specialties. Ophthalmologists are notorious for their alphabet soup vocabulary, which has served as fodder for a number of satirical articles.[6,7] In our busy clinics, abbreviations are crucial for concisely conveying important medical information. However, in the era of electronic health records, it is a simple matter of motivation to autoexpand abbreviations or include helpful smart phrases, at least for our patients for whom coordination of multispecialty care is particularly important. For example, "Macular imaging reveals early retinal changes that are concerning for hydroxychloroquine toxicity. Will coordinate with Dr. Garcia (rheumatology) to see if this can be safely discontinued," is infinitely more helpful—and respectful—than "OCT w EZ abnl, DFE mild RPE ch, d/c HCQ."

We can further address this issue by simply picking up the phone and consulting with primary care physicians, endocrinologists, and rheumatologists, much as we do with our colleagues in other ophthalmic subspecialties.

Moreover, ophthalmologists routinely educate their patients on incredibly complex topics. There is an art to precisely explaining a posterior vitreous detachment. Why not take a few minutes to do the same for our medical colleagues, be it an ad hoc conversation or the occasional webinar or dinner? We similarly stand to learn from other physicians in such interactive, interdisciplinary venues.

STRATEGY NO. 3. LOOK AT THE BIGGER PICTURE

Finally, we must also appreciate our role within the larger context of medicine. We will never be expert inpatient physicians, nor should we strive to be. We can, however, assume the mantle of keeping our sick, elderly, and vulnerable patients out of hospitals, freeing up resources for more systemically ill patients and protecting our patients from potential iatrogenic complications. In the short term, this means pushing through the growing pains as the logistics of telemedicine's use in ophthalmic disease are further clarified. By any account, a virtual visit in which the risk-benefit ratio of a penetrating keratoplasty in a functional 80-year-old vasculopathic patient with 20/30 vision in her other eye is thoroughly discussed, and unnecessary intubation avoided, is a win for the patient and the health care system.

It may behoove us to unlock our clinics after hours for the patient with a sudden visual field defect instead of directing him or her to the emergency room via ambulance, or to work in the same-day patient with a doesn't-sound-like-my-subspecialty eye problem from the primary care office across the street.

CONCLUSION

This year, 2020, was foreseen by many to be the "Year of the Ophthalmologist." (Again, pun intended.) However, it is hard to realize this vision in a world so fundamentally disrupted by COVID-19. But, as with so many other aspects of our society, this pandemic has offered an opportunity for us to introspect, transform, and grow. There is no denying that we are trained specialists who perform life-changing work. In 2020, we can bring those skills and knowledge back into the fold of the family of medicine. ■

The views and opinions expressed are those of the author and do not necessarily reflect the official policy or position of organizations with which the author may be affiliated.

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PROPOSED STRATEGIES FOR INTRAVITREAL INJECTIONS DURING THE COVID-19 PANDEMIC

Adjusting protocols for a new era in medicine.

BY ASHISH SHARMA, MD; NILESH KUMAR, MD; NIKULAA PARACHURI, MD; ROHINI SHARMA, MDS; BARBARA PAROLINI, MD; SENGUL OZDEK, MD, FEBO; BARUCH D. KUPPERMANN, MD, PHD; FRANCESCO BANDELLO, MD, FEBO; AND ANAT LOEWENSTEIN, MD, MHA

Most of the medical world (except for emergency medicine) has been shuttered during the COVID-19 pandemic, and cases continue to rise. It is expected that this situation may last for many more months until researchers find solutions for containing outbreaks and identify effective treatments.

During this period, we need to find the best possible ways to treat our patients who are at risk of vision loss if they forgo intravitreal injections. Reduction or elimination of anti-VEGF therapy could result in permanent visual disability for these patients.

Global ophthalmic authorities have provided general practice safety recommendations. However, we wish to focus on the best possible approaches in performing one of the most common retinal procedures, intravitreal injections, during this challenging time.

NEED FOR INJECTIONS

The data tell us how important intravitreal injections are to many retina patients. Approximately 2.6 million intravitreal injections of ranibizumab (Lucentis, Genentech) and aflibercept (Eylea, Regeneron) were administered in 2016.[1] That figure does not include the use of bevacizumab (Avastin, Genentech), a common practice in the United States.

The most common indications for intravitreal injections are cystoid macular edema (CME) secondary to retinal vein

AT A GLANCE

- Office visits for intravitreal injections during the COVID-19 pandemic may be necessary to preserve vision in some patients.
- Physicians must rethink pre-pandemic routines and plan accordingly.
- The authors offer measures to keep patients, physicians, and staff safe during the pandemic.

MILLIONS OF RETINA PATIENTS FROM AROUND THE WORLD WHO ARE AT RISK OF VISION LOSS SHOULD NOT BE FORGOTTEN DURING THE COVID-19 PANDEMIC. ADDITIONALLY, THE WELL-BEING OF HEALTH CARE PROVIDERS IS VERY IMPORTANT.

occlusion (RVO), center-involved diabetic macular edema (CI-DME), and neovascular or wet age-related macular degeneration (AMD).

Among these indications, treatment for wet AMD is most urgent. The natural history of RVO includes spontaneous improvement.[2] CI-DME manifests following systemic disease, and factors affecting diabetes may help to control disease activity. Further, given that diabetic patients have a higher risk of mortality from a COVID-19 infection,[3,4] the need to reduce the risk of exposure may outweigh the need to treat visual symptoms. Untreated wet AMD, however, may cause fibrosis or scarring, which can lead to permanent visual loss.

REDUCING RISK FOR PROVIDERS

Retina specialists are rightly concerned about the potential transmission of COVID-19 from patients to physicians and staff. A few strategies may help to reduce this risk.

Patient Selection

Classify patients by diagnosis. For patients who have been receiving injections for CME secondary to RVO or CI-DME, telephone communication about their general visual function may suffice. If they do not complain about a deterioration in vision since their most recent visit, counsel them that missing one or two injections is not likely to cause permanent harm and that deferring follow-up is safe.

The timing of deferred follow-up will vary based on clinical judgment, local transmission data, and recommendations from local authorities. It is important to remember that deferral may be safe for most patients but not for everyone.

Patients with wet AMD who have been undergoing regular injection schedules such as monthly or treat-and-extend (T&E) regimens should visit the hospital and meet the clinician for evaluation and, if needed, injection. Indeed, a visual acuity–based T&E strategy may be the safest regimen during this time. Monocular patients should receive timely injections irrespective of etiology. A telephone conversation to acquire a health update (eg, presence of flu-like symptoms, contact history with COVID-19 patients in the past 2 weeks, and travel history) should occur before confirming the appointment for injection.

Abbreviated Clinical Routine

When a patient who needs an intravitreal injection visits the clinic, he or she should enter the clinic alone, and the accompanying person should wait outside unless his or her presence is necessary. Patient reception—from entry to meeting the clinicians to exit—should be as quick as possible. To make this happen, regular evaluations with fundus photography, OCT, and formal detailed vision testing should be avoided. The clinician will have a record of such data from the patient's previous visit.

A dilated examination may also be postponed. Clinicians will receive adequate information about changes to a patient's visual function from a quick conversation with the patient. If anatomic data are needed, a quick, undilated central fundus examination and OCT imaging with a no-touch technique can be performed. However, the patient's visual assessment should be the primary driver for scheduling a follow-up visit.

Protection

There is a chance of COVID-19 transmission from an asymptomatic patient to a clinician and vice versa. Patients and clinicians need to wear masks. If possible, clinicians should protect their eyes with protective glasses or face shields. Clinicians can follow their regular injection protocol with standard precautions as long as they wear a mask (and, if possible, eye protection). Complete personal protective equipment (PPE) may not be warranted when managing asymptomatic patients.

The use of an N95 mask in lieu of a surgical mask and use of complete PPE should be weighed against PPE availability. In general, complete PPE should be reserved for managing high-risk patients. If available, an N95 mask may be used by the clinician and a surgical mask may be used by the patient.

A slit-lamp shield should be in place for patients who absolutely require slit-lamp examination during injection visits.

If needed, a quick intravitreal injection with minimal staff interaction can be performed in a dedicated outpatient injection room. This is common in Western nations. However, there are many countries, such as India, where

injections are predominantly given in an OR.[5] We encourage instead the use of a sterile injection room. This obviates the need for patients' change of clothing and minimizes exposure of the OR and staff. Disinfecting a dedicated procedure room is easier than disinfecting an OR. Furthermore, bilateral injections on the same day might be of help during this time.

Exit Instructions

Patients receiving injections should be instructed to report flu-like symptoms that arise in the ensuing 2 to 3 weeks. This helps with contact tracing if the patient tests positive for COVID-19 and reduces the risk of further transmission in the clinic. Patients with flu-like symptoms should undergo a different protocol, which should include extending treatment during recovery.

HELPING PATIENTS IN A TIME OF CRISIS

Millions of retina patients from around the world who are at risk of vision loss should not be forgotten during the COVID-19 pandemic. Additionally, the well-being of health care providers is very important.

The strategies suggested in this article are not derived from evidence-based medicine. Rather, they synthesize key points recommended by scientific authorities such as the AAO, the American Society of Retina Specialists, the Royal Academy of Ophthalmologists, and the All India Ophthalmology Society.[6-9] These recommendations are also based on the experience of clinicians who have been involved in the clinical care of retina patients for many years.

The authors wish to emphasize that the COVID-19 pandemic is a dynamic situation. It is impossible to suggest something right for all situations, and best practices may vary with time and according to region, state, and country. It is of utmost importance to follow regular updates from the authorities and to act upon them.

The exceptional situation we face calls on ophthalmologists to rely on clinical judgment rather than first-level evidence. With the suggestions put forth here, we believe that we are equipped to do just that in the COVID-19 era.[10] ■

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APPROACHING THE FIRST RETINA FELLOWSHIP APPLICATION CYCLE OF THE COVID-19 ERA


Will the use of virtual interviews change the application process permanently?

BY MICHAEL VENINCASA, MD, AND JAYANTH SRIDHAR, MD

Each year, a growing number of ophthalmologists seeks fellowship subspecialization in order to obtain new skills and to provide better and more specialized care to patients.[1] Recent surveys have found that most graduating ophthalmology residents in the United States and Canada (65% and 63%, respectively) plan to pursue a fellowship—double the numbers from the early 2000s.[2-4]

As the number of fellowship applicants continues to grow, the application process is rising in competitiveness. One of the most important aspects of the application process, according to fellowship program directors, is the interview.[4] Studies have highlighted the strengths and weaknesses of the current standard application process and, in the case of the ophthalmology residency match, have found that applicants desire improvements in the interview scheduling process, including the possibility to conduct videoconference interviews (VCIs).[5]

With the emergence of SARS-CoV-2, widespread changes are occurring in ophthalmology. Ophthalmologists are moving toward offering more telehealth medicine, surgical cases are being delayed or cancelled for the well-being of patients and providers, and the American Board of Ophthalmology is moving to a Virtual Oral Examination for 2020.

Such changes are not confined to ophthalmology. All of society is performing social distancing that will likely be required for years.[6] Although the virus may necessitate a temporary move toward more use of VCIs, the emergence of this option presents an opportunity for permanent, meaningful improvements to be made to the application process.

MAKING IT WORK

During the COVID-19 era, the most apparent need for change in the application process is social distancing. To avoid the requirement for cross-country travel and face-to-face contact, use of VCIs will likely play an important role in the 2020-2021 application cycle.

At least for residency programs, the use of VCIs does not appear to affect the ability of the program to evaluate a candidate.[7,8] Learners seem to perform just as well whether they were selected by VCI or in-person interview,[9] although the applicant's perception of his or her subjective fit into a program is an important factor in decision-making.[5,7]

With a VCI, there is a loss of opportunity to gather subjective impressions of a program. Participants can't tour the program's facilities, observe the attending-fellows dynamic, or explore the city where they will potentially live and work.

When designing a virtual interview day, programs must strive to mimic the process of an in-person interview as closely as possible.[8] Some elements of the socialization that takes place during a standard in-person interview day may be able to be digitized. Between interviews, for example, applicants could be invited to video chat rooms where they could speak with other applicants and with current fellows and attendings. This would give the applicants opportunities to ask important questions that might not have come up during the interview itself.

Programs could also provide applicants with answers to frequently asked questions (FAQs), including descriptions of fellowship structure and expectations, surgical numbers, didactic and research opportunities, call responsibilities, and city life.

Additionally, lectures that are normally delivered as part of an interview day could be digitized and made available on the program's website. In fact, if these lectures and FAQs were made available on the program's website year-round, applicants would be able to use this information when choosing programs. In turn, applicants might be more selective when sending applications, and this might help to relieve some of the administrative burden that programs may incur because of these changes.[5]

A move toward VCIs could also ease the financial burden on applicants. Interview-related travel—including cross-country flights, hotel stays, food, and other expenses—make up a large portion of overall match-related expenses.[5] By offering VCIs that can be completed in one's home, institutions could largely eliminate these travel expenses. Applicants would not be faced with inflated last-minute airline ticket costs or change fees when an interview itinerary must be modified.

LOGISTICAL ISSUES

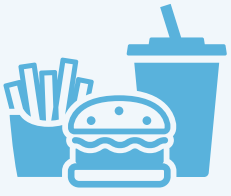
Use of VCIs could also lead to improvements in interview logistics. In residency matches, one of the most significant barriers to attending an interview has been navigating issues with dates and locations.[5] Instead of being forced to take a red-eye flight to interviews on opposite sides of the country on back-to-back days, with VCIs, an applicant could perform both interviews from the same location. He or she could therefore be well-rested and functioning closer to top form.

Interview timing could also be made more flexible for applicants with scheduling conflicts. Although it would be impossible to attend in-person interviews on the East and West Coasts of the United States on the same day, use of VCIs could allow interviews to be arranged at nontraditional times (eg, in the evening) to leave time for interviews with other programs or professional obligations during the day.

The Finances of Ophthalmology Residency Interviews

Retina fellowship interviews are not the only expensive task in the education of an ophthalmologist. Interviewing for residency incurs costs, too. In a 2020 study of costs associated with ophthalmology residency interviews, Venincasa et al[1] found the following:

Per interview, applicants estimated they spent:



< $50 on food

$101 to $201
on housing

$201 to $301
on transportation

In all, applicants estimate they spent **$5,704** (standard deviation $2,831) during the interview process.

Among applicants who had to acquire other sources of funding to pay for residency interview costs, approximately:

55% turned
to family support

26% took out
more loans

14% relied
on credit cards

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DOWNSIDES?

Despite the relative ease of interviewing and the significant financial and logistical benefits for some applicants with VCIs, the process may not be without downsides.

In the current system, applicants are often forced to cancel one or more

interviews due to any number of reasons. This newly freed interview slot is then generally offered to another applicant for a second-round invitation. With VCI attendance less restricted by travel, applicants may be less likely to require cancellation of an interview appointment. Also, because the marginal cost of attending an additional VCI (ie, the applicant's time) is lower than for an in-person interview (ie, the applicant's time plus the costs of lodging and transportation), applicants may aim to attend more interviews than they could previously. Therefore, if interview appointments are no longer being cancelled and offered to other applicants, this new system may hurt less-competitive applicants, and the process could become even more competitive.

To combat this, it is possible that fellowship programs will interview a larger number of applicants, although this would increase administrative costs. With FAQ information available on programs' websites, applicants may be able to be more selective regarding programs to which they apply,[5] but changes to match guidelines may be required as these trends are uncovered.

A VOLUNTARY OPTION

Because an applicant's sense of subjective fit is important in decision-making,[5,7] programs may wish to offer in-person interviews or tours during the current era with health-protective measures in place. If an applicant attends an in-person tour, the financial benefit of a VCI is virtually eliminated.[10] Therefore, during the COVID-19 era, when attending an in-person session means incurring risks to the health of the applicant and to those in the program, it will be important to ensure that attending an in-person session is completely voluntary.

Applicants should be evaluated similarly regardless of the type of interview they choose. In-person tours should not be perceived as more favorable, but rather as a voluntary opportunity for applicants to learn information for use in their decision. One way to ensure this would be to require earlier rank list finalization from programs than from applicants, and to hold these second-look tours in the interim.

CONCLUSION

Although no one is sure exactly what shape the fellowship interview trail will ultimately take, changes will surely be required for 2020-21 and likely beyond. From crisis can come opportunity. By preparing early, we may be able to convert temporary social distancing measures into permanent improvements in the application process. ■

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STRATEGIES FOR OPHTHALMOLOGIC SCREENING OF NEONATES DURING PANDEMIC

Recommendations for practitioner and patient safety are rapidly evolving; here is an update on current guidance.

BY MARÍA A. MARTÍNEZ-CASTELLANOS, MD; JUDITH A. ESPINOZA-NAVARRO, MD; LISSETH CHINCHILLA, MD; HEBER GALARZA, MD; AND PAULINA RAMIREZ-NERIA, MD

Retinopathy of prematurity (ROP) is a time-sensitive, blinding eye condition of premature neonates who may require regular retinal examinations over many weeks and in some cases may require urgent treatment. Preterm retinopathy presents as an emergent pathology for which diagnosis and treatment cannot be postponed. The AAO has listed it as an urgent and emergent ophthalmic procedure.[1]

Little is known about the perinatal effects of SARS-CoV-2.[2] Based on reports available at the time of this writing, newborn infants appear to be less affected by COVID-19 than adults.[3,4] Current knowledge on neonatal SARS-CoV-2 infection is limited. Neonates have underdeveloped immune systems, and they are considered susceptible to contracting the virus.

Neonates might acquire infection through close contact with virus-infected patients or virus carriers. Current case studies suggest no evidence that COVID-19 transmission occurs from mother to neonate in utero or via breastmilk.[5-8] However, case studies are limited, so caution must be taken.

Caring for preterm infants or neonates is on the list of aerosol generation procedures. The relevant aspects for ophthalmology include noninvasive ventilation (ie, use of continuous positive airway pressure and laryngeal masks), high frequency oscillating ventilation, and high-flow nasal oxygen.[9] When a child is crying, the respiratory inspiration-expiration ratio changes due to the shortening of inspiration and prolongation of expiration, increasing by 255% compared with quiet ventilation.[10]

To make diagnoses, our specialty strongly relies on physical examination performed at a short distance from the patient. The US Centers for Disease Control and Prevention

AT A GLANCE

- Little is known about the effects of SARS-CoV-2 in perinatal populations.
- Neonates who requires ophthalmic examination present a unique disease transmission dynamic.
- Transmission risk in this population may be mitigated by following a strict set of procedures.

REUSABLE LID SPECULUMS AND SCLERAL DEPRESSORS ARE CONSIDERED SEMICRITICAL ITEMS, AS THEY COME IN DIRECT CONTACT WITH TEARS AND CONJUNCTIVA. THEY REQUIRE CLEANING AND HIGH-LEVEL DISINFECTION OR STERILIZATION.

defines close contact as being approximately 2 m from a patient for a prolonged duration. Any contact longer than 1 to 2 minutes of exposure is considered prolonged until more is known about transmission risks.

Hence, the close proximity between ophthalmologists and premature babies under ventilation or crying during indirect or direct ophthalmoscopy and portable slit-lamp examination may pose a risk of cross-infection in health care providers and patients.[11,12]

The evidence so far indicates that conjunctival secretions and tears from patients with SARS-CoV-2 infection can contain viral RNA. Health care workers should assume that ocular fluids from all patients are potentially infectious.[1]

SCREENING GUIDANCE

Equipment Cleaning and Disinfection

For in-office and in-hospital exams, diagnostic equipment and instruments should be cleaned and disinfected between patients. Disposable gloves should be worn and discarded after devices are reprocessed. Examination tables and surfaces in contact with patients should be disinfected. Recommended disinfectants include diluted household bleach (1,000 ppm) and 70% alcohol solution.[13-15]

Binocular indirect ophthalmoscopes (BIO) and condensing lenses are not in direct contact with the skin or conjunctiva but are exposed to aerosolized particles. Manufacturers' instructions for cleaning and disinfection should be observed; most recommendations suggest using the same household bleach and alcohol solutions used for surfaces.[15]

BIO. Wipe surfaces with a soft cotton cloth dampened in soapy water or 70% alcohol solution. Avoid cloths that are excessively moist.

BIO lenses. Clean lens surfaces using a soft cotton cloth and mild detergent. Use clockwise movements to prevent loosening of the ring. For disinfection, 5,000 ppm sodium hypochlorite solution can be used. Soak the lens for 10 to 25 minutes, rinse thoroughly, and dry with a soft cotton cloth.

We do not recommend the use of direct ophthalmoscopes or portable slit lamps.

Retcam (Optos). The lens piece must be cleaned immediately after patient contact; the lens surface can be wiped with a soft tissue and then disinfected with a soft cloth saturated with 70% isopropyl alcohol, rinsed, and dried. Only the 4 mm distal part of the handpiece can be immersed. The rest of the system can be cleaned and disinfected at the end of the session with a soft soap-and-water solution and 5,000 ppm chlorine dilution.

Reusable lid speculums and scleral depressors are considered semicritical items, as they come in direct contact with tears and conjunctiva. They require cleaning and high-level disinfection or sterilization. Use of sterile disposable speculums and depressors is preferred. Disinfection with 70% isopropyl alcohol has failed to eliminate adenoviruses and bacteria, but it is effective against SARS-CoV-2; this can therefore be considered in units where sequential exams are performed with reusable metallic speculums.[13,16-18]

PROCEDURES FOR PERSONAL PROTECTIVE EQUIPMENT

Certain items of personal protective equipment (PPE), donned and doffed in a prescribed order, are necessary for protection from contact and droplets.

Putting on PPE

Perform hand hygiene with an alcohol-based hand rub, if available, or with soap and water.

Put on a long-sleeve gown. Gowns are used in addition to gloves if there is risk of fluids or blood from the patient splashing onto the health care worker's body. The same gown can be used when providing care to more than one patient, but only if those patients are in a cohort area and only if the gown does not have direct contact with a patient.

Plastic aprons should be used in addition to gowns if the material of the gown is not fluid-repellent and the task to be performed may result in splashes onto the health care worker's body.

Put on the appropriate mask. Wear a respirator mask when performing aerosol-generating procedures: N95, FFP2, FFP3, or equivalent.

Put on eye protection. Use a face shield or goggles. A

face shield can be attached with Velcro to the BIO or can be attached upside-down to the neck of the ophthalmologist.

Put on gloves. Ensure that gloves are placed over the cuff of the gown.[19,20]

Taking Off PPE

Ensure that infectious waste containers are available for safe disposal of PPE. Separate containers should be available for reusable items.

Remove gloves. Dispose of gloves in a proper receptacle.

Remove the gown. Ensure that the gown is pulled away from the body during removal and that clothing does not become contaminated. Dispose of the gown safely.

Perform hand hygiene. With an alcohol-based hand rub, rub the hands for 20 to 30 seconds. With soap and water, wash the hands for 40 to 60 seconds.

Remove eye protection. Remove the face shield and/or goggles.

Remove the mask. Ensure that you are taking the mask off by holding the straps; avoid touching the mask.

Perform hand hygiene again. Repeat the regimen above (ie, for alcohol-based options, rub hands for 20 to 30 seconds, for soap and water–based options, wash hands for 40 to 60 seconds).[21]

ENVIRONMENTAL CONTROLS

We suggest these steps to control the environmental milieu.

Screen the neonate through the closed incubator, as it is translucent. If the neonate is not in an incubator, we suggest the use of an acrylic box similar to the one used by anesthesiologists to intubate patients.

Limit the time spent with the patient and consider whether ophthalmic investigations—such as performing ocular imaging rather than physical exploration—are crucial to the decision-making process.

Regarding treatment, we suggest **administering antiangiogenic therapy under topical anesthesia,** rather than laser application, to limit time exposure.

To avoid contact with the patient's parents, **a teleconference can be conducted** to discuss the findings and treatment, if needed, rather than a face-to-face talk.

STAY TUNED FOR UPDATES

This article reflects our current knowledge regarding neonatal COVID-19. Because the outbreak and related information are changing rapidly, we highly recommend continuing to watch for updates. ■

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EFFECTS OF COVID-19 ON RETINA PRACTICES AND PATIENTS

A survey found that delays in care have been related to poor visual outcomes in some patients.

BY EROL ERI VERTER, MD, MS; PATRICK COADY, MD, MBA; DEVEN HUANG; AND JOHN J. HUANG, MD, MBA, CPE

COVID-19 has caused tremendous disruption to daily living as we knew it. As the fear of contracting the viral infection grew and stay-at-home orders were implemented, many patients found themselves in a conundrum: Do I try to see my doctor now or wait until the peak comes down?

Telehealth has been a saving grace for some providers, mainly in triaging patients. However, it is less than ideal, especially for patients who require immediate surgical attention or continued maintenance therapy.[1,2] We have seen reports of major coronary ischemic events or strokes occurring in patients who were afraid to call 911 or come to the hospital. Cancer patients who were scheduled to undergo resection of solid tumors have had their surgeries postponed, risking progression of their conditions. New concerns grew for patients needing bone marrow transplants who would require stays in an intensive care unit in a resource-constrained system.[2-4]

Delays in care for ophthalmic conditions have also caused detrimental results among our own patients. Following advice from the US Surgeon General and the Centers for Disease Control and Prevention, in March the AAO recommended cessation of care for nonurgent ophthalmic issues.[5]

In the field of retina, questions arose: Should patients come in for their routine intravitreal injections? Can we delay treatment for chronic diseases such as diabetic macular edema (DME) or wet age-related macular degeneration (AMD)?

AT A GLANCE

- Although telehealth has been helpful during the pandemic, it is less than ideal for patients who require continued maintenance therapy.
- Despite retina care being considered an essential service, retina practitioners responding to a survey in May and June said their volume had dropped to as low as 40% of pre-pandemic levels.
- Many patients with AMD, DME, and RVO delayed their intravitreal injections during the pandemic, leading in some cases to permanent vision loss.

Seeking to understand the impact of COVID-19 on retina practices and on patients with delayed maintenance intravitreal injections, we conducted a survey. Here we report some of the results of that survey.

METHODS

A web-based survey was sent to members of the American Society of Retina Specialists. Distribution was achieved via mass email. The survey consisted of 22 items, including questions regarding institution, demographics, location and type of practice, and the effect of COVID-19 on patients whose treatment for wet AMD, diabetic retinopathy (DR), or retinal vein occlusion (RVO) was delayed.

RESULTS

Demographic

From May 16 to May 23, 139 practicing retinal specialists responded to the survey. Of the respondents, 84% (117/139) were from United States. Among the US respondents, a plurality were from the Northeast (36/117; 31%).

There were similar numbers of participants from urban (71/139; 51%) and suburban (66/139; 49%) locations. A plurality were from retina-only practices (53/139; 38%). Other practice situations included multispecialty ophthalmology practices (29/139; 21%), academia (26/139; 19%), solo retina practices (24/139; 17%), and private equity–owned retina practices (8/139, 6%).

A plurality of the respondents practiced in cities where there was a moderate amount of hospitalization due to COVID-19 (58/139; 42%).

Clinical Volume Impact

Retina practices were deemed essential services and thus were kept open during the pandemic. However, many saw a decrease in clinical volume. Asked about how the pandemic affected practice volume, 31% of respondents said their practice volume was between 40% and 60% compared with pre-pandemic volume; 28% said volume was 20% to 40% compared to pre-pandemic volume; and 15% said volume was between 5% and 20% of pre-pandemic volume. A small percentage of practices (3%) said they did not see a decline in their clinical volume (Figure 1).

Most respondents said they believed that their drop in clinical volume was due either to patients' (46%) or families' (35%) fear of getting sick. Other reasons cited included lack of transportation (10%) and lack of personal protective equipment (5%).

Wet AMD Impact

Survey respondents said they believed that 48% of wet AMD patients experienced delays of intravitreal injections due to the pandemic. Of the patients experiencing delays, 43% were delayed by 2 to 4 weeks, 23% by 4 to 6 weeks, 15% by 6 to 8 weeks, and 19% were lost to follow-up.

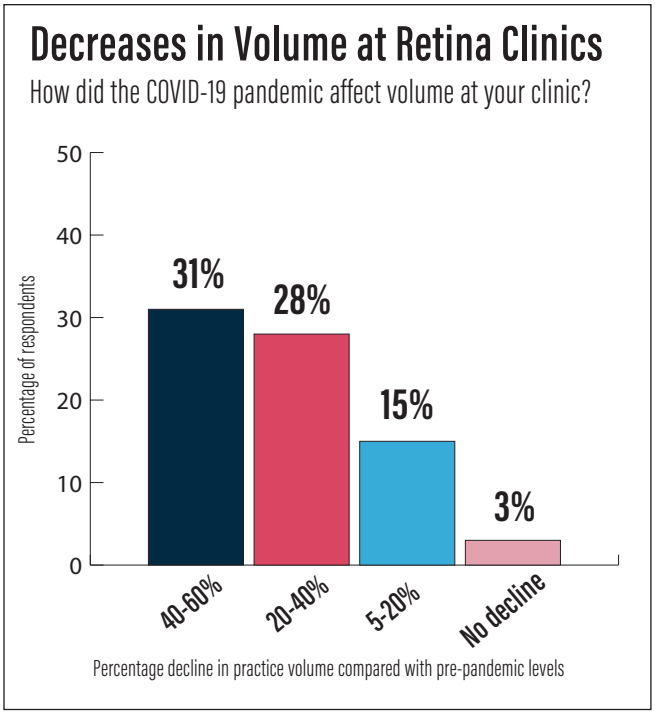

Figure 1. More than half of retina clinics reported that patient volume had fallen by at least 20%.

Patients with longer delays had worse visual outcomes, according to the survey respondents. Survey respondents said that some degree of permanent vision loss was noted in 14% of patients with injection delays of 2 to 4 weeks, in 27% of patients with delays of 4 to 6 weeks, and in 42% in those with delays of 6 to 8 weeks. Survey takers said that 13% of patients who delayed their injections by 6 to 8 weeks had no visual recovery potential.

DME Impact

Most of the respondents believed that approximately 20% to 40% of all diabetic patients presented with worsening a1c levels during the COVID-19 pandemic, and most respondents reported that up to 20% of all diabetic patients reported with weight increases of at least 5 pounds.

Survey respondents said that approximately 55% of DME patients delayed their visits (Figure 2). Of the patients who had delays, 38% were delayed by 2 to 4 weeks, 21% by 4 to 6 weeks, 21% by 6 to 8 weeks, and 20% were lost to follow-up.

Survey respondents said 12% of all their DR and DME patient delayed care by 6 to 8 weeks. Respondents anticipated no visual recovery potential in approximately 7% of patients who delayed injections by at least 6 weeks.

RVO Impact

Respondents estimated that 49% of RVO patients had

DME Patients, Delays in Treatment, and Permanent Vision Loss

Respondents estimated that patients with DME who delayed their injections saw permanent vision loss.

Delays of...	...led to vision loss in _ of patients.
2 to 4 weeks	10%
4 to 6 weeks	18%
6 to 8 weeks	22%

Figure 2. In patients with DME, higher estimates of permanent visual loss correlated with longer duration of delayed treatment.

delayed their visits and injections. Of the delayed group, 39% were delayed by 2 to 4 weeks, 23% by 4 to 6 weeks, 14% by 6 to 8 weeks, and 24% were lost to follow-up.

Again, those with longer delays had worse visual outcomes. Permanent vision loss was estimated to occur in 12% of patients with 2 to 4 weeks' injection delay, 20% in those with 4 to 6 weeks' delay, and 27% in those with 6 to 8 weeks' delay. Survey takers said they believed that 6% of patients who delayed their injections by 6 to 8 weeks had no visual recovery potential.

DISCUSSION

Our survey demonstrated that many retina specialists saw a decline in clinical volume during the pandemic. The reasons for delaying care were many, but the main factor was fear of becoming infected with SARS-CoV-2. Most survey respondents were optimistic in terms of clinical volume recovery and said they believed that their volume would return to pre-pandemic baseline within 1 year. Only 6% said they believed the decline would be permanent.

Many patients with wet AMD, DME, and RVO who delayed their intravitreal injection regimens experienced worsening vision, according to respondents. As would be expected, patients who were delayed the longest had the highest incidence of permanent vision loss with no potential for recovery.

Most respondents (82%) said they would continue in their current practice, and 12% said they might consider earlier retirement. A minority of the responding retina specialists said they would consider taking a job in a private equity–owned retina practice.

The impact of COVID-19 has not been limited only to patients exposed to the virus.[2,3] The economic, educational, medical, and mental health consequences of the COVID-19 pandemic are slowly being recognized by society. In our retina community, fear of COVID-19 has led patients to delay their treatments for wet AMD, DME, and RVO. These delays in treatment have had a substantial impact on retina practices around this country and around the world.

As this survey has pointed out, many of our patients now face increased morbidity and permanent damage to their vision. This survey demonstrates the importance of timely treatment for wet AMD, DME, and RVO, even in the era of COVID-19. The new normal for both patients and retina specialists will be to continue timely treatment while taking precautions by wearing proper personal protective equipment and practicing social distancing in the clinic setting.[6]

We hope that the information generated by this survey will be helpful for patients and retina specialists as, at the time of this writing, we are seeing a resurgence in the rate of COVID-19 infections around the United States as communities begin to ease restrictions related to COVID-19. ■

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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 mid-July.

GOING VIRTUAL

DUKE FELLOWS AVS
Duke Eye Center
Three Streaming Dates:
- September 24, 2020
- October 8, 2020
- October 22, 2020

More Information at: Visit MedConfs.com

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

AAO ANNUAL MEETING: RETINA SUBSPECIALTY DAY
November 13-14, 2020 (tentative)
More Information at: www.aao.org/annual-meeting/education/retina

AAO ANNUAL MEETING
November 14-17, 2020 (tentative)
More Information at: www.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

RETINA FELLOWS FORUM
Chicago, Illinois
December 4-5, 2020
More Information at: Visit MedConfs.com

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

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

RESCHEDULED

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

NEED UP-TO-THE MINUTE UPDATES?

For the latest on meetings in all of eye care, visit **Eyewire.news/events.**

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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