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eyetube

What's in the Retina Pipeline?

Tracking the treatments of tomorrow.

THE LATEST FINDINGS FROM AMD TREATMENT TRIALS

A LOOK AT FUTURE THERAPEUTICS FOR DIABETIC RETINOPATHY

THE PROMISE OF SUSTAINED-RELEASE POLYMER TECHNOLOGIES

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.

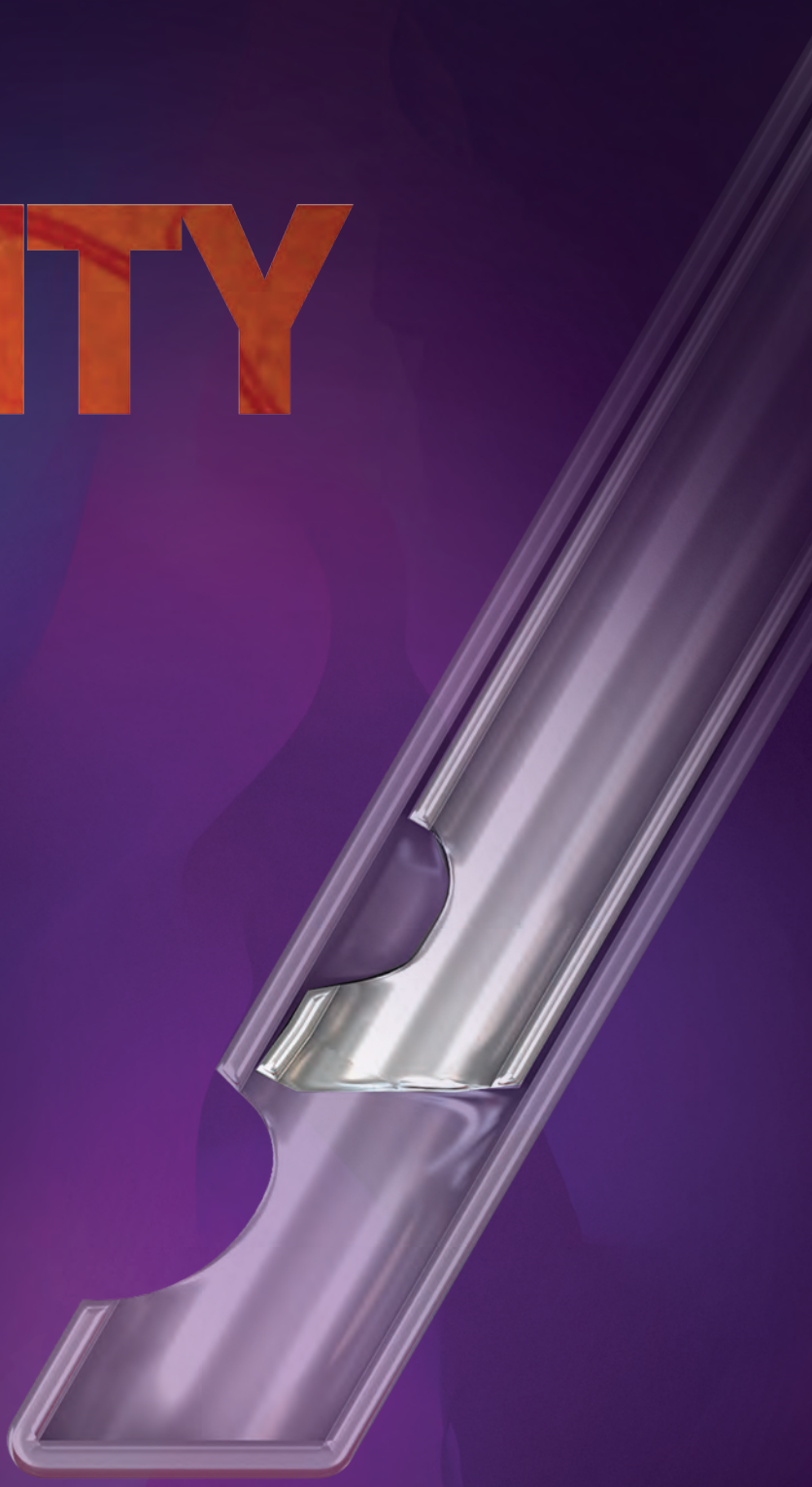
Reference: 1. Data on File. Alcon Laboratories Inc; May 2018. **2.** Data on File. Alcon Laboratories Inc; September 2017.

Alcon

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

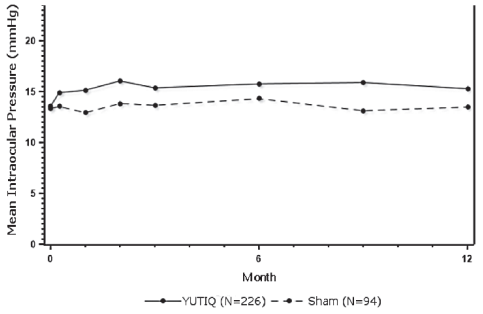
Ocular		
ADVERSE REACTIONS	**YUTIQ (N=226 Eyes) n (%)**	**Sham Injection (N=94 Eyes) n (%)**
Vitreous Hemorrhage	4 (2%)	0
Iridocyclitis	3 (1%)	7 (7%)
Eye Inflammation	3 (1%)	2 (2%)
Choroiditis	3 (1%)	1 (1%)
Eye Irritation	3 (1%)	1 (1%)
Visual Field Defect	3 (1%)	0
Lacrimation Increased	3 (1%)	0
Non-ocular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

RECALIBRATING ...


As we write this editorial for the last issue of *Retina Today* for 2020, we can't help but look back on the unprecedented year we've all experienced. It started out like any other year: we were traveling to meetings, booking surgeries, accepting invitations to lecture, writing our editorial for the January/February issue, and offering input on topics and authors as we planned for the March issue. By the time we began putting together our April issue, the novel coronavirus had fully made itself known, and from then until our September issue we dedicated much of each issue to topics related to both retina and COVID-19.

The pandemic is far from over—we all know that. We also know that a vaccine seems to be on the horizon, but as retina specialists we can't help with that. So we'll let the epidemiologists and scientists diligently work on that. In the meantime, we will do what we do best and cover timely topics, including COVID-19, in *Retina Today*.

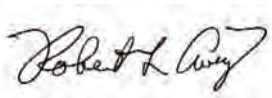
In this issue, we take a look at the retina pipeline, specifically early phase 1 and 2 studies exploring novel targets in the treatment of diabetic macular edema and AMD, later-stage trials for AMD, therapeutics for diabetic retinopathy, and extended-release polymer technologies. There are so many new agents, modalities, and technologies in clinical trials for the various conditions we treat, it's a refreshing reminder of the positive things happening in the world.

In addition, this issue contains ongoing Aspen Retinal Detachment Society coverage; a thought-provoking article on the importance of long-term inflammation control for patients with uveitis by Robert C. Wang, MD; a fascinating case of an extramacular dome-shaped elevation referred for suspicion of circumscribed choroidal hemangioma; an exploration of how to build networks to screen for retinal disease in underserved areas; and an article by a group of doctors from Portugal who discuss how OCT angiography can reveal early changes in hydroxychloroquine therapy.

Also, be sure to take in the beauty of the images in this issue's Visually Speaking column on page 56, where Sham Talati, MBBS, DO; Manish Nagpal, MBBS, MS, FRCS; and Navneet Mehrotra, MBBS, DNB, FRF, share the case of a patient with a choroidal mass. We've also brought back our 5Q column, and in this issue you'll get to know more about *Retina Today* contributor Brian C. Joondeph, MD, MPS, FACS.

As we close the book on 2020, we wish you all good health and happiness, and we look forward to seeing you in 2021! ■

ALLEN C. HO, MD
CHIEF MEDICAL EDITOR



ROBERT L. AVERY, MD
ASSOCIATE MEDICAL EDITOR

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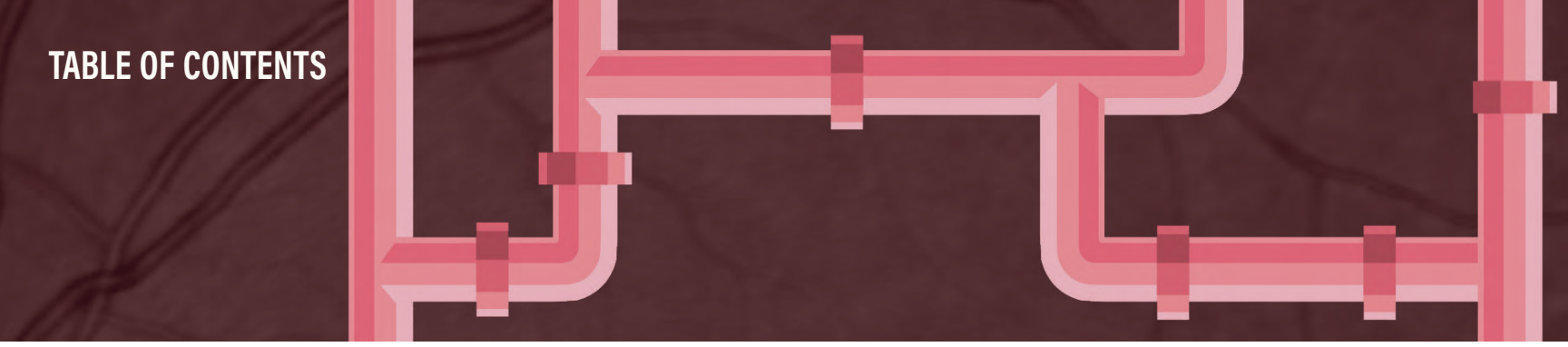

Cover image credit: ©iStockphoto.com

What's in the Retina Pipeline?

DEPARTMENTS

UP FRONT

MEETING MINUTES

IMAGING

MEDICAL RETINA

OCULAR ONCOLOGY

GLOBAL PERSPECTIVES

SPECIAL REPORTS

VISUALLY SPEAKING

IN THE BACK

DORC

FDA-approved TissueBlue™ is Ready for You.

Introducing

TissueBlue™

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The ONLY FDA-approved selective stain for the ILM. Easy open-and-inject application from a pre-filled, sterile syringe.

CONFIDENCE OF SUPERIOR PURITY[1] – FDA-approved, pharmaceutical-grade dye.

CONSISTENCY & CONVENIENCE – Pre-filled, sterile syringe eliminates need to mix or source via compounding pharmacies.

PROVEN SAFETY* – Trusted for ILM staining in over 350,000[2] procedures worldwide.

Confidence. Consistency. Convenience.

Visit **tissueblue.com** to learn more, **request a sample**†, and receive further updates.

* Marketed as ILM Blue Outside US since 2010.
† Sample available to registered US physicians only. Samples subject to availability.

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

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

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

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

WHO IS TISSUEBLUE FOR? TISSUEBLUE™ is for use in patients who, at the recommendation of their eye doctor or ophthalmic surgeon, could benefit from use of the product when treating vitreoretinal conditions requiring removal of the ILM.

WHAT WARNINGS AND PRECAUTIONS SHOULD I BE AWARE OF? Excess TISSUEBLUE™ should be removed from the eye immediately after staining. When using the syringe, surgeons or staff should make sure the plunger moves smoothly before injecting the solution.

Ask your patient about all the medicines they take, including prescription and over-the-counter medicines, skin products, vitamins and herbal supplements.

WHAT ARE THE POSSIBLE SIDE EFFECTS OF TISSUEBLUE? Adverse reactions that have been reported in procedures that included the use of TISSUEBLUE™ have often been associated with the surgical procedure. The complications include retinal (retinal break, tear, hemorrhage, and detachment) and cataracts.

WHAT ARE THE INGREDIENTS IN TISSUEBLUE?

Active Ingredient: Brilliant blue G

Inactive Ingredients: Polyethylene glycol and buffered sodium chloride solution (sodium chloride, sodium phosphate dibasic dodecahydrate, sodium phosphate monobasic dihydrate, water for injection).

WHERE SHOULD I GO FOR MORE INFORMATION ABOUT TISSUEBLUE? Go to **www.tissueblue.com** or call 800-75-DUTCH or 603-778-6929.

Dutch Ophthalmic, USA, 10 Continental Dr., Bldg. 1, Exeter, NH 03833, USA
dorc.eu | 800-75-DUTCH or 603-778-6929

tissueblue.com

RETINAL OXIMETRY GIVES CLUES TO CHOROIDAL MALIGNANCY

Noninvasive measurements taken with a retinal oximeter detected differences in oxygenation in eyes with choroidal melanoma that were not present in eyes with choroidal nevus, a recent study found. Eyes with choroidal melanoma showed increases in oxygen saturation in arterioles (ArtSat) and decreased saturation in venules (VenSat), leading to an increased arteriovenous difference that was not seen in eyes with choroidal nevus, the study authors reported in *Retina*.[1]

Currently, fluorescein angiography, an invasive imaging method, is commonly used to help differentiate choroidal metastasis from other lesions such as nevi, the authors pointed out.

"Our study identifies a new parameter that differs between [choroidal metastasis] and [choroidal nevus] (ie, increased oxygen use)," the authors said. "Because the observed differences […] are small, this will currently not be of use as a diagnostic criterion, but it demonstrates that melanoma-related vascular alterations are present."

In the study, retinal oximetry did not differ between the affected and fellow eyes of patients with choroidal nevi; mean ArtSat was 94.5% and 94.2% ($P = .56$), mean VenSat was 60.5% and 61.3% ($P = .35$), and mean arteriovenous difference was 34.0% and 32.9% ($P = .18$), respectively. In patients with choroidal melanoma, mean ArtSat was 94.8% and 93.2% ($P = .006$), mean VenSat was 58.0% and 60.0% ($P = .014$), and mean arteriovenous difference was 36.8% and 33.2% ($P < .001$), respectively.

"These changes [in eyes with melanoma] may be caused by inflammation and a higher metabolism, with larger oxygen consumption, leading to altered blood flow and intraocular oxygen relocation," the authors posited.

1. Brouwer NJ, Marinkovic M, Bleeker JC, et al. Retinal oximetry is altered in eyes with choroidal melanoma but not in eyes with choroidal nevi. *Retina*. 2020;40(11):2207-2221.

NEW CRISPR TECHNOLOGY SHOWS PROMISE FOR TREATING INHERITED RETINAL DISEASES

Correcting mutations in the *RPE65* gene using a novel gene editing technique, known as base editing, significantly restored retinal and visual function in mice with Leber congenital amaurosis, researchers recently found.

"After receiving treatment, the mice in our study could discriminate visual changes in terms of direction, size, contrast, and spatial and temporal frequency," said Krzysztof Palczewski, PhD, the Irving H. Leopold chair and a distinguished professor in the Gavin Herbert Eye Institute, Department of Ophthalmology at the UCI School of Medicine, in a press release. "These results are extremely encouraging and represent a major advance towards the development of treatments for inherited retinal diseases."

The preliminary data suggest that base editing can overcome initial gene therapy barriers, including unpredictable off-target mutations and low editing efficiency; in this study, the researchers were able to correct mutations precisely and predictably, explained first author Elliot Choi, an assistant specialist in the UCI Department of Ophthalmology, in the press release.

AAO UPDATES

CONTINUED IMPROVEMENT SEEN AT 1 YEAR WITH RPGR GENE THERAPY

An investigational gene therapy for the inherited retinal disease X-linked retinitis pigmentosa was well tolerated and demonstrated significant and sustained improvements in vision in a phase 1/2 trial, according to a presentation at the AAO 2020 Virtual Annual Meeting. The novel adeno-associated virus/retinitis pigmentosa GTPase regulator (AAV-RPGR) is being jointly developed by MeiraGTx and Janssen Pharmaceutical.

"The continuous upward trend in efficacy we've observed through 1 year with this gene therapy is extremely promising as a potential way to halt the progression toward blindness in these patients," said trial investigator Michel Michaelides, BSc, MB, BS, MD (Res), FRCOphth, FACS, of Moorfields Eye Hospital and University College London, who presented 12-month data on the therapy at a late-breaking paper session.

The primary endpoint of the trial is safety, and secondary endpoints are assessing changes in visual function at prespecified timepoints after treatment. The ongoing trial includes three phases: dose escalation with low, intermediate, and high doses of AAV-RPGR; dose confirmation; and dose expansion. Statistically

significant differences in mean retinal sensitivity were observed between treated and untreated eyes in the intermediate dose cohort and in central visual field progression rate in the low and intermediate dose cohorts, Dr. Michaelides said. In the high dose cohort, inflammation was evident in two of three adults, and measures of visual function were not improved.

In tests of vision-guided mobility at 9 months, five of six patients demonstrated improvement in walk time for the treated eye.

DATABASE ANALYSIS SHOWS PROGRESSION OF DRY AMD OVER 2 YEARS

Analysis of real-world clinical data from an AAO database showed significant disease progression over a 2-year period in more than 69,000 patients with geographic atrophy (GA), according to a presentation at the AAO meeting. Patients with GA in one eye secondary to dry AMD were more likely to develop new-onset wet AMD when wet AMD had already been detected in their contralateral eye, the analysis found.

"The data show that GA patients at their first encounter have useful vision that may be preserved if an effective treatment were available. The progressive loss of visual acuity observed in this study over a 2-year period underscores the urgent need for a therapy to slow disease progression," said Ehsan Rahimy, MD, who presented the findings at a late-breaking paper session.

The analysis of data from the AAO's IRIS Registry was conducted in collaboration with Apellis Pharmaceuticals, the data analysis firm Verana Health, and the AAO. Apellis is developing pegcetacoplan, a targeted C3 therapy currently in phase 3 clinical studies in patients with GA.

At 12 months, progression from GA to new-onset wet AMD was seen in 4.7% of patients with bilateral GA and 13.3% of patients with wet AMD in the contralateral eye. At 24 months, progression was seen in 8.2% and 21.6% of patients with bilateral GA and wet AMD in the contralateral eye, respectively.

Of note, a large proportion of patients with GA did not return for follow-up at 2 years. Of the patients potentially eligible for inclusion in the analysis, only 40% had a 2-year follow-up visit.

DATABASE PROVIDES INSIGHTS ON RISK FACTORS FOR RETINAL VASCULITIS WITH ANTI-VEGF AGENT

In 12,000 patients identified in the AAO's IRIS Registry, the highest observed risk for experiencing retinal vasculitis (RV) and/or retinal vascular occlusion (RO) in the 6 months after first treatment with brolucizumab (Beovu, Novartis) was prior intraocular inflammation (IOI) and/or prior RO in the 12 months before that first injection, according to an analysis presented at the AAO meeting. Michael S. Ip, MD, presented the results at the meeting.

The observed overall risk rate for RV or RO for all brolucizumab-treated patients in the registry was 0.46%, but risk increased to 3.97% in those with prior IOI and/or RO, the database analysis found.

In addition, in a post-hoc unmasked assessment of data from the phase 3 HAWK and HARRIER trials presented by Jeffrey S. Heier, MD, there was an observed trend toward increased incidence of RV or RO in patients with treatment-emergent anti-drug antibodies.

Further analyses of this data and additional data collection on this subject are ongoing, Novartis said in a press release recapping information presented at the AAO meeting.

SAFETY ENDPOINTS MET IN PHASE 1 DRY AMD STUDY

An investigational treatment for dry AMD met all the primary endpoints in a phase 1 clinical trial, with no treatment-related adverse events, according to a poster presentation at the AAO meeting.

In four ascending doses of a single intravitreal injection of GEM103 (Gemini Therapeutics) there were no dose-limiting toxicities, and all doses were well tolerated, according to presenter Arshad M. Khanani, MD, MA. In addition, visual acuity was generally maintained or improved in the majority of patients with advanced central GA in the open-label study.

Gemini is now evaluating GEM103 in the phase 2a ReGAtta clinical trial, a multicenter, open-label, multiple-dose escalation study in patients with GA secondary to dry AMD, the company said in a press release.

VITRECTOR HANDLE DESIGNED TO IMPROVE DEXTERITY

A new vitrector handle for use on Alcon's vitrectomy platform was introduced during the 2020 AAO Virtual Annual Meeting. The Finesse Reflex handle is designed to help surgeons move with ease, providing unrestricted movement and focused performance, according to the company.

Part of the Greishaber line of instrumentation for vitreoretinal surgery, the handle provides improved surgical dexterity with advanced ergonomic support and expanded extraocular working space during vitreoretinal surgery, the company said in a press release before the meeting. The ultralight-weight handle features stiff 25- and 27-gauge needle shafts for maneuverability and precision performance during ophthalmic surgery. ■

PEDIATRIC RETINAL DETACHMENTS REQUIRE DIFFERENT STRATEGIES

Each year, the Aspen Retinal Detachment Society (ARDS) hears from a select group of highly distinguished speakers. In several of our past meetings, we have made sure to reserve time on the podium to discuss pediatric retinal care.

ARDS leadership knows that most retina conferences give little attention to pediatric retina care. The reasons are obvious: Pediatric retina is a sub-subspecialty of eye care, and dedicating valuable podium time on an otherwise filled agenda to a discipline that only a small subset of attendees may practice could be unwise.

Still, we know our attendees. ARDS participants' hunger for learning deeply about a number of subjects is not limited to the topics that pertain most immediately to them and their practices. They're polymaths. They know that rounding out their retina education gives them a more holistic sense of the space. And hey, you never know when those pediatric retina pearls will come in handy.

Be sure to keep an eye on MedConfs.com for the latest updates about ARDS 2021 and our focus on an in-person meeting.

—Timothy G. Murray, MD, MBA

BEST APPROACHES FOR PEDIATRIC RETINAL DETACHMENTS

Presentation by Philip J. Ferrone, MD
Summarized by Abdallah Mahrous, MD

At this year's ARDS meeting, Philip J. Ferrone, MD, provided a rundown of surgical considerations for pediatric retinal detachments (RDs). He emphasized the important point that the anatomy of pediatric eyes is different from the anatomy of adult eyes, and he discussed the best approaches to use in a variety of presentations. This article summarizes portions of his presentation.

HISTORY AND EXAMINATION TIPS

Dr. Ferrone reported that pediatric RDs have an incidence of 0.53 per 100,000, compared with an incidence of 12 per 100,000 in the adult population.[1] Tractional RDs are even less common in children. RDs are sometimes challenging to diagnose in children, and they can present late or with other signs such as strabismus.

History is important, even in older children—details such as a baby's birth weight, a history of prematurity, or a family history of eye disease or RD, and trauma are important to document. Pediatric examinations can be made more challenging due to lack of cooperation, difficulty with drop administration, and poor dilation.

For babies less than 1 year old, examination can be made easier by having the patient lie on a parent's lap with the head by the knees and feet up to the parent's chest, while the parent helps stabilize the baby by holding his or her head. For uncooperative children up to 8 years of age, you can ask the parent to bear-hug the child while an assistant holds the head and the physician attempts to pry the eyelids open and examine. If this approach fails, examination under anesthesia is often necessary.

Stickler detachments are often complicated, with a redetachment rate of 45% due to proliferative vitreoretinopathy (PVR). By contrast, non-Stickler RDs often behave more like adult RDs with more promising results.

SURGICAL APPROACHES

The standard Alcon kit for 25-gauge vitrectomy can often be used for common pediatric RDs. Use of the special Alcon short 25-gauge instrumentation can be helpful in cases such as microphthalmic eyes, or eyes with persistent fetal vasculature (PFV) with central retinal stalk lines, or peripheral retinal folds in retinopathy of prematurity (ROP). The short system has the advantage of providing a trocar with no cannula.

Pediatric eye anatomy varies from that of adults. The pars plana–pars plicata complex extends on average for 1.87 mm posterior to the limbus at 40 weeks; therefore, introducing the cannulas at 1 mm from the limbus is appropriate for a term baby. By 6 months, the pars plana–pars plicata complex extends for approximately 3 mm posterior to the limbus, so a trocar incision at 1.5 to 2.0 mm from the limbus is appropriate for that age.

The eye's anatomy continues to change with the child's growth. The axial length increases by approximately 1.5 mm during the first 12 weeks of life. The eye grows on average 2 mm over the first 2 years of life and then another 2 mm from 2 years to 5 years. Between 5 years and 15 years the eye typically grows another 3 mm. After 15 years of age, there is typically no significant growth.[2] It is important to take this progression into account when scleral buckle surgery is considered and when you are placing sclerotomy wounds.

Eyetube Meeting Coverage at Aspen Retinal Detachment Society

Each year, the Society invites Eyetube to cover selected talks from the year's agenda.

ARTIFICIAL INTELLIGENCE AND PEDIATRIC RETINA

R.V. Paul Chan, MD, discusses how applying AI to pediatric patients aids in diagnosing conditions such as plus disease by characterizing and monitoring disease activity.

SUBRETINAL GENE THERAPY

Christina Weng, MD, MBA, gives insight into ongoing subretinal gene therapy pipeline candidates, specifically voretigene neparvovec for patients with a mutation of the *RPE65* gene.

BEST APPROACHES FOR PEDIATRIC RD

Philip J. Ferrone, MD, discusses how to properly care for and diagnose pediatric patients. Dr. Ferrone discusses how fundus autofluorescence, OCT, and other in-office imaging modalities can be used to obtain the best and most accurate imaging results.

NEUROPROTECTION FOR THE TREATMENT OF THE RETINA

Baruch Kuppermann, MD, PhD, discusses unmet needs in conditions such as retinal detachment, geographic atrophy, and dry AMD and what the right pathway may be for neural protection and enhancement.

Want to see the whole video collection? Head to bit.ly/ARDS2020.

CASE-BY-CASE CONSIDERATIONS

Pediatric RDs should be approached on a case-by-case basis. Retinal dialysis should preferably be buckled using a low and broad approach, as opposed to a high and narrow one. Stickler detachments, as previously mentioned, are highly proliferative with high redetachment rates. Addressing these RDs often requires time and patience. They might require multiple surgeries, with relaxing retinectomies and silicone oil.

Familial exudative vitreoretinopathy (FEVR) may present with a normal appearing fundus, but fluorescein angiography can reveal large areas of peripheral nonperfusion that can be lasered. If not treated, these areas can lead to dense preretinal proliferation with high-ridged retinal folds. The folds must be carefully dissected, taking care not to create any retinal breaks, which would be very difficult to repair.

Mutations in *KIF11* can cause microcephaly, microphthalmia, and con-

(Continued on page 15)

DOUBLE TROUBLE: A TALE OF TWO INTRAOCULAR FOREIGN BODIES

Imaging might be wise, even when one object is clearly visible.

BY REMYA MAREEN PAULOSE, MBBS, DNB, FLVPEI, FICO, FAICO, AND THOMAS CHERIAN, MS, FLVPEI

Intraocular foreign body (IOFB) injuries may result in a wide range of pathology and visual outcomes. Metallic IOFBs are often associated with high velocity, and once they penetrate the cornea, they tend to enter the posterior segment.[1-3] Additionally, IOFBs may present with varied clinical aspects that may limit their detection, and symptoms may only become apparent after a prolonged period of time.

However, in cases of visible IOFB, there are no clear guidelines regarding the need for additional imaging.

This report describes a unique case of a single penetrating wound with two metallic IOFBs, one of which would have been overlooked on a cursory clinical examination. It highlights the need for suspicion of additional foreign bodies even if one IOFB is clinically evident.

CASE

A healthy 24-year-old man presented urgently with a penetrating corneoscleral injury of the right eye following a reported history of a high-velocity projectile resulting from hammering a nail. He complained of poor vision, pain, and redness in the right eye.

His visual acuity was light perception in the right eye and 20/20 in the left. In the right eye, the conjunctiva was congested with a full thickness corneoscleral tear at 4 o'clock, extending 3 mm onto the cornea and 5 mm radially onto the sclera. The anterior chamber was shallow, and the pupil was mid-dilated with a relative afferent pupillary defect. Although a rosette cataract was present, the fundus could be visualized, showing a metallic IOFB embedded on the retina inferonasally

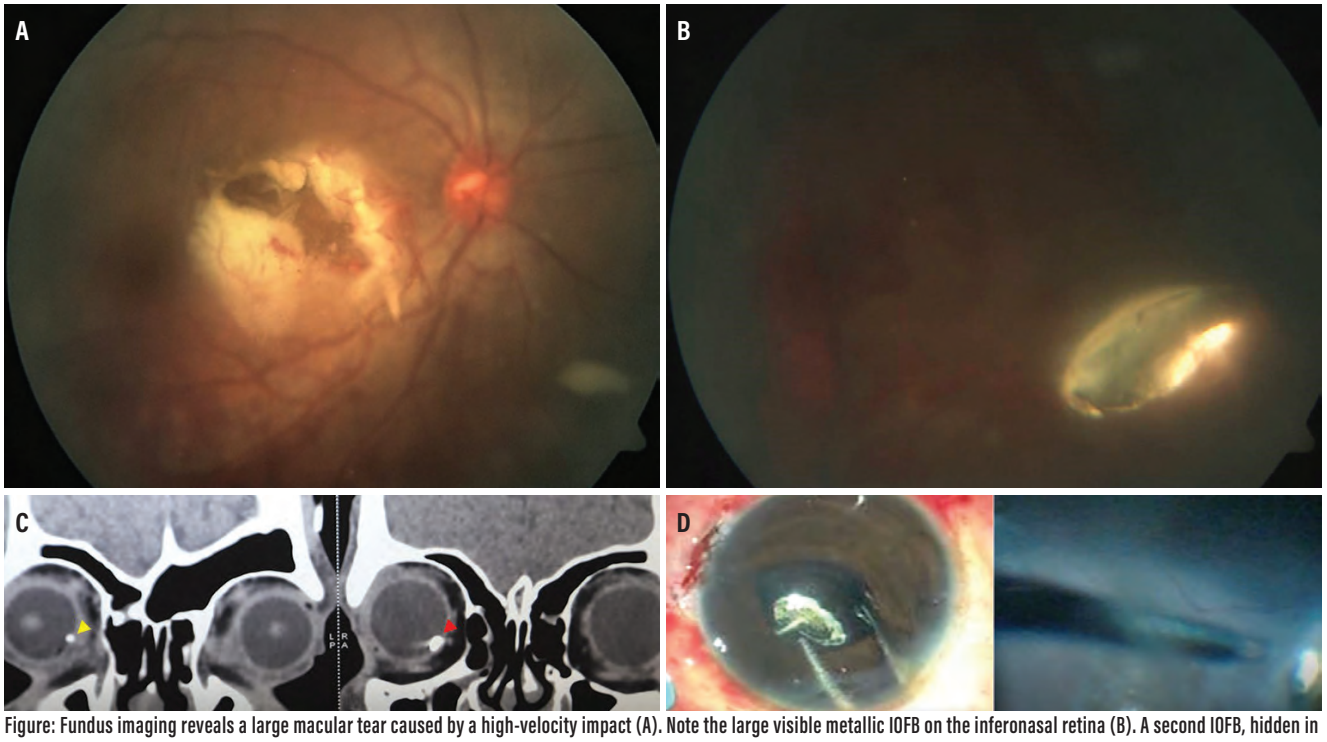

Figure: Fundus imaging reveals a large macular tear caused by a high-velocity impact (A). Note the large visible metallic IOFB on the inferonasal retina (B). A second IOFB, hidden in the inferonasal periphery, was localized with the help of a CT scan (C); the CT scan helped to localize the anterior smaller foreign body (left), while the larger foreign body is visible in a posterior scan (right). The larger visible foreign body was brought into the anterior chamber (left), and the smaller anterior foreign body in the periphery was localized with scleral indentation (right) (D).

(Figure, A). The macula showed a large retinal tear with an overlying hemorrhage (Figure, B).

The patient underwent fundus photography and emergency CT scan as per institution protocol. To our surprise, CT imaging revealed two separate IOFBs in the inferonasal aspect of the right eye (Figure, C).

The patient was scheduled for emergency 25-gauge pars plana vitrectomy and pars plana lensectomy with anterior capsulotomy. Posterior vitreous detachment nasally helped to avoid the extension of the macular tear. After vitrectomy, the larger of the two foreign bodies was removed through a clear corneal incision, while a thorough search with scleral indentation localized the second IOFB in the peripheral retina close to the ora (Figure, D). The second one was removed in a similar manner. Cryotherapy was applied to the peripheral break, followed by silicone oil tamponade. After silicone oil removal at 3 months postoperatively, visual acuity improved to counting fingers at 3 m with attached retina and scarring at the macula.

DISCUSSION

The identification of an additional foreign body can be challenging when the level of suspicion is low, as can be the case when one IOFB is clinically visible. General consensus is lacking regarding the need for imaging in cases with visible IOFB.

In one interventional case series of 69 eyes with IOFBs, 17 eyes had no imaging when the IOFB was easily visualized.[1] The researchers also reported that two eyes had an additional IOFB identified on radiological evaluation. Thus, the authors recommended radiologic imaging even when an IOFB is clearly visible on clinical examination. A retrospective review of imaging techniques in IOFB cases demonstrated the superiority of CT scan over other methods.[4]

To the best of our knowledge, this is a unique report of two metallic IOFBs from a single entry site caused by a hammering accident. I speculate that the force of the IOFB's impact on the macula may have caused the IOFB to split in two inside the eye. This case highlights the need for suspicion and imaging for additional IOFBs in the event of high velocity projectile injuries, even when one IOFB is clinically evident. ■

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genital retinal folds. Fluorescein studies may show peripheral nonperfusion as well. Retinal folds can sometimes have stalks that connect to the lens. The preferred surgical approach in these eyes is to use the short 25-gauge instruments, cutting the stalk anteriorly to free up the retina and letting it settle back down to a more normal anatomy, then approaching the rest of the retinal folds.

Optic pit RDs can sometimes self-resolve if given time; however, in cases that require surgery it is recommended to remove the vitreous stalk that goes right into the optic pit, followed by application of light intraoperative laser around the pit.

In Coats disease, the pathognomonic telangiectatic vessels are often accompanied by RDs. In these eyes, it is better to drain the subretinal fluid externally and apply extensive laser to the telangiectatic vessels; this might not provide ideal results but will preserve any vision possible.

Colobomas can present with very challenging RDs. Silicone oil is preferred in these eyes, but even with oil there are often redetachments due to the complexity of the retinal layers in the coloboma. Platelet-rich plasma can be helpful in these cases.

CONCLUSION

Pediatric RDs are different from RDs in adults. Children's eyes have a different anatomy that requires modification of surgical approaches. With the correct approach and patience, excellent visual and anatomic results are still possible. ■

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LONG-TERM INFLAMMATION CONTROL BENEFITS ALL TYPES OF UVEITIS

Preventing flare-ups is essential in the pandemic era.

BY ROBERT C. WANG, MD

Uveitis is a multifaceted disease that strikes in different ways, but the goal of treatment is always the same: to achieve quiescence with the fewest possible side effects. Whether a patient presents with iritis, panuveitis, or uveitis with systemic disease association, the retina specialist's objective is to eradicate vision-threatening inflammation and quell potential flares. To that end, we have an increasingly sophisticated arsenal of tools from which to choose.

By the time patients with noninfectious uveitis reach my clinic, they have typically been treated unsuccessfully with oral steroids and are then candidates for systemic immunosuppressives or intraocular corticosteroids. Options at this point include the bioerodible 0.7 mg dexamethasone intravitreal implant (Ozurdex, Allergan); the surgically placed 0.59 mg fluocinolone acetonide intravitreal implant (Retisert, Bausch + Lomb); and the injectable 0.18 mg fluocinolone acetonide intravitreal implant (Yutiq, EyePoint Pharmaceuticals).

When appropriate, I am partial to the newest option, the 0.18 mg fluocinolone acetonide intravitreal implant, because it is a low-dose implant that lasts up to 3 years. I've treated many patients with it who have then experienced long-term quiescence and few side effects. The 0.59 mg fluocinolone acetonide intravitreal implant is also an excellent option, but it requires surgical placement and delivers a higher dose of steroid.

As the following case studies illustrate, a thorough evaluation of the patient's clinical presentation and medical history guide the development of a well-suited uveitis treatment regimen, and frequent monitoring makes it possible to change course when necessary.

CASE 1: ANTERIOR UVEITIS

Presentation

A 9-year-old White child was brought to the clinic for evaluation and treatment. The patient had a history of psoriatic arthritis and decreased vision in her right eye. She presented with rebound iritis and worsening vision. The most common causes of vision loss in pediatric patients with anterior uveitis are cataract, band keratopathy, glaucoma, and cystoid macular edema (CME).

On presentation, the patient's VA was 20/40 OD and 20/20 OS, and OCT documented CME in the right eye. The patient had been treated on and off with systemic methotrexate and had been using topical prednisolone acetate in the right eye for the 2 months before presentation (Figure 1).

Treatment Course

I started the patient on topical 0.05% difluprednate ophthalmic emulsion (Durezol, Alcon) as a bridge to initiation of systemic adalimumab (Humira, AbbVie). With the topical treatment, the CME improved greatly, although the patient developed a mild steroid-induced IOP response, with elevation to 27 mm Hg.

I replaced the difluprednate with 0.5% loteprednol etabonate ophthalmic suspension (Lotemax, Bausch + Lomb) and gradually tapered the loteprednol to one drop daily. Adalimumab was started 2 weeks after the loteprednol taper, resulting in resolution of most of the CME. The patient's IOP returned to normal (11 mm Hg) and visual acuity stabilized at 20/25 (Figure 2).

AT A GLANCE

- The goal of uveitis treatment is to achieve quiescence with the fewest possible side effects.
- A number of implantable posterior segment steroid options exist for local control of inflammation.
- Ongoing coverage is a chief advantage of an implantable corticosteroid.

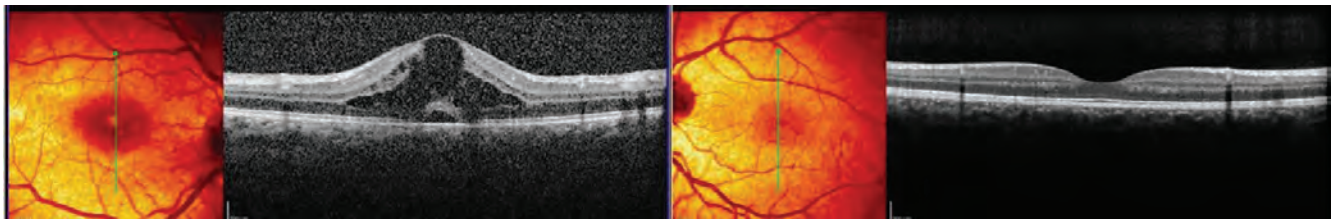

Figure 1. The Case 1 patient's OCT shows CME secondary to chronic iritis in the right eye (left panels), normal left eye.

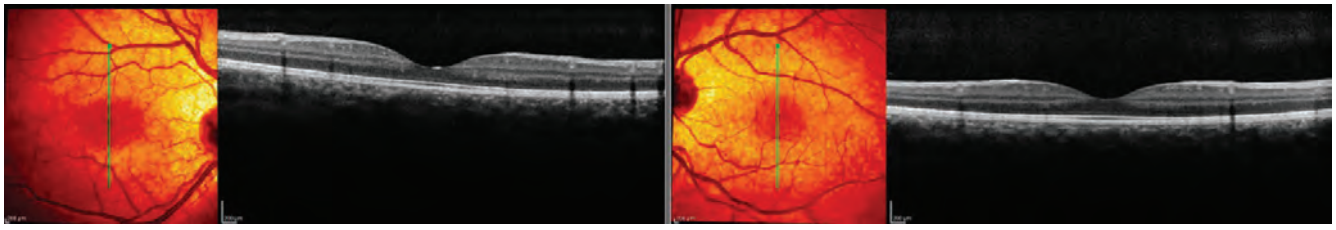

Figure 2. The Case 1 patient's OCT demonstrates resolution of CME in the right eye.

Current Status

Ten months after initiation of adalimumab, the patient's visual acuity remains 20/25 OD and 20/20 OS with normal IOP and no recurrence of inflammation or CME.

CASE 2: PANUVEITIS

Presentation

A 72-year-old White woman presented with panuveitis secondary to birdshot chorioretinopathy positive for histocompatibility leukocyte antigen (HLA)-A29. Birdshot chorioretinopathy is a rare form of chronic bilateral posterior uveitis. Despite its distinctive clinical phenotype and association with HLA-A29, delays in diagnosis and treatment are common, sometimes resulting in significant visual loss.[1]

Treatment Course

Because birdshot chorioretinopathy is thought to have an autoimmune etiology, therapy aims to regulate the body's immune response. I started the patient on oral prednisone and 50 mg of the antimetabolite azathioprine (Imuran, GlaxoSmithKline) three times daily. I began a taper of the oral steroids, and the patient achieved quiescence, but 4 months later she developed a recurrence of inflammation.

At that time, I initiated a pulse of oral steroids, which calmed the inflammation, and I prescribed 150 mg of azathioprine and 5 mg of prednisone daily for maintenance therapy. However, she again developed a flare 3 months later. We attempted to enroll her in a clinical trial of adalimumab, but the study had reached its closeout date. I consulted with rheumatology, intending to initiate systemic biologic therapy. With no other systemic diagnosis, however, the patient's insurance carrier would not approve any therapy.

I increased the dose of azathioprine to 200 mg daily, but the patient still demonstrated inflammation on exam. Next, I switched her to a daily regimen of 3,000 mg of mycophenolate mofetil (CellCept, Genentech) and initiated another steroid pulse. Despite the switch, the inflammation flared once again.

At that point, it was clear to me that the patient's disease would continue to flare without a move to local therapy. I placed a 0.7 mg dexamethasone intravitreal implant in the vitreous, after which the inflammation improved rapidly. This implant is expected to last up to 6 months, but I often find that its efficacy wanes by about month 3, and pharmacokinetic data supports that observation.[2]

I discussed with the patient the possibility of implanting the 0.59 mg fluocinolone acetonide intravitreal implant, but the patient was concerned about a higher incidence of glaucoma with this treatment in patients with birdshot chorioretinopathy.[3] In addition, the anticipated out-of-pocket cost was beyond her means. Instead, she elected to repeat the dexamethasone implant every 3 months for nine more treatments.

The 0.18 mg fluocinolone acetonide intravitreal implant subsequently became available. The patient was amenable to trying it when I explained that it would be implanted in an outpatient procedure under topical anesthesia, that it would last for 3 years, and that the reimbursement would be favorable.

Current Status

I placed the 0.18 mg fluocinolone acetonide intravitreal implant bilaterally in December 2019. Since then, her eyes have remained quiet with no other therapy needed.

CASE 3: UVEITIS WITH SYSTEMIC ASSOCIATION

Presentation

A 74-year-old White man presented with bilateral nyctalopia and vision loss. The patient had a history of autoimmune neuropathy predominantly affecting his right leg and, to a lesser degree, his left leg and both hands. He also had hearing loss, with cochlear implants bilaterally, and he was being treated with azathioprine for Sjögren syndrome. On examination, he had 20/20 VA OU and normal retina findings but very constricted visual fields bilaterally.

(Continued on page 21)

A MASQUERADER OF CIRCUMSCRIBED CHOROIDAL HEMANGIOMA

An extramacular dome-shaped elevation raised suspicion of an intraocular tumor.

BY AHMED SHEIKH, MD; PHILIP W. DOCKERY, MD, MPH; AND CAROL L. SHIELDS, MD

Circumscribed choroidal hemangioma is a benign vascular tumor characterized in part by its red-orange hue. Associated findings include serous retinal detachment, overlying photoreceptor atrophy, cystoid macular edema, retinal pigment epithelial alterations, and subretinal fibrosis.[1]

Although choroidal hemangioma frequently manifests these distinct clinical features, it has often been confused with other chorioretinal abnormalities, such as macular edema, retinal detachment, central serous chorioretinopathy, choroidal melanoma, and choroidal metastases.[1] Conversely, other pathologies can masquerade as choroidal hemangioma, specifically dome-shaped maculopathy.[2]

Here we present a case of extramacular dome-shaped elevation that was referred to our practice for suspicion of circumscribed choroidal hemangioma.

CASE REPORT

A 79-year-old Hispanic man with an ocular history of advanced open-angle glaucoma was referred to the Ocular Oncology Service at Wills Eye Hospital for suspicion of a choroidal tumor in the left eye. His medical and ocular histories included cataract surgery in the left eye, trabeculectomy and glaucoma tube shunt implantation in the left eye, diabetic retinopathy with macular edema in the left eye, left facial synkinesis, and left eyelid trauma. He reported no symptoms related to the choroidal lesion.

On examination, VA was light perception OD and 20/400 OS. There was a relative afferent pupillary defect in the right eye. IOP measured 22 mm Hg OD and 12 mm Hg OS. Anterior segment examination revealed no abnormalities except for the presence of the glaucoma tube shunt and a superior iridotomy in the left eye. No ocular melanocytosis or heterochromia was noted.

Fundoscopy revealed advanced cupping of the optic nerve and scattered intraretinal hemorrhages in both eyes, with macular edema in the left eye. Just inferior to the optic disc in the left eye, a red-orange lesion was noted, measuring 6 mm by 5 mm in basal diameter (Figure 1A). There was no abnormal autofluorescence pattern noted overlying the lesion (Figure 1B).

AT A GLANCE

- Circumscribed choroidal hemangioma is a benign vascular tumor with distinct clinical features such as a red-orange hue, subretinal fibrosis, overlying photoreceptor atrophy, and retinal pigment epithelial alterations.
- Choroidal hemangioma has been confused with macular edema, retinal detachment, and other chorioretinal abnormalities.
- The tessellated, red-orange appearance of extramacular dome-shaped elevation can clinically simulate a tumor such as choroidal hemangioma, but ancillary testing with EDI-OCT, FA, and ICGA may help distinguish this abnormality.

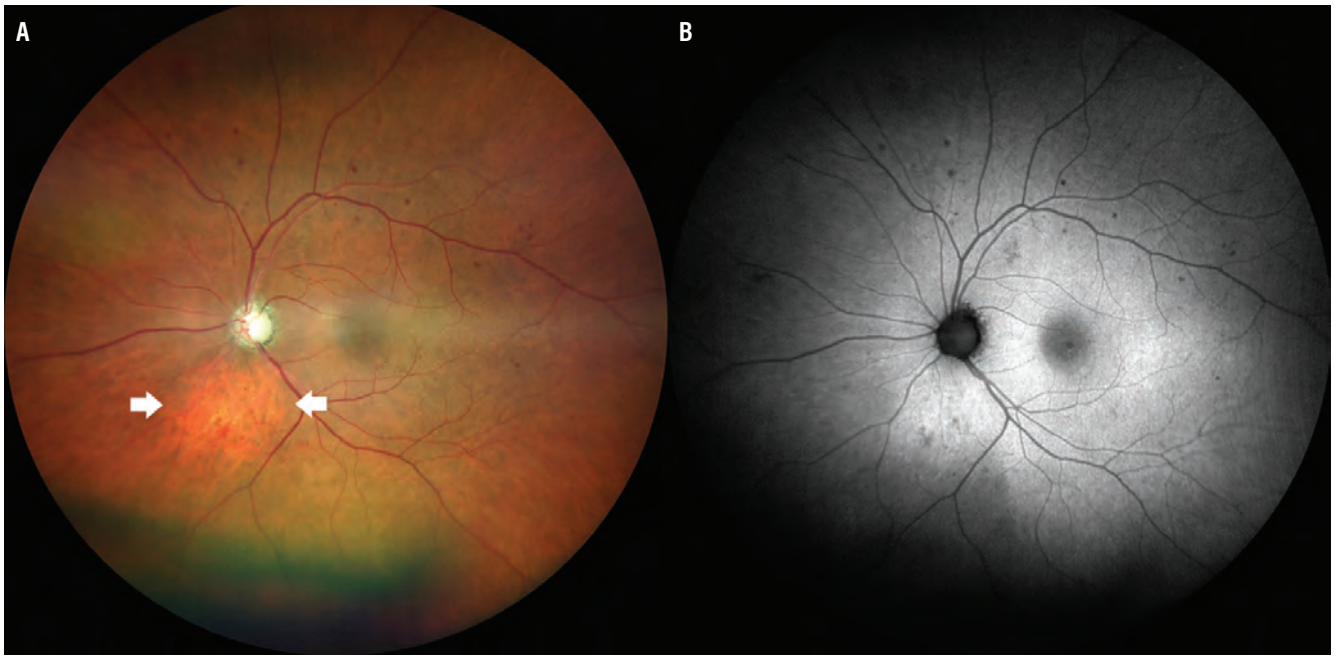

Figure 1. Fundus photography shows a tessellated red-orange lesion inferior to the optic disc (arrows), measuring 6 mm by 5 mm in basal diameter; scattered intraretinal hemorrhages are more prominent superiorly (A). Fundus autofluorescence shows no abnormalities at the location of the lesion inferior to the optic disc (B).

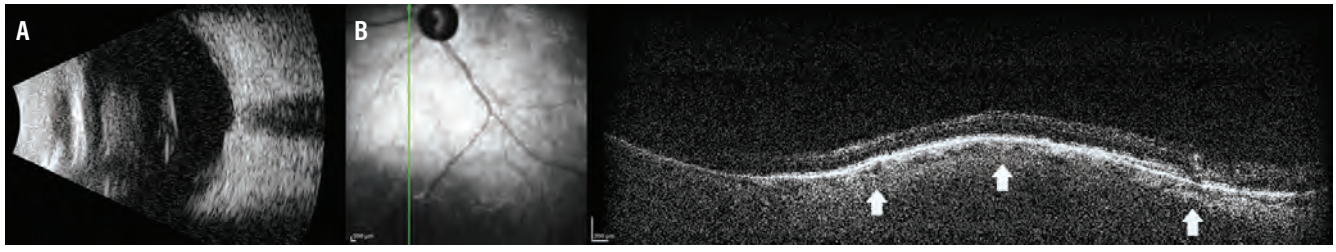

Figure 2. B-scan ultrasonography shows a 2.3 mm elevation of the solid lesion inferior to the optic disc (A). EDI-OCT over the lesion shows scleral elevation (arrows) rather than choroidal thickening. Normal retinal architecture was maintained over the lesion, and no SRF or edema was noted (B).

B-scan ultrasonography demonstrated an apparent dome-shaped mass with solid echogenicity and a thickness of 2.3 mm (Figure 2A). There was no subretinal fluid (SRF) and no overlying vitreous abnormalities. Enhanced depth imaging OCT (EDI-OCT) revealed a dome-shaped elevation of the retina without SRF or choroidal neovascularization (Figure 2B). On EDI-OCT, scleral elevation without choroidal thickening could be noted. No related abnormalities were seen on fluorescein angiography (FA) or ICG angiography (ICGA) (Figure 3).

Ultimately, the clinical and imaging features suggested that the lesion was in fact not a tumor, but rather an extramacular dome-shaped elevation of the sclera that required no treatment and merited observation alone.

DISCUSSION

Dome-shaped maculopathy is a convex protrusion of the sclera, pushing the internal structures inward and occasionally simulating an intraocular tumor.[2,3] Although most commonly associated with myopia or staphyloma, it has been reported in emmetropes and hyperopes as well.[3] In an analysis of 58 eyes, Errera et al found that the mean refractive error associated with dome-shaped maculopathy was approximately -7.00 D.[4] This condition can be found with other abnormalities, such as Best vitelliform macular dystrophy and oculocutaneous albinism.[5,6] Additionally, EDI-OCT has confirmed that dome-shaped maculopathy is secondary to focal scleral thickening.[2]

In an analysis of 52 highly myopic eyes, Viola et al found that dome-shaped maculopathy was associated with serous retinal detachment (17 eyes, 33%), choroidal neovascularization (13 eyes, 25%), extrafoveal retinoschisis (two eyes, 4%), and lamellar macular hole (one eye, 2%).[7] Further, 39 of the 52 eyes had a horizontally oriented oval-shaped dome, and 12 had a vertically oriented oval-shaped dome. Only one eye demonstrated a circular dome. Mean spherical equivalent in these eyes was -14.00 D and mean BCVA was 0.32 logMAR (Snellen equivalent of 20/40).[7]

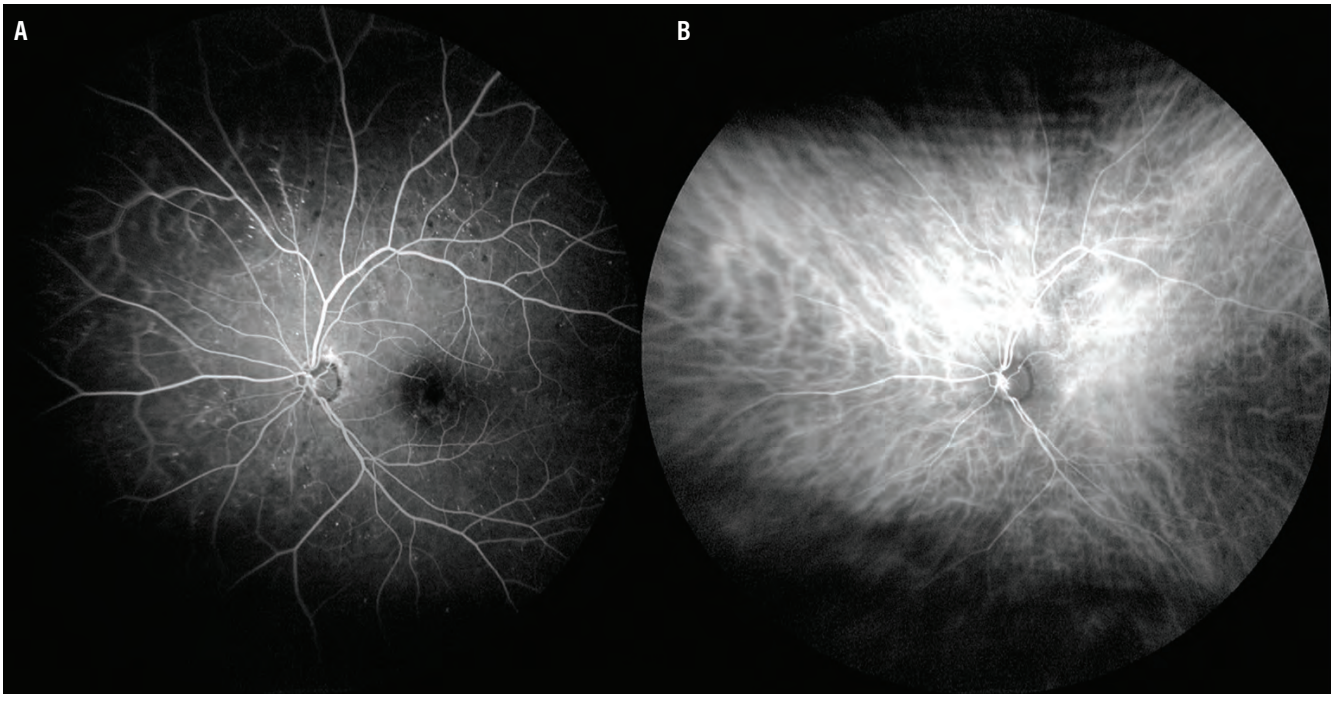

Figure 3. Fluorescein angiography shows scattered hyperfluorescent extramacular microaneurysms but no abnormalities over the lesion inferior to the optic disc (A). ICG angiography shows no abnormalities (B).

In another study, Saito et al found that 37 of 82 eyes (45%) with a dome-shaped macula did not demonstrate a posterior staphyloma, indicating that dome-shaped maculae can develop independently from a posterior staphyloma.[8]

As its name suggests, dome-shaped maculopathy typically appears in the macula. However, extramacular dome-shaped elevation has been reported, and a similar pathophysiology to dome-shaped maculopathy has been theorized.[9]

The treatment strategy is targeted toward the management of SRF. In a retrospective case series by Lorenzo et al, 29 of 56 eyes demonstrated SRF at presentation. Of those 29 eyes with SRF, 10 eyes were observed without intervention. The other 19 eyes were managed with one of the following treatments: eight (42%) with low-fluence photodynamic therapy (PDT); seven (37%) with intravitreal bevacizumab (Avastin, Genentech), and four (21%) with intravitreal ranibizumab (Lucentis, Genentech). Resolution of SRF was seen in one (13%) of those treated with PDT (mean of 1.9 sessions), in one (14%) of those treated with intravitreal bevacizumab (mean of 1.9 injections), and in none (0%) of those treated with intravitreal ranibizumab (mean of 1.8 injections).

Overall, only four of the 29 eyes exhibited complete resolution of SRF, including one that received low-fluence PDT, one that received bevacizumab, and two that resolved spontaneously. The data show no statistically significant difference between eyes that were treated for SRF versus those that were not (P = .42).[10]

OTHER PATHOLOGIES CAN MASQUERADE AS CHOROIDAL HEMANGIOMA, SPECIFICALLY DOME-SHAPED MACULOPATHY.

Burke et al also noted no difference in BCVA between eyes that received therapy and those that received no therapy (0.52 vs 0.45 logMAR, P = .19).[3]

In our patient, the fundus revealed a red-orange elevation with focal choroidal vascular tessellations that, at first glance, was concerning for choroidal hemangioma. Notably, however, the vascular pattern was normal. The dense echogenicity on ultrasonography would suggest either choroidal hemangioma or dome-shaped maculopathy. The most revealing points of differentiation were seen on EDI-OCT, FA, and ICGA, which excluded choroidal hemangioma because hemangioma would have demonstrated choroidal thickening with preservation of the choriocapillaris on EDI-OCT, hyperfluorescence with

diffuse late staining on FA, and hypercyanescence with late wash-out on ICGA.[2] Dome-shaped elevation typically shows normal fluorescence patterns other than staining when there is SRF.

CONCLUSION

Dome-shaped elevation of the sclera can occur in eyes with or without a history of myopia. The tessellated, red-orange appearance of extramacular dome-shaped elevation can clinically simulate a tumor such as choroidal hemangioma. Ancillary testing with EDI-OCT, FA, and ICGA may help distinguish this abnormality. In this case, observation alone was sufficient because of the lack of SRF or retinal edema.[3] ■

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(Continued from page 17)

Treatment Course

Blood testing for antiretinal and optic nerve antibodies was performed, demonstrating reactivity to retinal and optic nerve antigens. Systemic evaluation revealed no neoplasms, and intravenous immunoglobulin (IVIG) therapy was initiated for presumed autoimmune retinopathy.

Three months later, his peripheral visual field loss was resolved and, incidentally, hearing loss improved. The patient was treated with IVIG infusions every 3 months for 5 years. Two years after cessation of therapy, the patient again developed worsening of his peripheral field.

Current Status

IVIG infusions were resumed, and the patient's visual field loss resolved. Continued monthly IVIG therapy has been maintained to keep his vision stable.

FORGING AHEAD

We have more uveitis treatment options in our armamentarium than ever before, yet there are about 30,000 new cases of blindness each year in the United States resulting from uveitis that is undiagnosed or inadequately treated.[4] It is critical to diagnose and treat uveitis before irreversible damage occurs. It is equally important to ensure that treatment for chronic noninfectious uveitis is ongoing because a lapse in therapy can cause a flare, resulting in damage and vision loss.

Ongoing coverage is a chief advantage of an implantable corticosteroid. With a long-lasting implant, patients aren't required to keep up with a complicated regimen of topical steroids, and they can feel confident that the implant will control inflammation and limit the risk of vision-threatening flares. Furthermore, implantable corticosteroids don't require the expertise of a retina surgeon nor the input of a rheumatologist. Any trained ophthalmologist can implant one and monitor the patient's IOP. In the event that a cataract subsequently develops, an ophthalmologist can take care of that as well.

The benefits of long-term therapy are especially advantageous during this pandemic. People with severe chronic conditions and those in an immunocompromised state are more likely to experience dangerous symptoms if they become infected with COVID-19. Given this added risk, it is advisable to avoid prescribing medications that will suppress the immune system when alternatives exist. ■

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SubLiminal Laser for Center-Involving Diabetic Macular Edema

BY ALEJANDRO FILLOY-RIUS, MD, PHD, FEBO, AND VICTOR CHONG MD, FRCS, FRCOPHTH

Diabetic retinopathy (DR) is a major microvascular complication of diabetes. It is estimated that by 2030, nearly 200 million people will be affected by this disease.[1] During this period, vision-threatening DR will increase from 37 million to 56 million people globally.[1] Center-involved diabetic macular edema (CI-DME) is the most common cause of decreased visual acuity in DR patients, affecting more than 750,000 patients in the United States alone.[2]

TREATMENTS FOR DME: PAST AND PRESENT

Today's treatment landscape offers several options for treating CI-DME. Currently, the standard of care for diabetic macular edema (DME) treatment-related conditions, including CI-DME, is serial intravitreal injections of anti-VEGF drugs. Though proven successful anti-VEGF therapies are expensive and require an arduous timetable of regularly scheduled office visits for repeat injections. Furthermore this regimen has been associated with a portfolio of issues, including residual edema in 25 to 64% of eyes[3] and is not devoid of complications. This process may be difficult for patients to maintain. In lower socio-economic countries with limited resources, access to expensive anti-VEGF therapy may not be an option and is unaffordable to many populations and health care systems.

CI-DME may be caused either by inflammation/exudation, by ischemia, or by a combination of both. In the foveal avascular zone, the only mechanism for extracellular fluid resorption is the retinal pigment epithelial (RPE) pump, which may explain the more significant accumulation of edema fluid at this location. A recent study concluded that in 15 to 30% of DME cases, a sub-foveal serous retinal detachment is present.[4] Laser is a useful tool in the treatment of CI-DME and although less potent than intravitreal therapy, there is no shortage of scenarios, specifically using subthreshold SubLiminal laser therapy in which laser is all you need to safely, effectively, and efficiently control CI-DME. We will summarize these in the next section but they all show that the edema is predominantly inflammatory.

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 a laser instead of the usual "continuous" beam of a conventional laser. This allows the RPE to cool between pulses, preventing a critical amount of heat from accumulating in the tissue and the consequential RPE, as well as retinal scarring which is unnecessary to obtain significant clinical response.

Finally, another treatment approach to CI-DME is vitrectomy with release of macular traction, internal limiting membrane peeling, laser photocoagulation, and perioperative intraocular corticosteroid therapy. Compared to anti-VEGF, vitrectomy is less expensive, reduces the frequency of required office visits, and yields longer-lasting effects. However, a small prospective randomized clinical trial using focal/grid laser as a control arm demonstrated that vitrectomy thins the edematous macula but inconsistently improved visual acuity.[5]

THREE IDEAL CI-DME SCENARIOS FOR SUBLIMINAL LASER TREATMENT

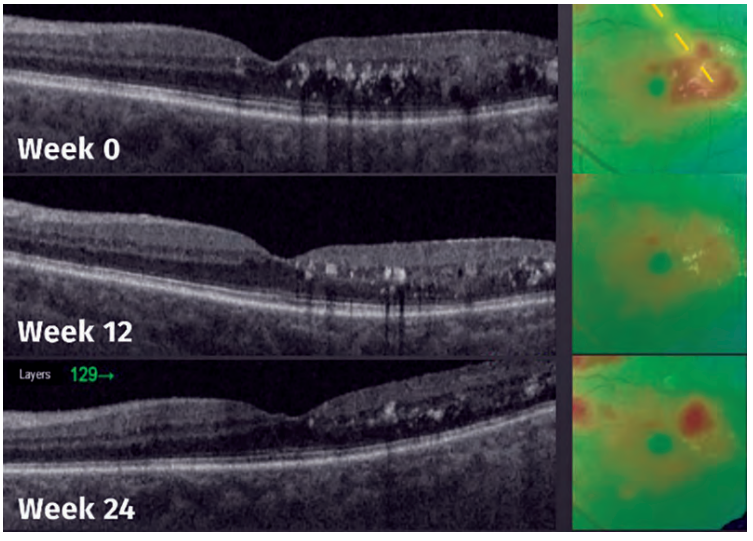

Figure 1. Clinically significant extrafoveal edema.

There are three significant diagnostic scenarios of CI-DME where SubLiminal laser should be considered before any other treatment modality. In my practice and related study,[6] I use the EasyRet 577-nm yellow SubLiminal laser (Quantel Medical).

The first is clinically significant extrafoveal edema. In these cases, the edema is distant enough from the fovea to keep the central vision safe. The benefits of using SubLiminal laser therapy in cases like this are the durability and repeatability of the laser treatment since there is no damage to the RPE, so the area can be retreated in future edematous resurgences (Figure 1).

The second scenario consists of a fovea-involving case with decreased visual acuity. Here there is an option of combination

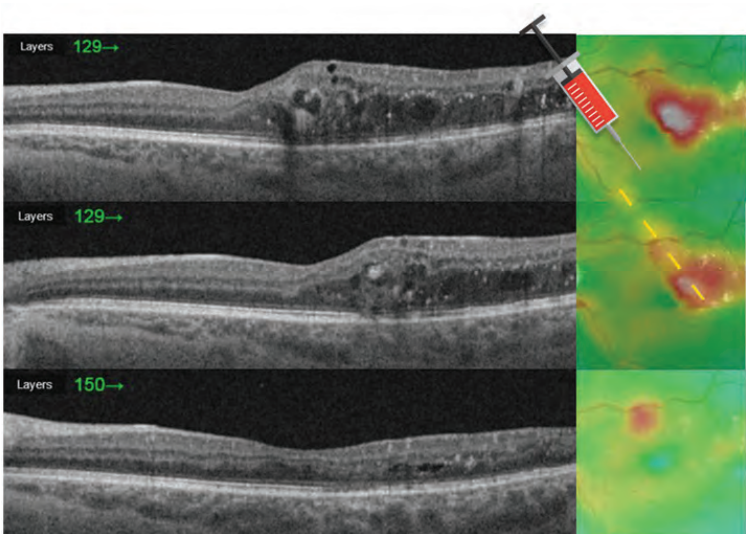

Figure 2. Combination treatment in thicker fovea/decreased visual acuity (inject first).

treatment (laser following intravitreal injection). When the fovea is involved and the vision is reduced, the priority is to "rescue" the fovea from the inflammatory environment to improve the long-term visual prognosis, so intravitreal therapy would be the first-line treatment thanks to its quicker action. We inject first until the edema is cleaned away from the fovea and then laser the remaining thickened area, which will provide a better and more durable response at times with one single injection (example shown in Figure 2).

The third scenario is a fovea-involving mild edema with good vision. In these cases, the treatment decision is more controversial. Is observation the best path forward, risking further deterioration? Should we spend money and risk complications such as endophthalmitis injecting a good eye? Conventional laser should not be considered close to the fovea. However, SubLiminal laser can work safely next to the fovea and make a significant difference in the growing severity of the edema while reducing or eliminating the need for intravitreal injections. SubLiminal laser is, in our opinion, the best option for this scenario and has proven effective in a range of cases with low levels of complications (Figure 3).[5]

We performed a study which demonstrated success in terms of safety and efficacy, and it stabilized visual acuity for these patients.[6] From week 1 to week 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 the cases were resolved. None of the treated patients experienced deterioration requiring a shift to combination intravitreal treatment during the follow-up.

SUBLIMINAL LASER TREATMENT—HOW IT IS DONE

For CI-DME, it is recommended to follow the guidelines provided by Victor Chong MD, FRCS, FRCOphth, the leading research physician and industry expert in SubLiminal laser therapy of DME. First, it is essential to treat large areas to stimulate a high number of RPE/Müller cells to obtain a clinically significant response. For the same reason, treat densely and avoid leaving blank spaces so that you can recruit every cell in the treatment area. Lastly, it is recommended to use the appropriate amount of power. Too much energy per area unit will result in a "suprathreshold" treatment that may result in cell damage. Titration of power at one-half of the minimum energy to cause a barely visible burn in the healthy peripheral macula is recommended. Since the term "barely visible" is quite subjective, it might be safer for the beginner to start at a lower power (i.e 1/3 and work his or her

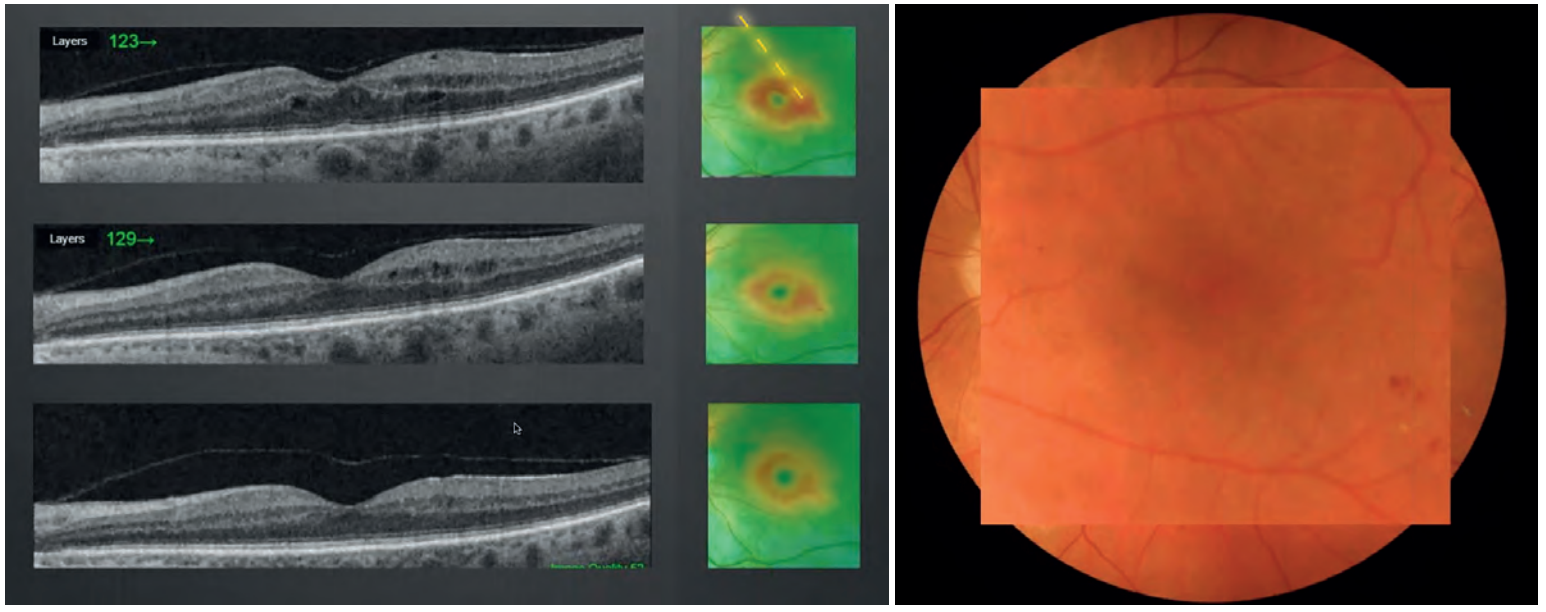

Figure 3. Fovea-involving edema with good vision after SubLiminal laser (< 400 µm thick).

way up from there). The rest of the parameters can be universalized (spot size 160 µm, 5% duty cycle). Following these recommendations will avoid insufficient spots, which has been identified as the primary cause for treatment failure.[7]

SHOULD WE TREAT THE FOVEA? HOW CLOSE CAN WE GO?

This question has two correct answers. First, if the recommended treatment guidelines are followed precisely, treating through the fovea is possible and safe. Nevertheless, Dr. Chong does not recommend transfoveal treatment, especially for new SubLiminal laser users and particularly in cases of DME in which we are treating OCT-guided treatment areas. Indeed, the fovea is extremely small. After treatment of the areas surrounding the fovea, the beneficial effect of the laser treatment will extend to the foveal area without treating it directly (Figure 4). Adding a few additional laser spots to include the fovea has not been proven to be more effective and should be reserved for physicians with extreme proficiency and expertise. Second, the preferred protocol is to exclude the fovea during treatment as you will see equally satisfying results. You can treat close to the fovea, up to 100 µm. So, can you treat the fovea? Yes. Do you need to? No, the few spots necessary to cover it will hardly make any change in the overall results.

For each case, it is recommended to evaluate at 8 to 12 weeks using both OCT slides and thinness maps, as well as autofluorescence, to check for any RPE disturbances from potential suprathreshold treatment. With that you can adjust your parameters to optimize your results.

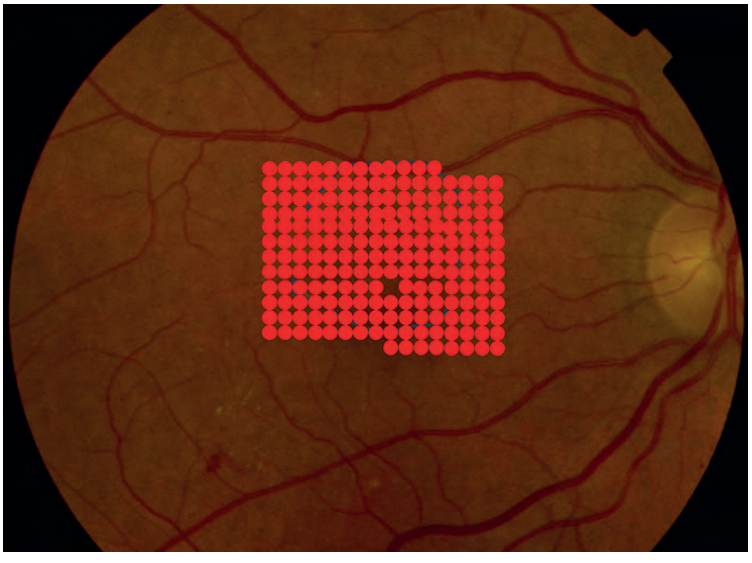

Figure 4. SubLiminal laser treatment excluding the fovea.

CONCLUSION

The main takeaway we learned from our study is that SubLiminal laser is an effective and safe treatment alternative for fovea-involving DME with good vision.[6] A strong point for new practitioners is sparing the fovea from treatment does not worsen the results while providing extra safety. Choosing to hold off treatment to observe will require a high frequency of follow-up visits. Also, you can expect one-third of observed patients will experience deterioration that will require intravitreal treatment.[8]

When considering SubLiminal laser for CI-DME, patient selection is key. SubLiminal laser therapy is a viable first-line treatment option for CI-DME patients with clinically significant extrafoveal edema and patients with fovea-involving mild edema with good vision. SubLiminal laser can reduce, or eliminate, the use of intravitreal injections and associated risks, costs, and a demanding in-office treatment schedule. In our experience, the more we 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 good responses. The two cornerstones to successful SubLiminal laser treatment are surface area and density. It is important to practice patience with this process and to educate the patient on realistic expectations. A flawlessly performed laser takes from 6 to 16 weeks to begin showing its effect, so be patient. Finally, as with any surgical procedure, if you take the time to audit your processes, laser application proficiency, and results, you will get better with time. ■

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Macular Research on the Move

Phase 1 and 2 studies are exploring novel targets in the treatment of AMD and DME.

BY FUAD MAKKOUK, MD; BRIAN B. BERGER, MD; AND GRACE ANDRES

Early clinical studies are under way assessing the safety and tolerability of several novel molecules that may potentially show efficacy in the treatment of macular edema or macular degeneration. The studies outlined in this article are expected to yield insights into new treatment targets to improve the management of both wet and dry age-related macular degeneration (AMD) and diabetic macular edema (DME). The Retina Research Center has experience with all of these drugs through participation in these clinical trials (Figures 1 to 3).

ONE-TWO PUNCH

BI 836880 (Boehringer Ingelheim) is a bispecific nanobody drug. Administered via intravitreal injection, it targets VEGF and angiopoietin-2 (Ang-2) by incorporating antigen-binding areas that are present in antibodies of VEGF and Ang-2. By inhibiting VEGF and Ang-2 receptors, the compound is thought to block signaling pathways for neovascularization and address the effects of wet AMD.[1]

Study Design

An open-label, nonrandomized, uncontrolled phase 1 study (NCT03861234) with projected enrollment of 42 patients was initiated last year. The purpose of the study, which will include a single rising dose phase followed by a multiple rising dose phase, is to evaluate the safety, tolerability, and pharmacodynamics of BI 836880 in intravitreal injections.

The primary endpoint in the single rising dose portion is to measure ocular dose-limiting events within 43 days of administration. Secondary endpoints include drug-related adverse events (AEs) or any ocular AEs in the study eyes.

The primary endpoint in the multiple rising dosage portion is drug-related AEs occurring from administration up to 169 days. Secondary measures include changes from baseline in central subfield thickness and BCVA at 12 weeks for each dose administration, time to recurrence after last treatment, and number of patients with ocular AEs in the study eye.[1]

Looking Forward

The study began in June 2019, and completion is projected for October 2021.

AT A GLANCE

- Multiple compounds that address novel targets in AMD and DME are undergoing early clinical evaluation.
- Mechanisms beyond the well-known anti-VEGF include inhibition of Ang-2, the complement pathway, the HtrA1 enzyme, and plasma kallikrein.
- Results of some phase 2 studies may be available next year.

Image courtesy of Yong Ren

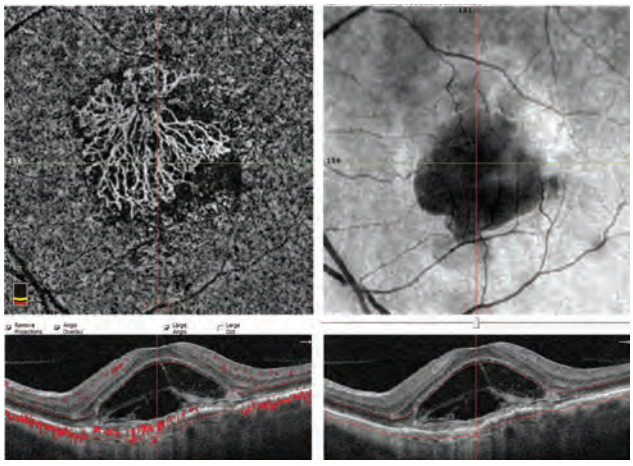

Figure 1. This OCT angiography image demonstrates a neovascular AMD lesion with type 1 (below RPE) and type 2 (above RPE) mixed choroidal neovascularization at the outer retina and choriocapillaris segmentations.

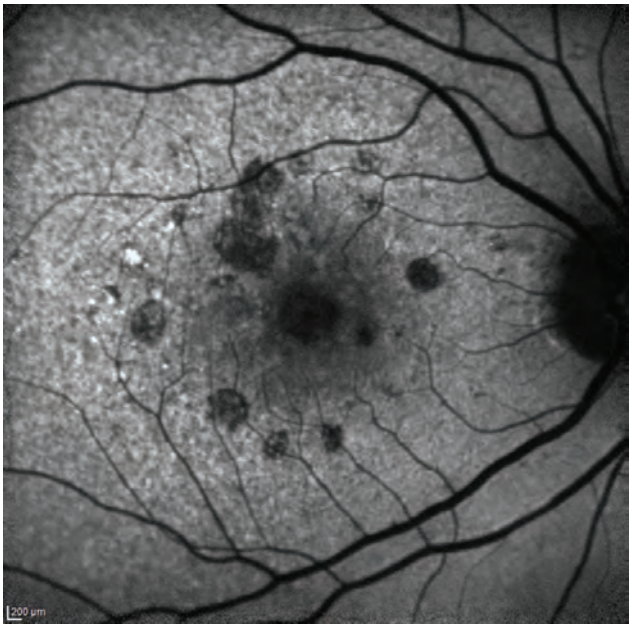

Image courtesy of Yong Ren

Figure 2. This fundus autofluorescence image from a dry AMD patient shows small size GA lesions in the macula away from the fovea.

EASE THE STRESS

Mitochondria-mediated oxidative stress is considered a likely contributing factor to the underlying pathologic processes of AMD, as reactive oxygen species (ROS) cause injury to the photoreceptors, the retinal pigment epithelium (RPE), and the choriocapillaris. Elamipretide (MTP-131 and SS-31, Stealth BioTherapeutics) is an aromatic-cationic tetrapeptide that penetrates cell membranes and transiently localizes to the inner mitochondrial membrane.

Elamipretide has been shown to improve cellular adenosine triphosphate levels in dysfunctional mitochondria and prevent pathologic ROS formation and opening of the mitochondrial permeability transition pore, which can reduce the extent of apoptosis and necrosis. The drug is administered with a novel delivery system as a subcutaneous injection.

Study and Results

The ReCLAIM study was a phase 1, single-site, open-label clinical trial to evaluate the safety and tolerability of subcutaneous elamipretide in individuals with dry AMD. Patients were placed into one of two groups: those with noncentral geographic atrophy (GA) or those with high-risk drusen (HRD) without GA.

Noncentral GA was defined as an area greater than 1.27 mm^2 and less than 10.16 mm^2 as determined by fundus autofluorescence, with sparing of the fovea. HRD was defined as the presence of either at least one large (≥ 125 µm) druse or multiple medium-sized (63–124 µm) drusen.

All patients received daily subcutaneous 40 mg elamipretide, and outcomes were assessed at week 24. In the noncentral GA subgroup there was a mean increase in BCVA of 4.6 ± 5.1 letters from baseline (P = .003), and the mean change in square root area of GA was 0.13 ± 0.14 mm as measured on OCT. (The GA growth rate was less than the 24-week growth rate in the placebo control arms of other clinical trials.) At week 24 in the HRD group, there was a mean increase in BCVA of 3.6 ± 6.4 letters from baseline (P = .025). Most AEs were limited to injection site reactions.[2]

Looking Forward

ReCLAIM-2 (NCT03891875) is a phase 2 randomized, double-masked, placebo-controlled clinical trial, initiated last year, to evaluate the safety, efficacy, and pharmacokinetics of elamipretide in individuals with AMD with noncentral GA. About 180 patients will be enrolled and randomized in a 2:1 ratio to receive either elamipretide or placebo through the elamipretide delivery system. The participants will self-administer either elamipretide 40 mg or placebo via daily subcutaneous injections using the delivery system for 48 weeks, followed by a 4-week follow-up period.

The primary efficacy endpoint is the change in low-luminance BCVA. Secondary outcome measures include change in BCVA, reading acuity, and size of GA. Estimated completion date for ReCLAIM-2 is December 2021.

SLOW PRODUCTION

IONIS-FB-LRx (Ionis Pharmaceuticals) is an antisense oligonucleotide that reduces the production of complement factor B (FB). The FB protein is a primary fluid-phase regulator of the alternative complement pathway. Genetic association studies show that variants of the FB gene that provide modest increases in FB activity increase the incidence of GA. IONIS-FB-LRx is administered subcutaneously and is proposed to decrease the progression of GA.[3]

Image courtesy of Yong Ren

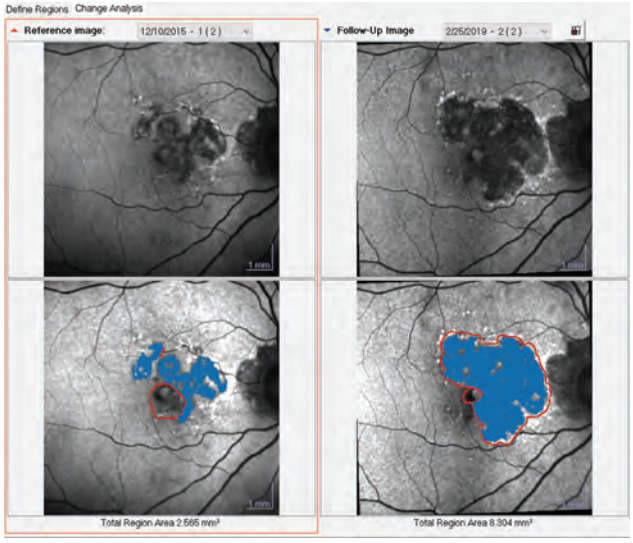

Figure 3. Fundus autofluorescence images of the same patient from two different visits (left, 2015; right, 2019) illustrates GA (secondary to dry AMD) increasing from a total region area of 2.565 mm^2 to 8.304 mm^2. The GA progression has not reached the foveal center.

Study and Results

A phase 1 placebo-controlled masked study of IONIS-FB-LRx in 54 healthy volunteers demonstrated the ocular and systemic safety of the drug when given subcutaneously. The study demonstrated reduction of pharmacodynamic endpoints such as plasma FB levels and complement alternative pathway activity. An approximately 70% reduction in plasma FB was accompanied by an equivalent reduction of the FB split product, Bb. A long duration of action was observed, suggesting the potential for monthly administration.

Looking Forward

GOLDEN (NCT03815825) is a phase 2 randomized, placebo-controlled, double-masked study currently recruiting participants with GA secondary to AMD to assess safety and efficacy of multiple doses of IONIS-FB-LRx. Approximately 330 participants will be randomly assigned into one of two groups. The first group will receive IONIS-FB-LRx with random assignment to one of 3 dosage levels, administered subcutaneously every 4 weeks for 45 weeks.

A second stage will expand two of the three dosing cohorts in a new randomized group of participants. The second group will receive a matching placebo solution administered in the same manner. The primary outcome measure will be absolute change from baseline in GA area at week 49, as determined by imaging.[3]

STYMIE PROGRESSION

RG6147 (Genentech) is a potent inhibitor of high-temperature requirement A1 (HtrA1), an enzyme that causes the breakdown and elimination of extracellular matrix proteins, resulting in atrophy of the photoreceptors, RPE, and Bruch membrane choroid. HtrA1 may affect the visual cycle as well as the stability of proteins required for photoreceptor and RPE cell survival.[4] As an anti-HtrA1 antibody, RG6147 should theoretically target this novel pathway in GA secondary to AMD, potentially slowing the progression of lesion growth.

Study and Results

A phase 1 multicenter, open-label, single-dose, dose-escalation, and multiple-dose study assessed the safety, tolerability, pharmacokinetics, and immunogenicity of intravitreal injections of RG6147 in patients with GA secondary to AMD. The study found that RG6147 was well tolerated at doses up to 20 mg per eye, with no dose-limiting toxicities, serious ocular AEs, or treatment-related systemic or ocular AEs in all 28 patients. Furthermore, an enzyme activity-based pharmacodynamic assay suggested the potential for 8-week target inhibition at higher doses.

Looking Forward

GALLEGO (NCT03972709) is a phase 2 multicenter, randomized, single-masked, sham-controlled study that began enrolling last year. It will assess the safety, tolerability, and efficacy of intravitreal injections of RG6147 in patients with GA secondary to AMD. Approximately 285 patients will be randomly assigned into one of four study arms: RG6147 or sham injection dosed every 4 or 8 weeks. The primary outcome is the change in GA area at 18 months.

Secondary endpoints include the percentage of patients with ocular and nonocular AEs, serious AEs, and AEs of special interest.[5] Completion of the trial is expected in 2022.

A STABLE TARGET

THR-149 (Oxurion) is a bicyclic peptide inhibitor targeting plasma kallikrein (PKal). Through the inhibition of the PKal-kinin system, THR-149 prevents induction of retinal vascular permeability, inflammation, and angiogenesis.[6] Individuals with DME have elevated levels of PKal, and the vitreous level of PKal varies less than vitreous levels of VEGF. This may enable THR-149 to serve as a target in the treatment of DME more effectively than VEGF.

Study and Results

A phase 1 open-label, US multicenter, nonrandomized trial evaluated the safety of a single intravitreal injection of THR-149 at three ascending dose levels in 12 participants with visual impairment due to center-involved DME. The primary outcome measure was incidence of dose-limiting toxicities up to the day 14 visit.

Secondary outcome measures included incidence of systemic and ocular AEs, including serious AEs, and laboratory abnormalities detected up to the end of the study. No

(Continued on page 55)

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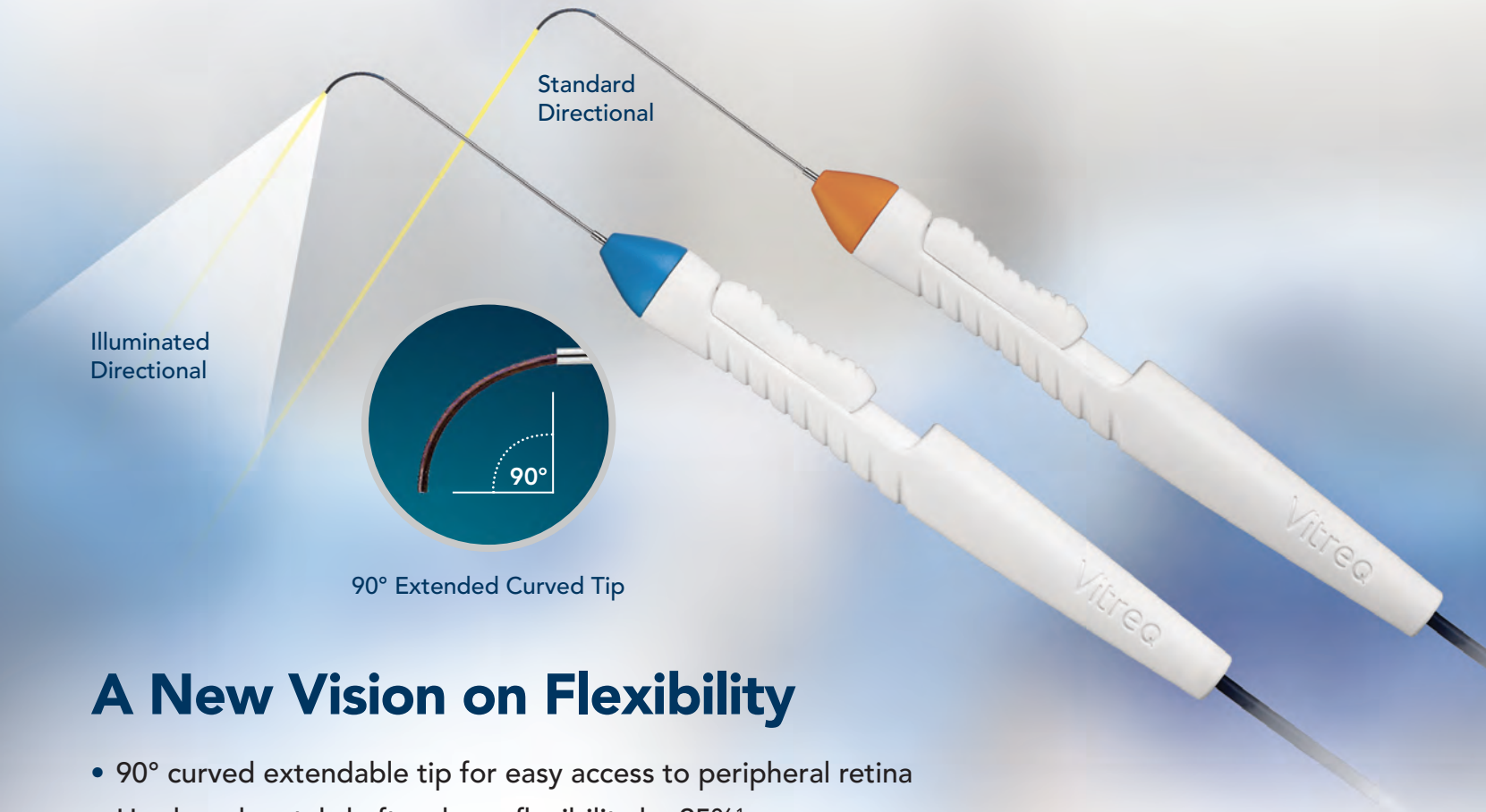

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A Timely Debut for Extended-Release Polymer Technologies

A look at sustained-release therapeutics in the retina pipeline.

BY MICHAEL WEAVER, MS; TREMAYNE KOOCHIN, BKIN; AND HEERAL SHAH, MD; EDITED BY JORDANA G. FEIN, MD

Even though most retina practices across the country have been preoccupied this year with changes brought on by the coronavirus pandemic, 2020 is still an exciting year because of the potential of new ophthalmic treatments in the pipeline. In this article, we discuss some of these potential new developments in retina, focusing on extended-release polymer technology. As is the case with many emerging therapeutics, some of these treatments have not yet released peer-reviewed data and should be evaluated with caution.

OCULAR THERAPEUTIX

OTX-TKI (axitinib intravitreal implant, Ocular Therapeutix) is a sustained-release tyrosine kinase inhibitor (TKI) implant targeting VEGF-induced retinal leakage, delivered through intravitreal injection for the treatment of exudative macular degeneration. Using a bioresorbable hydrogel, this injectable is designed to deliver its drug for up to 12 months. In a preclinical study, Dutch belted rabbits (n = 9) were dosed bilaterally with OTX-TKI, then challenged with VEGF at 2, 3, and 6 months. Compared with control eyes (n = 4), OTX-TKI significantly suppressed leakage at all challenge points.[1] In a follow-up study, OTX-TKI was evaluated for 12-month dosing.[2] Using a similar setup, 15 rabbits were bilaterally dosed and then challenged with VEGF injections at 3, 6, 9, and 12 months. Leakage was significantly suppressed at all challenge points in comparison with control eyes (n = 4). Ocular Therapeutix began recruiting for a phase 1 clinical trial outside the United States in 2018 evaluating safety, durability, and tolerability in individuals with wet AMD. Completion is anticipated in November 2021.[3]

GRAYBUG VISION

GB-102 (sunitinib maleate, Graybug Vision) is an injectable intravitreal TKI suspended in polymer microparticles (MP). Due to concerns regarding the possibility of MPs blocking the visual axis, GB-102 was modified to promote aggregation

AT A GLANCE

- A number of sustained-release polymer implant technologies with potential therapeutic applications in retina are undergoing clinical evaluation.
- Several of the drugs deployed by these implants are inhibitors of tyrosine kinase or other kinases, and one is a drug-polymer conjugate.
- Results for most of these potential therapeutics have not undergone peer review and should be evaluated with caution.

of the MPs to form a depot after intravitreal injection; the MPs later biodegrade to form lactic acid and glycolic acid.[4] The drug inhibits multiple intracellular tyrosine kinases, thereby inhibiting VEGF receptors 1, 2, and 3. It also inhibits platelet-derived growth factor receptors A and B, stem-cell growth factor receptor, and colony stimulating factor. A study using a murine model for type 2 neovascularization (NV) found that 10 µg of MPs injected intravitreally significantly reduced incidence of NV for 24 weeks.

Of note, subconjunctival injection of GB-102 was also explored in murine models. Histologic examination revealed significant differences for 2 µg and 20 µg MP dosing compared with empty MP injection. The noninjected fellow eye was also examined and found to have no significant difference compared with empty MP injection, suggesting little systemic spread of the compound. The follow-up time for subconjunctival injection was minimal, and this route must be further explored. Additionally, the study appeared to support neuroprotective effects of GB-102, with significantly greater outer nuclear thickness and higher rhodopsin kinase levels in comparison with free aflibercept (Eylea, Regeneron).[4]

In results announced in a press release by Graybug Vision, the ADAGIO phase 1/2a multicenter trial, including 32 patients with wet AMD who had previously responded to anti-VEGF therapy, met its primary endpoints of safety and tolerability. According to the company, GB-102 was "well-tolerated with no dose limiting toxicities, drug-related serious adverse events or inflammation" in the trial. Graybug Vision also reported that, in a secondary endpoint, 88% and 68% of participants in the trial were maintained on a single dose of GB-102 at 3 and 6 months, respectively.[5] These results are cause for cautious optimism, although a well-powered study will be necessary to verify these unrefereed results.

Another trial evaluating GB-102 in patients with diabetic macular edema (DME) and retinal vein occlusion (RVO) was recently completed, but no results had been announced at the time of the writing of this article.[6] A phase 2b trial in individuals with AMD has concluded patient enrollment and is ongoing.[7]

KODIAK

KSI-301 (Kodiak) is an anti-VEGF–biopolymer conjugate being examined for use in wet AMD, DME, and RVO to rapidly reduce VEGF burden and provide extended durability. KSI-301 uses an antibody-biopolymer conjugate platform that is 950 kDa in size, compared to 48 kDa for ranibizumab (Lucentis, Genentech) and 115 kDa for aflibercept. Results of clinical trials to date are available only via meeting presentations,[8] so caution is advised in their interpretation until they have been peer-reviewed.

In a phase 1b study in patients with wet AMD, DME, or RVO, participants were given three baseline injections of KSI-301 at 1-month intervals, then monitored with protocol-guided treatment from 12 to 148 weeks, with mandated injections at least every 6 months for AMD patients.

KSI-301 was deemed to be well tolerated in 546 total doses given to 130 participants. Intraocular inflammation was seen after 0.37% of injections (2 of 546) with either trace or 1+ vitreous cell. Both cases had complete resolution of inflammation without vasculitis or retinitis. The adverse event profile was considered consistent with intravitreal anti-VEGF agents.

According to data from the phase 1b trial presented this year, preliminary results in AMD (n = 51) indicate that BCVA improved by 5.8 letters from baseline at 44 weeks. The first retreatment was given before 3 months, at 4 months or longer, at 5 months or longer, or at 6 months for 18% (9), 82% (40), 66% (27), and 49% (20) of patients, respectively.

Preliminary results in DME (n = 35) indicate that BCVA improved by 6.6 letters from baseline at 44 weeks. The first retreatment was given at or before 3 months, at 4 months or longer, at 5 months or longer, or at 6 months or longer for 24% (8), 76% (25), 70% (23), and 67% (22) of patients, respectively. At 44 weeks, 45% (15) of patients had yet to require a retreatment.

Preliminary results in RVO (n = 35) indicate that BCVA improved by 22.4 letters from baseline at 44 weeks. The first retreatment was given at or before 2 months, at or before 3 months, or at 4 months or longer for 33% (11), 44% (14), and 56% (18) of patients, respectively. At least once during follow-up, 71% (24) of patients achieved a treatment interval of greater than 4 months.

Kodiak is recruiting for phase 3 trials for patients with wet AMD, DME (two separate trials), and RVO.[9-12]

AERIE PHARMACEUTICALS

AR-13503 (Aerie Pharmaceuticals), an inhibitor of rho kinase and protein kinase C (PKC), is a sustained-release implant being investigated for the treatment of wet AMD and DME. Suspended in a bioerodible polymer, AR-13503 provides controlled release of its active ingredients. Preclinical studies of AR-13154, a precursor molecule to AR-13503, demonstrated reduction of choroidal neovascularization of 35% ($P < .001$), and a significantly superior effect when used in combination with aflibercept (57%, $P < .005$).[13] Initial reports have shown linear drug release in vitro for more than 100 days. In rabbits, concentrations of AR-13503 were sustained at or above therapeutic levels established by an in vitro study for 5 months, followed by gradual decline in month 6. Drug concentrations in nontherapeutic regions (cornea, lens, vitreous) never exceeded 20% of those seen in the retina, retinal pigment epithelium, and choroid.[14] Phase 1 clinical trials have

finished recruitment, and completion is anticipated in September 2021.[15]

AR-1105 (Aerie Pharmaceuticals) is a bioerodible dexamethasone implant being investigated for use every 6 months in individuals with DME, RVO, or uveitis. In a pharmacokinetics and tolerability study in cynomolgus monkeys, therapeutically relevant dexamethasone concentrations were detected in the retina, choroid, and vitreous for at least 6 months with minimal anterior chamber and systemic exposure. Additionally, there was no implant-related effect on IOP.[16] In a September 2020 press release, Aerie reported results of a recently completed phase 2 multicenter study of 49 patients. The implant "demonstrated positive and sustained treatment effects with both formulations as shown by increases in best corrected visual acuity and reductions in macular edema," according to the company.[17] At the time of this writing, no statistics are available for review, and no timeline for phase 3 trials has been made public.

LOOKING AHEAD

Therapeutic approaches to the range of retinal vascular diseases continue to evolve. Although currently available treatments provide far greater benefit than was conceivable 15 years ago, we have much to look forward to with drugs and implants now in the pipeline, including the possibility that they will offer enhanced efficacy and durability. ■

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The AMD Pipeline: A Look At The Latest Results

Myriad therapeutics are making their way through clinical trials. Here's a look at recent data.

BY NIKA BAGHERI, MD; ALLEN CHIANG, MD; ROBERT L. AVERY, MD; AND ALLEN C. HO, MD

AMD is the leading cause of permanent impairment of central vision in individuals 65 years of age and older, affecting more than 1.8 million Americans 40 years of age and older.[1] No cure exists for the condition, but myriad therapeutics and drug delivery systems are moving through the development pipeline.

This article provides a brief overview of some of the novel therapies under investigation for the treatment of dry and wet AMD.

DRY AMD

OpRegen (Lineage Cell Therapeutics) is being evaluated in a phase 1/2a study. In the trial, a single injection of human retinal pigment epithelium (RPE) cells, derived from an established pluripotent cell line, is transplanted in suspension and delivered subretinally in patients with advanced dry AMD with geographic atrophy (GA).[2] The company announced completion of patient enrollment in November, and interim results were presented at the 2020 Virtual ARVO Meeting.[3]

The open-label, dose-escalation safety and efficacy trial includes four cohorts of patients with advanced dry AMD and GA. Patients in cohorts 1–3 have worse baseline VA (< 20/200); cohort 4, which includes patients with an average VA of 20/125 and smaller areas of atrophy, is still recruiting. Eyes with the poorest vision were implanted with 50,000 to 200,000 OpRegen cells. The trial's primary objective is to assess the therapy's safety and tolerability. A secondary objective is evaluating the cells' survival and possible effects of OpRegen treatment by assessing changes in retinal structure and visual function.

At the interim analysis, patients in cohorts 1–3 had no marked, sustained reductions in visual acuity.[3] The five patients in cohort 4 demonstrated improved vision with up to 1 year of follow-up. One patient experienced a 10-letter gain that was sustained for 15 months.[3] There were no reports of acute or delayed inflammation, but all patients reported at least one adverse event.

Apellis Pharmaceuticals announced positive 18-month data from its phase 1b study of **pegcetacoplan (APL-2)**, a pegylated cyclic peptide inhibitor of complement C3, in patients with advanced GA secondary to AMD.[4] Subsequently, Apellis announced the results of its FILLY phase 2 study.[5] In this 246-patient, multicenter, randomized, single-masked, sham-controlled trial, pegcetacoplan was administered as an intravitreal injection monthly (n = 86) or every other month (EOM, n = 79) for 12 months, followed by 6 months of monitoring post-treatment. The primary efficacy endpoint was the change in mean GA lesion area from baseline to month 12 in patients treated with pegcetacoplan compared with those treated with sham.

AT A GLANCE

- A number of new pharmaceuticals are making their way through the pipeline for the treatment of both dry and wet AMD.
- Novel approaches include the use of human retinal pigment epithelium cells, pegylated cyclic peptides, recombinant human anti-VEGF and anti-complement bispecific fusion proteins, gene therapy, biosimilars, a port delivery system, humanized single-chain antibody fragments, and bispecific antibodies that binds to and inactivate Ang-2 and VEGF-A.

The results of FILLY showed a 29% reduction in lesion growth in the monthly treatment group and 20% reduction in those treated EOM compared with sham. Overall, pegcetacoplan was well tolerated; however, new onset exudation appeared to be higher in the treatment groups (20.9% in the monthly group, 8.9% in the EOM group, and 1.2% in the sham group). Notably, the incidence was higher in those with wet AMD in the fellow eye. Patients with exudation were treated with anti-VEGF therapy, and no negative impact on visual acuity was observed. The phase 3 DERBY and OAKS trials of pegcetacoplan for GA were fully enrolled as of July 2020, with results expected in Q3 2021.

Investigators recently published results from the multicenter, randomized, double-masked GATHER1 phase 2/3 clinical trial evaluating **avacincaptad pegol** (Zimura, Iveric bio) in patients with GA secondary to AMD.[6] Avacincaptad, a novel complement C5 inhibitor, met the trial's primary efficacy endpoint at 12 months. The reduction in the mean rate of GA growth over 12 months for the 2 mg avacincaptad group compared with the corresponding sham control group was 27.4% (P = .0072), and for the 4 mg avacincaptad group compared with the corresponding sham control group the reduction was 27.8% (P = .0051).[7] Avacincaptad was generally well tolerated in the GATHER1 clinical trial, and there was no avacincaptad-related inflammation. At 18 months, new onset exudation was noted in 15.7%, 11.9%, and 2.7% of the 4 mg, 2 mg, and sham groups, respectively.[8] In a second phase 3 clinical trial (GATHER2), an estimated 400 patients will be randomly assigned to receive either monthly administration of 2 mg avacincaptad or sham for 12 months.

Collectively, these results for pegcetacoplan and avacincaptad suggest that both agents have the potential to slow the progression of GA secondary to AMD by modulating complement inhibition. However, the exact mechanisms of action for each drug differ, as do study methodologies, making comparisons across clinical trials inadvisable.

WET AMD

Results of Innovent Biologics' phase 1 open-label, multicenter, dose-escalation clinical trial of **IBI302**, a first-in-class ophthalmic recombinant human anti-VEGF and anti-complement bispecific fusion protein, were presented during the 2020 AAO Virtual Annual meeting. The trial evaluated the safety and tolerability of a single intravitreal injection of IBI302 in patients with wet AMD.

A total of 31 patients were enrolled, and no serious adverse events or dose-limiting toxicity were reported. The study demonstrated good safety and tolerability. Researchers observed improved vision and a reduction of retinal edema 1 week after administration; after 28 days, BCVA in all patients had increased by an average of 6 letters from baseline. Additionally, average central retinal thickness decreased by 141.2 µm compared with baseline, and the effect lasted until 6 weeks after administration for some.[9]

In October 2020, RegenxBio announced positive interim

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results from its phase 1/2a trial for **RGX-314** for the treatment of wet AMD.[10] This therapy involves subretinal delivery of the NAV adeno-associated virus (AAV8) vector that encodes an antibody fragment designed to inhibit VEGF. The study includes 42 patients with severe disease who require frequent anti-VEGF therapy. At 1 year, therapy was generally well tolerated across all five dosing cohorts—ranging from $3x10^9$ to $2.5x10^{11}$ GC/eye—with 77% of nonserious adverse events classified as mild. One possible drug-related adverse event of visual loss was reported in a patient with preexisting retinal pigmentary changes and extensive previous treatment who developed additional pigment changes. Patients across several cohorts had changes in retinal pigmentation, most of which were peripheral and inferior. There were no reports of clinically determined immune responses or drug-related inflammation beyond what is expected following routine vitrectomy.[10]

Cohorts 4 and 5 (dosed at $1.6x10^{11}$ and $2.5x10^{11}$ GC/eye, respectively) showed 61% and 85% reduction of anti-VEGF injections at 1 year, respectively. Both cohorts also experienced stable vision (mean BCVA change of +4 letters and -2 letters from baseline, respectively) and decreased retinal thickness (mean change of -61 µm and -79 µm, respectively). A dose-dependent increase in RGX-314 protein expression was observed across all five cohorts at 1 year, which was stable over 2 years in cohort 3, and over 1 year in cohorts 4 and 5. The reduction in injection burden in the higher dose cohorts correlated with higher protein measurements in these groups.

In September 2020, RegenxBio announced the initiation of its phase 2 trial, AAVIATE, investigating the efficacy, safety, and tolerability of RGX-314 delivered with the in-office SCS suprachoroidal microinjector.[11]

Adverum Biotechnologies announced positive interim data from cohorts 1–4 of its OPTIC phase 1 clinical trial of **ADVM-022** intravitreal injection gene therapy in patients with wet AMD who require frequent anti-VEGF injections.[12] The data further demonstrate the potential for the drug to greatly reduce the injection burden for patients with AMD. The therapeutic maintained efficacy at both high and low doses (n = 30); durability out to 92 weeks with zero supplemental injections in cohort 1 (high dose); and elevated

TRIAL DATA ON THE HORIZON

Several other ongoing studies for dry and wet AMD therapies are worth keeping an eye on:

Gyroscope Therapeutics recently announced the initiation of its phase 2 HORIZON trial evaluating **GT005** for patients with GA secondary to dry AMD. This single-dose AAV-based gene therapy is designed to increase production of the complement factor I (CFI) protein, thereby restoring balance to an overactive complement system. The GT005 program includes three clinical trials, all of which are in progress. The phase 1/2 FOCUS open-label clinical trial is evaluating the safety and dose response of three doses of GT005 in approximately 45 patients.[1]

HORIZON and EXPLORE are both phase 2, multicenter, randomized, controlled trials evaluating the safety and efficacy of a single subretinal injection of GT005 with a primary endpoint of progression of GA over 48 weeks.[1] EXPLORE is evaluating the therapy in patients with GA who have rare variants in their CFI gene, while HORIZON has a broader patient base.

AXT107, Asclepix Therapeutic's investigational drug candidate that inhibits VEGF-A/-C and activates Tie2, is showing potential as a single intravitreal injection with yearly dosing to treat wet AMD. In 15-month animal studies, the unique intravitreal self-assembling gel depot formation was well tolerated and demonstrated superiority to and greater durability than aflibercept, according to the company. Asclepix has received new investigational new drug application for AXT107 in December 2020 and plans to begin a first-in-human clinical study in Q4 2020.[2-5]

Chengdu Kanghong Biotechnology recently announced successful completion of week-36 primary endpoint visits for its phase 3 clinical development program, PANDA, evaluating **conbercept** (Lumitin) for the treatment of wet AMD. Two masked, randomized, controlled trials are evaluating the efficacy, safety, and durability of 0.5 mg conbercept every 8 weeks and 1.0 mg conbercept every 12 weeks in comparison with 2.0 mg aflibercept every 8 weeks. The primary outcome measure is BCVA, and secondary outcomes including the mean change in central retinal thickness at 36 weeks, change in visual acuity up to 96 weeks, and adverse events up to 96 weeks. Already approved for use in China, the drug recently gained approval in Mongolia as well.[6-8]

HMR59 (AAVCAGsCD59, Hemera Biosciences, recently acquired by Janssen), a transgene product that is a soluble form of CD59 that blocks complement at the membrane attack complex, remains under investigation for both dry and wet AMD. HMR-1001, a phase 1, open-label, multicenter, dose-escalating safety and tolerability study, evaluated safety after a single injection of HMR59 in treatment naïve eyes with dry AMD with GA. Hemera is also beginning a phase 2 trial for HMR59 for dry AMD to evaluate intravitreal high- or low-dose HMR59 with a sham injection. HMR-1002 is an ongoing phase 1 proof-of-concept study evaluating 25 eyes with new-onset wet AMD treated with anti-VEGF followed by HMR59 7 days later.[9-11]

GB-102 (sunitinib malate, Graybug Vision), a microparticle depot formulation, is showing promise for the use of tyrosine kinase inhibitors (TKIs) to treat wet AMD. In the ADAGIO phase 1/2a clinical trial, GB-102 met its safety endpoint and provided evidence of durable biological activity for up to 8 months from a single intravitreal injection. To read more about this therapy, see *A Timely Debut for Extended-Release Polymer Technologies* on page 30.[12]

Ocular Therapuetix reported interim phase 1 results for **OTX-TKI**, a bioresorbable, hydrogel fiber implant incorporating axitinib, delivered by intravitreal injection. The TKI implant was generally well tolerated, and a clinically meaningful decrease in subretinal and intraretinal fluid was seen in some patients. Find more about this therapy in *A Timely Debut for Extended-Release Polymer Technologies* on page 30.[13]

Clearside Biomedical is planning a study of suprachoriodal delivery of **axitinib** for wet AMD in the Oasis trial scheduled to begin in December 2020.[14]

Eyepoint Pharmaceuticals has announced plans for a phase 1 study of **vorolanib**, a TKI, released from the company's intravitreally injected implant.[15] This TKI has previously been tested orally in a trial for wet AMD and showed signs of reduced treatment burden; however, some patients developed systemic side effects.[16] The slow-release, intravitreal dose is markedly lower than the systemic dose, and systemic side effects are not expected.

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aqueous anti-VEGF protein expression at 18 months in cohort 1 in the two patients reported. Most patients in the trial were free from supplemental anti-VEGF injection, and ADVM-022 was generally well tolerated; inflammatory events were managed with topical steroids, although a minority of patients remained on these drops at 1 year after injection.

At the AAO meeting, investigators presented 1-year results from a randomized, double-masked, multicenter phase 3 study of **SB11** (Samsung Bioepis), a proposed biosimilar to ranibizumab (Lucentis, Genentech), in patients with wet AMD.[13] Of the 705 patients enrolled, 634 had completed the study up to week 52. Patients were randomly assigned to receive monthly injections of SB11 or 0.5 mg ranibizumab. The study met its primary endpoints, changes from baseline in BCVA at week 8 and central subfield thickness at week 4. Secondary endpoints included long-term efficacy, safety, pharmacokinetics, and immunogenicity, which were comparable between SB11 and ranibizumab.

Results from the phase 3 ARCHWAY study of the **Port Delivery System** (PDS, Roche) were presented at the ASRS and AAO 2020 meetings. Patients received either the PDS, a permanent refillable eye implant refilled every 6 months with a customized formulation of ranibizumab, or monthly 0.5 mg ranibizumab injections. Over 98% (n = 244/248) of patients in the PDS group were able to go 6 months between refill injections.[14] In addition, patients in the PDS group maintained stable vision comparable to the monthly ranibizumab group. The PDS was generally well-tolerated, with a favorable benefit-risk profile. The most common complication reported was mild conjunctival bleb or leak (6.5%).

Roche and Genentech have also initiated two global phase 3 clinical trials in wet AMD investigating **faricimab**, a bispecific antibody that simultaneously binds to and inactivates angiopoietin-2 (Ang-2) and VEGF-A. Phase 2 clinical trial data revealed that faricimab dosed every 12 or 16 weeks resulted in visual acuity and central subfield thickness changes similar to monthly ranibizumab. The multicenter, randomized, double-masked, active-comparator-controlled phase 3 TENAYA[15] and LUCERNE[16] studies will evaluate the efficacy, safety, and durability of faricimab compared with aflibercept for wet AMD. Nearly 1,300 patients have been randomly assigned to receive either faricimab every 16 weeks (with an option to drop to every 12 or 8 weeks), or aflibercept every 8 weeks. The primary endpoint of each study is the change in BCVA at week 48 from baseline.

KSI-301 (Kodiak) is an anti-VEGF–biopolymer conjugate under investigation for the treatment of wet AMD. KSI-301 is designed to rapidly reduce VEGF burden and provide extended durability.[17] Preliminary data from a phase 1b trial show that BCVA improved by 5.8 letters from baseline at 44 weeks in treated patients.[17] The company's phase 2b/3 DAZZLE study is evaluating KSI-301 once every 3, 4, or 5 months after 3 monthly doses compared with aflibercept every 2 months after 3 monthly doses.[18] ■

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The Future Looks Bright: The Therapeutics Pipeline for Diabetic Retinopathy


New agents, new modalities, different dosages, all now in clinical trials.

BY JOHN HINKLE, MD, AND JASON HSU, MD

Treatments for diabetic retinopathy (DR) and diabetic macular edema (DME) have made tremendous advances in recent decades, but modalities with better efficacy and longer durability are still needed. Many ongoing trials are aiming to validate new treatment options. These range from new drugs to advances in dosing or administration of established pharmaceuticals to entirely new modalities. In this article, we provide an overview of some phase 2 and 3 studies (Table) that, if successful, may revolutionize the treatment of DR and DME.

PHASE 3 STUDIES

Faricimab

RHINE (NCT03622593) and YOSEMITE (NCT03622580) are two phase 3 clinical trials designed to evaluate the efficacy of intravitreal injections of faricimab (Roche) for the treatment of DME in more than 900 participants each. Faricimab is a humanized immunoglobulin G antibody against two targets: VEGF-A and angiopoietin-2 (Ang-2). VEGF upregulates Ang-2, which further destabilizes retinal vasculature and increases inflammation.

Patients with type 1 or type 2 diabetes, abnormally increased central subfoveal thickness (CST), and VA of 20/40 to 20/320 at baseline are eligible for inclusion. The trials exclude patients who have high-risk proliferative DR (PDR) or have received anti-VEGF treatment within the preceding 3 months. The primary endpoint for both studies is change in BCVA from baseline to 1 year.

In two arms of each trial, participants receive injections of faricimab. Both experimental arms begin treatment with 6.0 mg injections dosed every 4 weeks for 20 weeks. Thereafter, one arm is treated every 8 weeks and a second experimental arm is treated every 12 weeks as long as the patient's CST does not increase and require more frequent treatment. The comparison arm is 2.0 mg aflibercept (Eylea, Regeneron) dosed every 4 weeks for 16 weeks, then every 8 weeks thereafter. All study arms will be continued for 100 weeks.

Primary outcome data for RHINE and YOSEMITE are expected at the end of 2020.

Brolucizumab

Positive results in the HAWK and HARRIER trials in patients with AMD led to the FDA approval of brolucizumab-dbll (Beovu, Novartis) for that indication.

The safety and efficacy of brolucizumab for treatment of DME is now being investigated in three phase 3 trials (NCT03481634). The potential benefits of brolucizumab stem from the low molecular weight of the drug, allowing the injection of a much higher molar dose compared with currently available therapeutics.

KESTREL (NCT03481634) is a randomized, double-masked, noninferiority study including participants with type 1 or type 2 diabetes with VA of 20/32 to 20/320 and abnormally increased CST on OCT. Individuals who have previously undergone any treatment for DME or have proliferative disease are excluded. The experimental arms of the studies

AT A GLANCE

- Multiple trials are under way with the promise of advancing treatment for diabetic eye disease.
- In addition to novel therapeutics, some trials are assessing alternative treatment schedules, delivery systems, and dosages.
- Gene therapy and photobiomodulation are also being investigated.

compare 3.0 mg and 6.0 mg doses of brolucizumab given every 6 weeks for five injections followed by maintenance injections every 8 or 12 weeks until the end of the study. The comparator for noninferiority is 2.0 mg aflibercept dosed every 4 weeks for five injections and then every 8 weeks as maintenance until completion of the study.

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The PDS With Ranibizumab Enters Phase 3 Trials.

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KESTREL reached full enrollment with 571 patients in March 2020. Study completion is expected in 2021.

Similarly, KITE (NCT03481660) is an international, randomized, noninferiority trial comparing brolucizumab with aflibercept for DME. This study includes patients with type 1 or type 2 diabetes with nonproliferative DR and previously untreated DME. Patients in one study arm will undergo treatment with 6.0 mg doses of brolucizumab given for five loading doses followed by maintenance therapy. The comparator is 2 mg aflibercept also administered for five loading doses followed by maintenance therapy. The primary outcome is change in BCVA from baseline to week 52.

KITE is still active and has completed enrollment with 361 patients. In September, Novartis announced that preliminary data show the trial met its primary noninferiority endpoint.

KINGFISHER (NCT03917472) is another phase 3 study assessing the effectiveness of brolucizumab in DME. This trial randomly assigns participants with DME to one of two treatment arms: 6.0 mg of brolucizumab every 4 weeks or 2 mg of aflibercept every 4 weeks. Patients with proliferative DR or prior medical or laser treatment for ocular disease are excluded. The primary outcome is change in BCVA from baseline to 12 months.

Data from the full enrollment of 521 patients in KINGFISHER are expected in 2021.

Ranibizumab via PDS

Two ongoing phase 3 studies are investigating the safety and efficacy of a new, higher concentration (100 mg/mL) of ranibizumab (Hoffman-La Roche) as delivered via the Port Delivery System (PDS) in DME (PAGODA) and DR (PAVILION). The PDS is an intraocular implant, surgically placed in the pars plana, that provides continuous delivery of a medication into the vitreous. The implant can be refilled as needed in an in-office procedure.

PAGODA (NCT04108156) is a noninferiority trial evaluating PDS with 100 mg/mL ranibizumab compared with intravitreal 0.5 mg ranibizumab (Lucentis, Genentech) injections in patients with DME. Participants have type 1 or type 2 diabetes, increased CST, and VA of between 20/32 and 20/320; patients with high-risk PDR are excluded. One arm of the study begins with four injections of ranibizumab, administered every 4 weeks. This treatment period is followed by insertion of the PDS, which is then refilled every 24 weeks with 100 mg/mL ranibizumab. A second study arm starts with 16 intravitreal injections of 0.5 mg ranibizumab, administered every 4 weeks, followed by insertion of the PDS. Change in BCVA from baseline to week 64 is the primary endpoint to demonstrate noninferiority, and assessments of the patient experience and quality of life are also included.

Recruitment for PAGODA is ongoing, progressing toward a target enrollment of 545 participants, and primary outcome data are expected in 2021.

PAVILION (NCT04503551) is designed to evaluate the PDS with ranibizumab 100 mg/mL versus intravitreal 0.5 mg ranibizumab injections in patients with moderately severe or severe nonproliferative DR. Importantly, patients with DME are excluded from this trial. The primary endpoint is the percentage of participants with an improvement of greater than 2 steps from baseline on the ETDRS Diabetic Retinopathy Severity Scale at 1 year. Participants will receive two intravitreal 0.5 mg ranibizumab injections before PDS insertion, and then the PDS will be refilled with 100 mg/mL ranibizumab every 36 weeks. A comparator arm will undergo regular examinations every 4 weeks until crossing over to receive the PDS implant.

PAVILION is actively recruiting, aiming for 160 patients.

Aflibercept

Building on the findings of its Protocol T, the Diabetic Retinopathy Clinical Research Network (DRCR.net) has initiated Protocol AC (NCT03321513), a phase 3 study to compare initial versus deferred treatment with aflibercept in DME, to look for differences in visual outcomes. In the experimental arm of the study, treatment is initiated with 1.25 mg bevacizumab (Avastin, Genentech) and then patients are changed to 2.0 mg aflibercept when CST meets the criteria for switching treatment. In the comparator arm, 2.0 mg aflibercept is administered from the beginning. The study will evaluate 260 patients with diabetes with increased CST and VA of 20/50 to 20/320; patients who have recently received treatments are excluded. The primary outcome is mean change in visual acuity at 2 years.

Protocol AC is fully enrolled, and completion and outcomes data are expected at the end of 2021.

PHOTON (NCT04429503) is a phase 2/3 randomized double-masked study designed to investigate the efficacy and safety of 8.0 mg aflibercept, referred to as high-dose (HD) aflibercept, compared with the current FDA-approved dose of 2.0 mg aflibercept. The target population is patients with DME, excluding patients with PDR or recent treatment for DME. In the two

TABLE. AN OVERVIEW OF THE DIABETIC RETINOPATHY PIPELINE

STUDY	PHASE	TARGET DISEASE	INTERVENTION	MECHANISM OF ACTION	COMPARATOR
RHINE/YOSEMITE	3	DME	faricimab	anti-VEGF and anti-Ang-2	aflibercept
KESTREL	3	DME	brolucizumab	anti-VEGF	aflibercept
KITE	3	DME	brolucizumab	anti-VEGF	aflibercept
KINGFISHER	3	DME	brolucizumab	anti-VEGF	aflibercept
PAGODA	3	DME	PDS (ranibizumab)	sustained delivery via surgical implant	ranibizumab IVI
PAVILION	3	DR	PDS (ranibizumab)	sustained delivery via surgical implant	ranibizumab IVI
Protocol AC	3	DME	bevacizumab with deferred aflibercept	anti-VEGF	aflibercept
PHOTON	2/3	DME	high-dose aflibercept	anti-VEGF	aflibercept
INFINITY	2	DME	ADVM-022	intravitreal anti-VEGF gene therapy	aflibercept
ALTITUDE	2	DR	RGX-314	suprachoroidal anti-VEGF gene therapy	observation
Protocol AE	n/a	DME	photobiomodulation	red/infrared light	sham

Abbreviations: Ang-2, agiopoietin-2; IVI, intravitreal injection; PDS, Port Delivery System

experimental arms of this trial, patients will receive HD aflibercept monthly for three injections and then either every 12 or every 16 weeks through the end of the study period. Patients in the control arm will receive five monthly doses of 2.0 mg aflibercept followed by injections every 8 weeks until the study concludes. The primary endpoint will be change in BCVA from baseline.

This study is ongoing and aims to recruit more than 600 patients. Estimated study completion is in 2023.

PHASE 2 STUDIES

ADVM-022

INFINITY (NCT04418427) is a randomized, double-masked trial investigating ADVM-022 (Adverum), a synthetic adeno-associated virus vector (AAV.7m8) carrying a coding sequence for aflibercept. This therapeutic candidate harnesses the technological advances of gene therapy, inducing cells in patients' eyes, to produce the drug. ADVM-022 is administered in a single intravitreal injection. Phase 1 data showed improved visual acuity and CST with two doses of the vector, but only 21 patients were treated, and follow-up was limited.

INFINITY is actively recruiting, seeking a total of 33 patients. Eligible patients will be randomly assigned to receive one of two doses of ADVM-022 or aflibercept. The primary goal is to assess the durability of a single injection of ADVM-022 for DME. All patients will be followed for 48 weeks. Completion is expected in 2021.

RGX-314

ALTITUDE (NCT04567550) is a randomized controlled clnical trial investigating another viral vector developed for anti-VEGF gene therapy. RGX-314 (RegenxBio) uses an adeno-associated virus vector (AAV8) to deliver a gene encoding an anti-VEGF monoclonal antibody fragment. The vector is delivered into the suprachoroidal space rather than intravitreally. This study will include individuals with type 1 or type 2 diabetes with VA better than 20/40 and without DME. The primary endpoint is improvement in DR severity at week 48 versus observational controls.

ALTITUDE is recruiting toward a goal of 40 patients, and primary outcome data are anticipated in 2021.

Photobiomodulation

DRCR.net Protocol AE (NCT03866473) is assessing the effect of photobiomodulation compared with sham on CST in eyes with center-involved DME and good vision. In photobiomodulation, far red or near infrared light is used to decrease diabetes-induced retinal inflammation, likely by stimulation of mitochondrial cytochrome C oxidase. In the experimental arm of this study, patients will undergo two 90-second sessions each day using a device that delivers 670-nm wavelength light, while those in the control arm will receive sham treatment. The primary outcome is mean change in CST at 4 months.

Initially, Protocol AE was designed as a crossover trial, but COVID-19 forced changes to the protocol. This study is active and fully enrolled at 134 patients.

CONCLUSION

As the preceding list makes clear, several ongoing phase 2 and 3 trials have the potential to revolutionize the treatment of DR and DME. New molecules such as faricimab and brolucizumab are aiming at established and novel targets. Familiar pharmaceuticals are being investigated at higher doses, with alternative timings, and via different delivery methods. Viral vectors and novel phototherapeutics are being investigated. This broad range of scientific inquiry, with multiple therapeutics now in phase 3 trials, may lead to exciting improvements in the management of diabetic retinal disease in the not-too-distant future. ■

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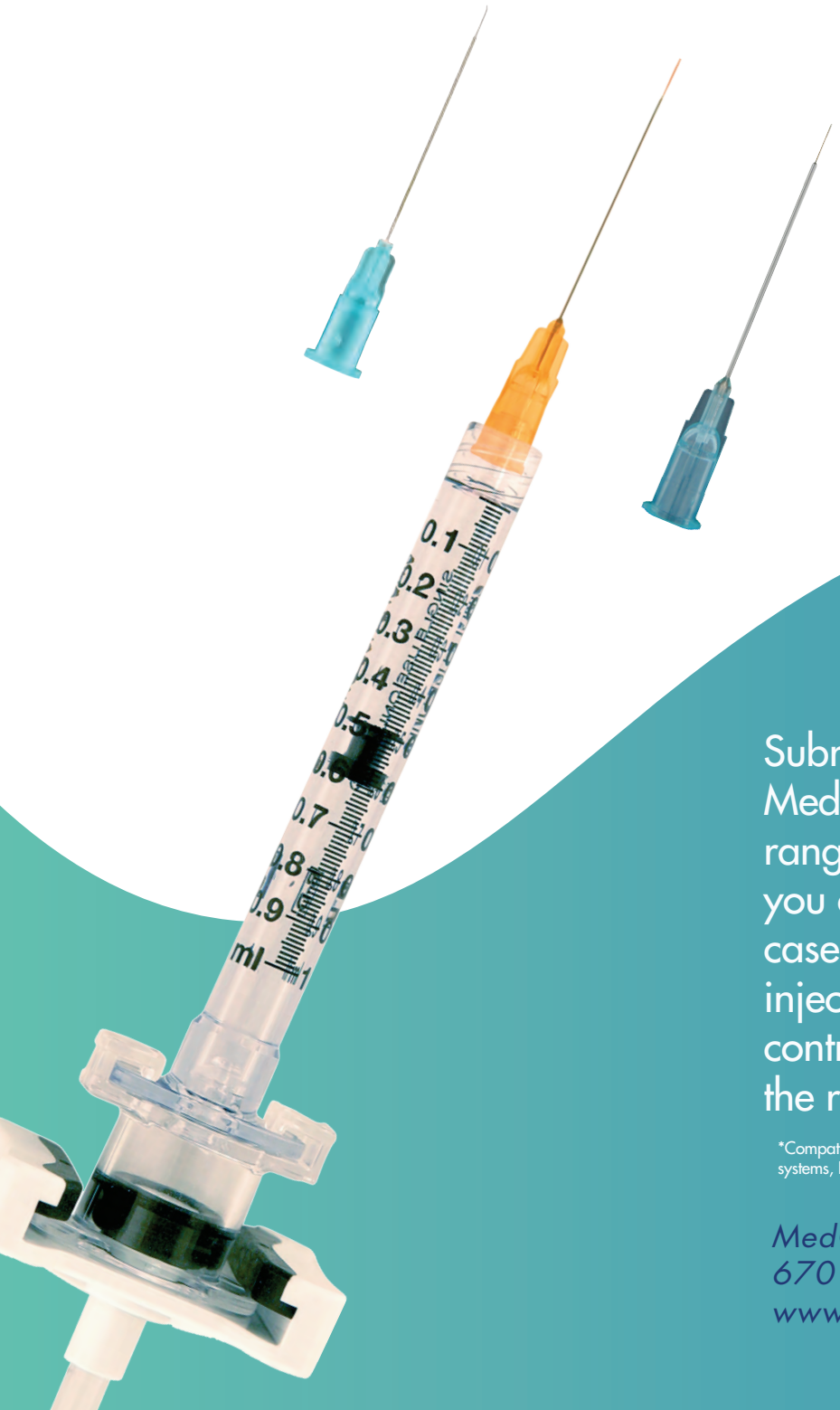

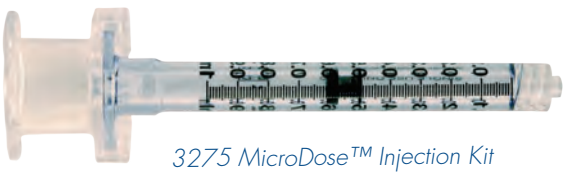

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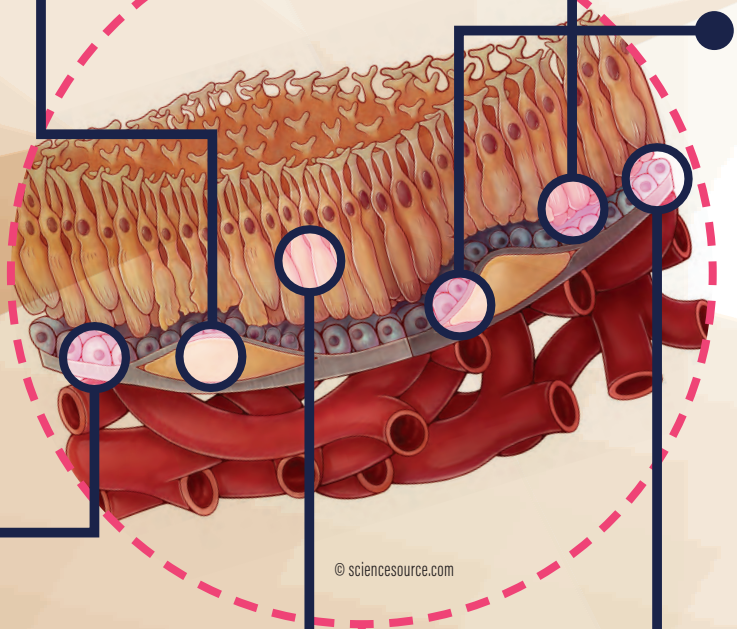
RETINA PIPELINE
A VIEW INTO ONGOING INNOVATION

Knowing where everything stands helps prepare you for the next era in retina.

BY PETER K. KAISER, MD



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THE STATE OF PIPELINE

In designing the second edition of *Retina Today*'s pipeline poster for wet and dry age-related macular degeneration (AMD), we focused largely on expanding the schematic used to illustrate the complement system. For many of us, the complement system is a relic of our medical training, something to be dusted off when conversation turns down a more erudite path. In the coming years, however, the complement system may well be key to unlocking therapies for dry AMD that could affect millions of patients.

In a way, we have attempted the impossible by illustrating the complement pathway. An artistic representation of a cascade that takes place on the cellular surface must (by virtue of graphic limitations) be depicted away from that surface, giving the impression that the events occur in some vacuous space between cells. They do not. Still, we know that our readers understand this and are even more certain that a detailed map of the complement system's steps is more important than a strict biologic geography lesson.

This edition of this poster consists of more than just cosmetic changes. We eliminated failed drugs, added new therapeutic candidates, and enlarged the complement system illustration to include new therapeutic targets.

Meetings might be paused for the foreseeable future, but that doesn't mean that education has stopped. Turn to this poster (and its digital interactive facsimile, found at bit.ly/retina-pipeline) to keep yourself sharp.

And remember: this poster is for you. Tear it out. Mark it up. Send us suggestions for how to improve it. We're already thinking about ways to develop it for next year's edition, and we need to hear from our audience about what works and what doesn't. ■

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LAYING THE FOUNDATIONS FOR INTERNATIONAL RETINA CARE

A discussion with two surgeons about building networks.

AN INTERVIEW WITH ERIC D. HANSEN, MD, AND CHRISTOPHER B. KOMANSKI, MD; BY BENJAMIN J. THOMAS, MD

In a 2016 article in *New Retina MD* entitled "The Next Chapter: Forging a Concept of International Retinal Care," I wrote about the task of crowdsourcing the answers to two central questions. First, what should be the primary goals for vitreoretinal surgeons interested in engaging on an international scale? Second, what are the most responsible, effective, and sustainable means of achieving those goals? In search of detailed answers, I recently reached out to two vitreoretinal surgeons with strong résumés of international involvement to ask for their insights on how to build networks for screening for retinal disease in underserved areas.

Benjamin J. Thomas, MD: Ophthalmology has a broad history of working internationally and delivering care across multiple cultural and economic contexts, but a uniting concept of international retina remains relatively new. How would you define the primary interests, tasks, and goals of international retina?

Eric D. Hansen, MD: 12.5 million people are blind or severely visually impaired due to AMD and diabetic retinopathy alone.[1] Another significant proportion of visual impairment, hidden in the broad strokes of global surveys, falls within the scope of vitreoretinal care. Diseases such as myopic degeneration, uveitis, oncology, trauma and its sequelae, toxicity, surgical complications, and inherited disease all contribute to the more than 200 million people worldwide with (as yet) uncharacterized visual impairment.

The task presented to the international retina community is understanding policy and public health principles and applying this understanding to a highly specialized field that provides high-acuity care while also treating chronic disease within a coordinated, multidisciplinary paradigm.

This task, as expressed, is admittedly daunting. Individuals and organizations working within this space must rely on a broad history of global ophthalmology initiatives—both the successes and failures—to present an organized, prioritized, adaptable blueprint for integrating medical and surgical retinal care into a universal eye health system.

This model will differ from that which has been successful in the realm of cataract blindness. Here, the timing of presentation influences outcomes considerably. Additionally, availability for frequent follow-up alongside reliable access to consumables and specialized therapeutics is requisite for the success of international retina.

Dr. Thomas: What prompted your own interest in international retinal work, and with what projects have you had the opportunity to be involved?

Dr. Hansen: I am not sure I can identify a particular prompt. Life and calling unfold as a story—a river of opportunities and decisions that empty into one's present. I see the interconnectedness of humanity and of life on this planet in a way that drives me to invest energy in a common future. So, with this perspective as an anchor, and a roster of incredible mentors as a catalyst, I waded into the world of global health as a medical student and immersed myself in the community of international ophthalmology following residency. I have worked with the Moran Eye Center and the Himalayan Cataract Project for more than 4 years—first as a global ophthalmology fellow then onward through vitreoretinal training—in their efforts to build capacity locally in Utah and in other parts of the world.

Christopher B. Komanski, MD: I was fortunate to complete my residency at a program with a global outreach division at Wake Forest. My first hands-on experience was

performing cataract surgery in San Pedro Sula with Tim Martin, MD; Matt Giegengack, MD; and Paul Dickinson, MD. The experience was impactful, and it motivated me to look for opportunities to apply my retina training in a similar way. During fellowship, I worked with incredible mentors such as Paul Bernstein, MD, PhD; Akbar Shakoor, MD; and Al Vitale, MD, who have all made tremendous contributions to international retina and uveitis.

BARRIERS TO CARE

Dr. Thomas: Considering the endeavor of international retina from both a personal perspective and a more global context, what are the primary barriers you perceive to the delivery of retinal care in resource-poor settings?

Dr. Hansen: Common barriers include patient access due to geography or distance; cost of treatment for the patient and cost of consumables for the hospital; procurement and maintenance of equipment; and the maintenance of a reliable supply chain of necessary pharmaceuticals, consumables and instruments. In addition, vitreoretinal training opportunities are limited. And even when identified and available, there is often a significant opportunity cost associated with an ophthalmologist leaving a community for 1 to 2 years to train.

Dr. Komanski: Patient expectations and how they align with cultural barriers; the need for frequent follow-up in chronic disease; the importance of timing in presentation and its influence on outcomes, especially compared with cataracts—to name a few.

Dr. Hansen: Medical retinal care, in particular, requires integration with primary care and other medical specialties. Often, we are fighting a losing battle if we cannot address or control the underlying pathology.

Dr. Thomas: Mature cataracts can be diagnosed with minimal dilation and a flashlight. Not so for retinal diseases, such as diabetic retinopathy, which usually require advanced techniques, equipment, and training to detect. How does this aspect of retinal care change our strategy for expanding into new or underserved regions?

Dr. Komanski: Imagine a hub-and-spoke model, with screening programs established in underserved communities that integrate primary care systems or community health workers with a center of excellence employing retina-trained physicians. After screening and disease confirmation, intervention may be organized by the center of excellence to be carried out in any number of locations, including the hub, a peripheral referral center, or even in more rural sites depending on the type and severity of disease and the appropriate intervention.

Dr. Komanski joined an international team of providers to bring much-needed eyecare to underserved patients in San Pedro Sula, Honduras.

Dr. Hansen: It's important to recognize that great models exist that are worth emulating, including Aravind in India, various US telehealth systems, and a mobile diagnostic program that was studied in Nepal.[2] Ophthalmology-extending mechanisms, such as ophthalmic technicians and trained community health workers using mobile diagnostics, are also great tools, but each must be tailored for use within specific geographic and socioeconomic contexts.

Dr. Komanski: Mobile diagnostics and other technologies can empower community health workers, primary care physicians, optometrists, and cataract surgeons, thereby expanding the network of caregivers involved in vitreoretinal work.

Dr. Hansen: Difficulties still exist with solving the problems of costly treatments and arduous travel. In the United States, we solve the problem of dispersed populations by having physicians travel to these communities at regular intervals. Why can't we do this internationally?

Mobile vision vans (or boats) with injection and laser capabilities, traveling at regular intervals to surrounding communities, can be a great way to bring modern medical retina therapeutics to more patients. For example, the Moran Eye Center partners with the Federation of Micronesia and the sole ophthalmologist in the country to expand his capacity for providing ophthalmic care in his country. Micronesia is a country composed of hundreds and hundreds of islands reachable only by boat. Obviously, the calculus is not tilted in his favor. However, by training nurses and community health workers on individual islands to perform screenings, and

Dr. Bernstein proctors as Akwasi Ahmed, MD, performs the first vitreoretinal surgeries in Kumasi, Ghana, at the Komfo Anokye Teaching Hospital. Supported by the Himalayan Cataract Project and Moran Eye Center, Dr. Ahmed completed vitreoretinal fellowships at Tilganga Insitute of Ophthalmology in Nepal and Aravind Eye Hospital in India. In 2018, Dr. Bernstein and Dr. Hansen traveled to Ghana for hospital-based, in-country training to support Dr. Ahmed's role as the first vitreoretinal surgeon in the Kumasi region.

equipping a team traveling from island to island by boat with interventional capacity, we can begin to reach Micronesians where they live and address their overwhelming need for diabetic eye care.

BUILDING A FOUNDATION

Dr. Thomas: What would you list as the core elements of a high-quality retinal screening program?

Dr. Hansen: This comes down to three As: awareness, access, and accountability. Awareness includes advertising and dissemination of information within the context of an individual community. Access requires established avenues for providing necessary follow-up and care. Accountability means we should not just study disease, but study outcomes and the effects of a given program. Don't just identify problems, solve them; don't just start a project, sustain it.

Dr. Hansen screening patients outside of Dodoma, Tanzania.

Dr. Thomas: What are the relative advantages and disadvantages of a specific screening program (eg, one focused on diabetic retinopathy) versus a more general screening strategy?

Dr. Hansen: Focused screening offers simplicity. Broadening a screening strategy will likely identify additional treatable diseases, but it also inflates and complicates the concurrent obligations of providing additional mechanisms of treatment. A strong screening and treatment algorithm for a common retinal disease, such as diabetic retinopathy, facilitates a goal-directed, high-impact program.

Even with a specific screening strategy focused on a single disease entity, it is likely that many other retinal pathologies will also be identified in the course of screening. This may offer important epidemiologic information and provide direction for future work in the region. It also impels an organization to have a plan for addressing this reality.

Dr. Thomas: How can technology aid us in expanding screening and detection efforts, particularly in resource-poor settings? What have we learned recently about low-cost techniques and technologies for detecting retinal disease, and how might they work if employed on a large scale?

Dr. Komanski: I think technology has immense potential to expand the detection and monitoring of retinal disease in resource-poor and geographically remote settings. For instance, the development of the RETEval DR (Welch Allyn), a low-cost electroretinogram to detect vision-threatening diabetic retinopathy, is particularly exciting as it allows rapid screening of at-risk patients unable to undergo a formal eye exam. I imagine some combination of this with a nonmydriatic widefield imaging system, such as the Zeiss Clarus or Optos, as a means of allowing retina specialists to remotely confirm high-risk diabetic retinopathy. But I also hesitate to elevate these technologies as a panacea, given that they do little to remove barriers to delivery of care on the back end. They must be employed within an organized and prioritized framework that addresses both sides of the equation. ■

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OCT ANGIOGRAPHY REVEALS EARLY CHANGES WITH HYDROXYCHLOROQUINE THERAPY

Patients without signs and symptoms of retinopathy may have significant loss of vascular density.

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Hydroxychloroquine (HCQ) is a drug often used effectively in the treatment of autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, Sjögren syndrome, and other connective tissue disorders.[1,2] Although HCQ is associated with a lower incidence of retinal toxicity compared with chloroquine, it still has the potential to cause irreversible vision loss. Given that patients with HCQ-associated retinopathy are initially asymptomatic, screening for this condition plays an important role in its early identification.

The most important risk factors for toxic retinopathy are daily dosage, duration of use, renal disease, tamoxifen use, and concomitant macular disease.[3] Currently, several examination techniques are used to screen for retinopathy because no consensus exists on the most sensitive screening process. The most recent recommendations from the AAO suggest that evaluations should include biomicroscopy, computed static perimetry (protocol 10-2), and one or more objective tests, including spectral domain OCT (SD-OCT), multifocal electroretinogram (mfERG), and background fundus autofluorescence (FAF).[3-5]

OCT angiography (OCTA) is an imaging modality developed to study retinal and choroidal vascular perfusion by detecting capillary blood cell flow without the need for contrast injection.[6] OCTA evaluation of a symptomatic patient with evidence of HCQ-associated retinopathy shows a reduction in vascular density in the deep retinal plexus and choriocapillaris (CC), as reported by Kam et al.[7]

We performed a study to evaluate vascular density in different retinal plexuses using OCTA in asymptomatic patients without evidence of retinal toxicity under treatment with HCQ to understand the tool's utility in early screening for retinal toxicity.

MATERIAL AND METHODS

This retrospective study was conducted between March 2018

AT A GLANCE

- Hydroxychloroquine (HCQ), a drug often used in the treatment of autoimmune diseases, has the potential to cause irreversible vision loss.
- The authors performed a retrospective study using OCT angiography to compare vascular density between asymptomatic patients treated with HCQ and a control group.
- Patients without signs and symptoms of HCQ retinopathy may have significant loss of vascular density compared with controls.

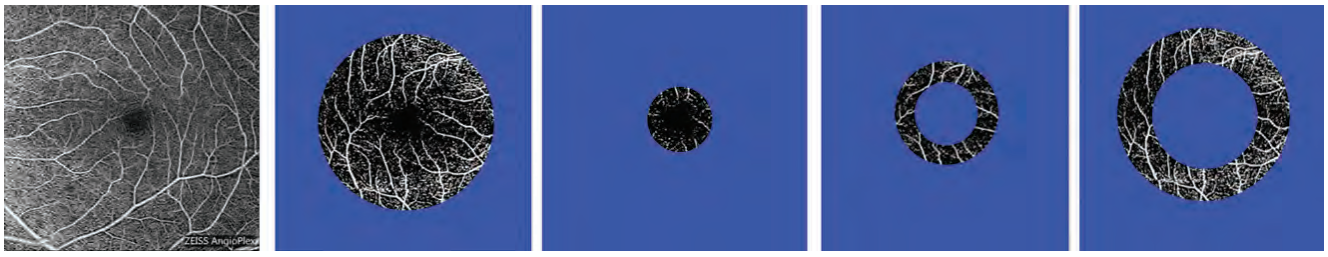

Figure. Methodology for calculating vascular density with the Image J program. From left to right: 6 x 6-mm OCTA image; macular region; foveal region; parafoveal region; perifoveal region.

and January 2019 in accordance with ethical standards and the tenets of the Declaration of Helsinki. Thirty eyes of 15 asymptomatic patients under treatment with HCQ and attending rheumatology consultation were included in the study. Patients showed no signs or symptoms of HCQ-associated retinopathy and showed no evidence of toxicity on screening tests, including 10-2 visual fields, SD-OCT, and FAF. Exclusion criteria included the presence of any retinal or optic nerve pathology or media opacity. An age- and sex-adjusted control group of patients not under treatment with HCQ and without evidence or history of any eye disease was recruited.

Clinical history measures included age, sex, rheumatologic diagnosis, duration of HCQ use, daily and cumulative dose of HCQ, visual symptoms, and other systemic medications and conditions. All patients underwent a complete ophthalmologic evaluation including BCVA, biomicroscopy, IOP measurement via Goldmann applanation tonometry, and fundoscopy. Screening exams included good quality central 10° perimetry with the Octopus automated perimeter (Haag-Streit); SD-OCT and FAF using the Cirrus HD-OCT (Carl Zeiss Meditec); and OCTA using the Cirrus HD-OCT 5000 (Carl Zeiss Meditec).

This last device is an SD-OCT scanner with a resolution depth of 5 µm and an acquisition speed of 27,000 scans per second. Scan volumes with a topographic dimension of 6 x 6 mm centered on the macula were obtained. Automated segmentation of full-thickness retinal scans into the superficial capillary plexus (SCP), deep capillary plexus (DCP), and CC were performed.

All OCTA 6 x 6 mm images of the different plexuses were exported into the Image J program (National Institutes of Health) for analysis of vascular density, as the Cirrus software analyzes only SCP. The foveal avascular zone (FAZ) of the superficial vascular plexus was automatically calculated by the OCTA software.

To calculate vascular density with Image J software, a previously described method was used in which images were binarized using a threshold strategy.[8,9] The vascular density value was derived from a ratio of white pixels, representing vessels, to total number of pixels. We analyzed regions of the macula including the foveal region (1.5 mm diameter), parafoveal region (ring between 1.5 and 2.5 mm diameter), and perifoveal region (ring between 2.5 and 4 mm diameter) in both groups (Figure).

Sets of values were compared between the two groups for each layer of segmentation. Statistical analysis was performed using SPSS version 23.0, and statistical significance was defined by *P* value less than .05. The primary outcome measures were vascular density in the macular, foveal, parafoveal, and perifoveal regions in the superficial, deep, and CC layers.

RESULTS

A total of 30 eyes of 15 patients undergoing HCQ treatment were included in the study. Mean patient age was 54.3 ± 19.5 years (range, 26–76 years). The treatment group

TABLE 1. CLINICAL AND DEMOGRAPHIC CHARACTERISTICS OF HCQ GROUP AND CONTROL GROUP

	Patients (n = 15)	Controls (n = 15)
Age (years)		
Mean ± standard deviation (SD)	54.3 ± 19.5	52.4 ± 1.0
Range	26–76	30–70
Gender, n (%)		
Female	15 (100%)	15 (100%)
Male	-	-
Rheumatic disease, n (%)		-
Systemic lupus erythematosus	7 (46.7%)	
Rheumatoid arthritis	4 (26.7%)	
Sjögren syndrome	4 (26.7%)	
Daily dose (mg/kg/day)		-
Mean ± SD	5.81 ± 1.37	
Range	3.50–7.84	
< 6.5 mg/kg/day	10 (67%)	
> 6.5 mg/kg/day	5 (33%)	
Cumulative dose (g)		-
Mean ± SD	1,231 ± 619.3	
Range	438–2,774	
< 1,000 g	6 (40%)	
> 1,000 g	9 (60%)	
Treatment duration (years)		-
Mean ± SD	8.9 ± 4.0	
Range	3–14	

TABLE 2. RESULTS OF SCP ANALYSIS BY IMAGE J PROGRAM

SCP Vessel Density (%)			
	Patients	Control	*P* value
Macular	20.0 ± 5.1	26.6 ± 5.4	< .001*
Foveal	8.1 ± 6.2	12.3 ± 4.8	<. 001*
Parafoveal	16.8 ± 6.7	22.4 ± 6.7	.001*
Perifoveal	23.8 ± 4.8	30.6 ± 5.3	< .001*

*Statistically significant value (*P* < .05)

TABLE 3. RESULTS OF DCP ANALYSIS BY IMAGE J PROGRAM

DCP Vessel Density (%)			
	Patients	Controls	*P* value
Macular	33.7 ± 5.9	37.5 ± 5.2	.010*
Foveal	12.6 ± 6.0	15.6 ± 4.6	.001*
Parafoveal	34.0 ± 7.4	36.7 ± 6.8	.061
Perifoveal	38.0 ± 5.7	41.8 ± 5.1	.008*

*Statistically significant value (*P* < .05)

TABLE 4. RESULTS OF CC ANALYSIS BY IMAGE J PROGRAM

CC Vessel Density (%)			
	Patients	Controls	*P* value
Macular	37.3 ± 5.6	40.2 ± 5.8	.052
Foveal	-	-	-
Parafoveal	30.8 ± 6.6	35.9 ± 8.4	.044*
Perifoveal	41.0 ± 5.2	43.5 ± 4.9	.067

*Statistically significant value (*P* < .05)

TABLE 5. RESULTS OF SCP ANALYSIS BY CIRRUS SOFTWARE

SCP Vessel Density (%)			
	Patients	Controls	*P* value
Central	13.8 ± 17.4	20.2 ± 9.5	.001*
Internal	32.0 ± 8.5	38.5 ± 8.9	.002*
External	37.6 ± 7.4	41.6 ± 7.9	.012*
Total	35.6 ± 7.4	40.3 ± 8.1	.005*

*Statistically significant value (*P* < .05)

comprised seven patients (46.7%) with a diagnosis of systemic lupus erythematosus, four (26.7%) with rheumatoid arthritis, and four (26.7%) with Sjögren syndrome (Table 1). No statistically significant difference was seen in age and sex of the HCQ group and control group (*P* = .441). Five patients (33%) had a cumulative dose greater than 1,000 g, and nine patients (60%) had a daily dose greater than 6.5 mg/kg. No patient reported relevant visual symptoms. Ophthalmologic evaluation revealed no relevant findings in biomicroscopy, fundoscopy, or screening examinations.

OCTA evaluation revealed significant changes in vascular density in all capillary plexuses in the HCQ group compared with the control group. Image J vascular flow analysis showed a significant reduction in the SCP (*P* < .001) and DCP (*P* = .010) in the overall macular region.

Regarding the macular regions, in the SCP there was a statistically significant reduction in vascular density in the foveal, parafoveal, and perifoveal regions (Table 2). Analysis of the DCP showed a statistically significant reduction in the foveal and perifoveal regions (Table 3). In the CC layer, there was a significant reduction in vascular density only in the parafoveal region (Table 4).

Quantitative vascular analysis with the Cirrus OCTA software in the SCP confirmed the results obtained by Image J evaluation. The data reveal a significant reduction in vascular density in the overall macula (*P* = .005) as well as each specific region of the macula: foveal, *P* = .001; parafoveal, *P* = .002; and perifoveal, *P* = .012 (Table 5).

In the HCQ group, the FAZ did not show a statistically significant difference from the control group (*P* = .940). There was also no significant correlation between vascular density in the different plexuses and cumulative dose of HCQ or duration of treatment (*P* > .05).

DISCUSSION

Although rare, HCQ retinopathy is potentially irreversible, and cellular damage may continue even after the medication is discontinued; thus, early detection is essential to prevent serious retinal damage.[10,11] In 2016, the AAO published a review of screening recommendations for HCQ retinopathy that suggested patients treated with a daily HCQ dose above 5 mg/kg/day (the most important toxicity factor) and those with renal disease, macular disease, or concomitant tamoxifen treatment should be evaluated frequently.[3] The AAO also recommended that subjective findings of toxicity be confirmed with at least one objective screening test.[3] Even though visual fields are potentially more sensitive, they depend on several factors, and isolated scotoma points are often found in patients taking HCQ with no evidence of retinopathy.[12]

In our study, we aimed to evaluate OCTA as a new, objective screening test. To the best of our knowledge, this is one of the first retrospective studies to analyze and compare vascular density using OCTA in patients under HCQ treatment without evidence of retinopathy and age- and sex-matched

healthy controls.

Similar to other studies, patients treated with HCQ in our study showed reduced vessel density in the SCP and DCP in the overall macular region and also significant reduction in vascular density in the parafoveal region of the CC layer. Goker et al found a larger FAZ and reduced vessel density of the fovea in the SCP and DCP in patients undergoing daily use of HCQ for more than 5 years compared with healthy individuals.[13] In 10 patients treated with HCQ, Forte et al showed reduced vessel density in the central, nasal, and temporal subfields of the DCP, enlargement of the FAZ, and reduced CC density in the central subfield compared with healthy controls.[14]

Studies comparing patients taking HCQ for more than 5 years with patients taking HCQ for less than 5 years also show a positive correlation with reduced vessel density. Ozek et al found that the parafoveal deep temporal and deep hemi-inferior vascular plexus densities were reduced in patients taking HCQ for more than 5 years despite having normal perimetry.[15] Bulut et al found significantly reduced vascular density (SCP and DCP) and wider FAZ in high-risk patients under treatment with HCQ compared with a low-risk group.[16]

Our study revealed a significant reduction in vascular density in the DCP, supporting the structural changes found in high-resolution OCT analysis and in the superficial layers.[17]

The pathophysiology of retinopathy secondary to HCQ is still unclear. Some studies suggest that retinal toxicity could be detected at an earlier stage through the measurement of the inner layer thickness using SD-OCT.[18,19] However, other studies that use SD-OCT show a distinctive loss of the perifoveal inner segment/outer segment photoreceptor junction, suggesting that HCQ retinal toxicity mainly affects the external retina/photoreceptor layer, particularly in the parafoveal and perifoveal regions, before causing structural damage involving the retinal pigment epithelium and the inner retinal layers.[17,20-23]

Patients treated with HCQ but without symptoms or signs of retinopathy appear to have a significant loss of vascular density. These OCTA findings may help clinicians to monitor patients and eventually stratify their risk of retinal damage. Future work with larger sample sizes will be important to reinforce the potential role of OCTA in screening for and detecting the progression of HCQ-associated retinopathy. ■

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OPHTHALMIC PRESENTATIONS OF PITUITARY ADENOMA


The ocular examination can aid diagnosis and help guide treatment.

BY HANNE GEHLING, BS, AND KIMBERLY M. WINGES, MD

Pituitary macroadenomas are benign tumors. The most common subtype is clinically nonfunctioning pituitary adenomas, which are defined by an absence of clinical evidence of hormonal hypersecretion.[1] Patients with pituitary macroadenomas may present to an eye clinic with symptoms related to mass effect on surrounding structures, which can include headache, bitemporal visual defects, and ocular motor deficits (see *Key Ocular Findings in Pituitary Macroadenoma*).[2-4]

If you suspect that a patient has a nonfunctioning pituitary adenoma, the following steps are warranted: visual acuity testing, color plates, a cranial nerve examination, an assessment for a relative afferent pupillary defect, an evaluation of the optic discs' appearance, visual field testing, and OCT imaging. In addition to narrowing the differentials, the information gathered by these assessments can guide treatment strategies, predict prognostic factors for recovery, inform providers' and patients' expectations, and document postoperative recovery after resection or radiotherapy.[5]

KEY OCULAR FINDINGS IN PITUITARY MACROADENOMA

- Visual field defects
  - Superior progressing to complete bitemporal hemianopsia
  - Junctional scotoma (postfixed chiasm or anterior tumor spread)
  - Rarely, macular bitemporal hemianopsia or homonymous visual field loss (prefixed chiasm or posterior tumor spread)
- Pituitary apoplexy
- Diplopia
  - Hemifield slide
  - Cranial nerve palsies, especially multiple
- See-saw nystagmus
  - Thinning of the binasal macular ganglion cell layer and temporal retinal nerve fiber layer on OCT
  - Temporal or bow-tie atrophy of the optic disc on examination

VISUAL FIELD DEFECTS

Visual field testing is central to the workup of pituitary adenomas. In a review of eight studies, visual field disturbances were the most common symptoms at presentation, found in approximately 46% of all patients.[4] It is important to note, however, that slow tumor growth may delay patients' presentation to an eye clinic, and some asymptomatic cases are detected incidentally on glaucoma screening.

Bitemporal hemianopsia can occur as a result of suprasellar growth of the pituitary lesion and direct inferior compression of the optic chiasm first, where the axons that give rise to the superior temporal visual field cross (see *Differential Diagnosis of Bitemporal Hemianopsia*).[6]

Tumors may grow asymmetrically, and different configurations of the optic chiasm relative to the pituitary gland can contribute to the observed pattern of presentation. If the optic chiasm sits anterior to the pituitary gland within the tuberculum sellae, referred to as a *prefixed chiasm*, a pituitary adenoma is more likely to compress the posterior chiasm and optic tracts to produce a macular bitemporal hemianopsia or homonymous visual field loss. Conversely, *postfixed chiasms* overlying the dorsum sellae may produce patterns of visual field loss related to the optic nerve or a junctional scotoma due to compression at the confluence of the optic nerve and chiasm.[6]

OCULOMOTOR DEFICITS

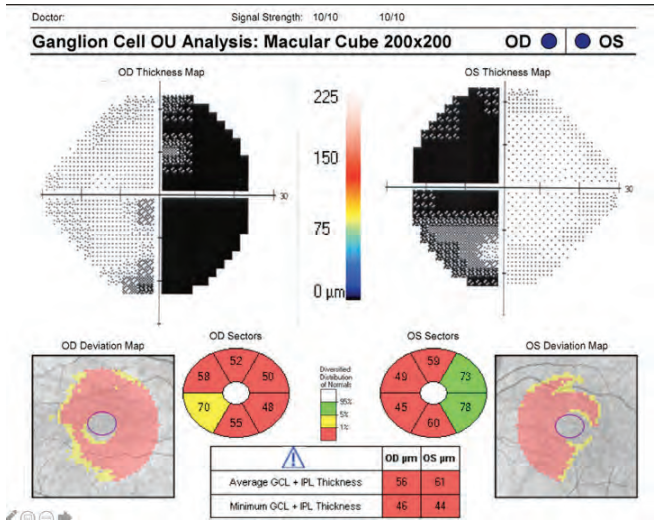
Cranial nerve (CN) palsies occur as a result of compression caused by the direct extension of a tumor out of the sella and into the adjacent cavernous sinuses. Multiple palsies of CN III, IV, V1, V2, and/or VI localize to this region. A patient with any of several CN palsies will complain of diplopia and, in severe cases, may present acutely with headache as a result of pituitary apoplexy.

Acute-onset diplopia and headache in this scenario should prompt immediate neuroimaging (see *Pituitary Apoplexy*). Pituitary adenomas may also cause diplopia due to decompensation of a preexisting phoria by the lack of crossover of the remaining visual field in the setting of complete hemianopsia (see *Hemifield Slide*).

DIFFERENTIAL DIAGNOSIS OF BITEMPORAL HEMIANOPSIA

- Extrinsic = compression
  - Pituitary adenoma
  - Parasellar meningioma
  - Craniopharyngioma
  - Parasellar internal carotid artery aneurysm
- Intrinsic = chiasmal in origin
  - Glioma/astrocytoma
  - Demyelinating lesion
  - Rarely, sarcoid or inflammatory lesion
- Not chiasmal = optic nerve anomalies (generally do not respect vertical midlines well)
  - Tilted nerve
  - Atypical glaucomatous optic neuropathy
- Other
  - Trauma with chiasmal contusion
  - Hydrocephalus

See-saw nystagmus (SSN) is a rare ocular-motor syndrome characterized by a cycle of elevation and intorsion of one eye with synchronous depression and extorsion of the other, a scenario that is inverted in the next half-cycle. Two patterns of SSN exist. The pendular-type SSN is more typical of parasellar masses, and it is differentiated from jerk SSN by its smooth and rolling movements.[7] Although the underlying pathophysiology of pendular SSN remains a subject of debate, a two-hit hypothesis has been proposed. First, compression of the chiasm may lead to a retinal calibration error of the vestibulo-ocular reflex, causing a disturbance in the roll plane (see *Hemifield Slide*). Second, compression of the interstitial nucleus of Cajal or the rostral interstitial nucleus of the medial longitudinal fasciculus can lead to nystagmus in the pitch and roll planes.[7]



Original field and OCT scan courtesy of Randy Kardon, MD, PhD

Figure 1. Binasal macular GCL atrophy mirrors bitemporal hemianopsia in pituitary adenoma chiasm compression. Fields are shown overlying their respective eyes on OCT for direct comparison.

OCULAR IMAGING IN DIAGNOSIS AND MANAGEMENT

OCT imaging is useful for visualizing the retinal nerve fiber layer (RNFL) and macular ganglion cell layer (GCL) in patients with visual field loss from chiasmal compression (Figure 1). Pituitary adenomas cause compression of the axons from the nasal retinal fibers, which correspond to the temporal visual fields. This damage is reflected after weeks to months in binasal macular ganglion cell atrophy and its corresponding temporal and then nasal peripapillary RNFL. When the superior and inferior RNFL quadrants are relatively spared, atrophy with a characteristic bow-tie or band appearance eventually occurs.[8]

Recent studies show that OCT imaging can provide useful guidance on treatment strategy. Because extensive RNFL thinning and macular GCL thinning indicate retrograde atrophy of fibers from chiasmal compression, patients with intact RNFL and GCL on OCT at diagnosis may have a greater potential for recovering optic nerve function and visual fields after surgical intervention.[8]

MANAGEMENT

MRI of the brain and/or orbits, with and without contrast, with attention to the sella is the recommended medium for diagnosis (Figure 2). A patient with a confirmed pituitary macroadenoma should be referred to both neurosurgery and endocrinology. Asymptomatic patients with incidental macroadenomas should receive continued ophthalmologic surveillance because any new visual symptoms strongly indicate a need for surgical intervention. Although there are no established guidelines for the length of ophthalmologic follow-up, lesion size and a progression of visual field defects should inform decisions regarding timeline.

If visual impairment secondary to pituitary macroadenoma is confirmed or progressive, firstline treatment is surgical resection with endoscopic or microscopic transsphenoidal surgery.[9] Bromocriptine can be used for prolactin-secreting adenomas (usually small). Large masses may require superior craniotomy approaches, whereas gamma knife radiotherapy is reserved for large tumor remnants and the management of regrowth after surgery.[9] In a review of 19 studies that describe visual outcomes after resection, approximately 40% of patients recovered completely, 80% showed an overall improvement, and 2% reported further deterioration in visual function.[10] Preoperative visual field assessments are essential to estimate visual outcomes after resection and to set both patients' and providers' expectations.

CONCLUSION

By understanding the clinical signs associated with pituitary adenomas, you can ensure that patients with associated visual defects receive an early diagnosis and a thorough

preoperative assessment. The information gathered can inform treatment plans and better predict ophthalmologic outcomes after treatment. ■

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PITUITARY APOPLEXY

Pituitary apoplexy is a rare vascular emergency caused by infarction or hemorrhage of the pituitary gland. Although eye care providers are unlikely to see a patient with apoplexy in the clinic, it is important to educate patients with a history of pituitary adenoma about the red flags.[1,2]

- Sudden changes in vision, especially peripheral visual field loss or diplopia
- Abrupt onset of severe thunderclap headache, usually retroorbital
- Altered mental status or personality changes from acute changes in cerebral blood flow
- Nausea, vomiting, or loss of appetite
- Low blood pressure
- Hormone insufficiency

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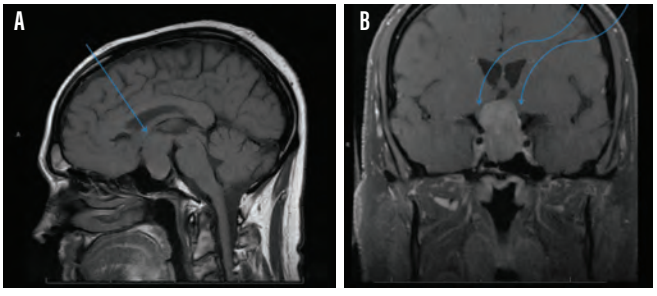

Figure 2. Sagittal midline precontrast T1-weighted MRI showing enlargement of the sella turcica and superior extension of a pituitary macroadenoma (arrow, A). Coronal T1-weighted MRI with contrast showing the optic chiasm stretched and compressed over the mass (arrows, B).

HEMIFIELD SLIDE

Diplopia without oculomotor involvement, referred to as *hemifield slide*, can occur with bitemporal hemianopsia in patients who are experiencing compression of the optic chiasm. This syndrome arises when the eyes no longer share an area of visual field, leading to a loss of binocular fusion in a patient with preexisting phoria. When the eyes move apart from one another in decompensated exophoria, the patient may perceive the nasal hemifields overlapping centrally as a central strip. In esophoria, intermittent crossing of the eyes may be observed as a central strip of diplopia, causing visual confusion. In decompensated esophoria, the two nasal visual fields may appear to separate, leaving a linear central scotoma.[1] Similarly, a vertical phoria may produce a superior or inferior segment of missing or jumbled vision (Figure).

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Figure. Hemifield slide can arise from a loss of motor alignment in patients with pituitary adenoma by interfering with the binocular visual field. Exotropia creates an overlapping strip of nasal visual field that causes visual confusion, esotropia creates a central strip scotoma, and hypertropia results in a superior or inferior segment scotoma and central visual field misalignment.

THE WINNING PITCH CHALLENGE: HELPING INNOVATORS IN THE TRENCHES

How to birth the next great innovation in retina.

BY DANIEL CHAO, MD, PHD

You have had a *eureka* moment after identifying a gap in the practice of retina. Now that you have a new idea or product to improve patient care, where do you go from here? Whom should you talk to about this? Has someone already had this idea? Who is going to fund it?

The Winning Pitch Challenge (https://winningpitchchallenge.net) is an independent organization that empowers nascent ophthalmology innovators with resources and a support network to turn their ideas into reality. The signature event is a "Shark Tank"–style competition to help innovators in retina get their ideas off the ground. Here's how it works:

(1) Participants submit innovation concepts and are paired with experienced industry mentors who provide guidance and advice on developing a pitch. These ideas are at early stages, generating little or no revenue. It is recommended that applicants have at least submitted a provisional application for a patent.

(2) Judges select three finalists who present their ideas to a panel of venture capital and industry veterans in a live event (the February 2021 presentations will be virtual due to the COVID-19 pandemic). A total of $45,000 in prize money is awarded to these top three participants. Beyond the prize money, participants gain the opportunity to work with industry mentors who critique and refine their ideas and engage with other participants in the ophthalmology innovation ecosystem.

Since 2017, numerous retina innovators have competed in this event, from seasoned clinicians to those just starting in practice. Their proposals have encompassed the full gamut of retina, from surgical devices and diagnostics to pharmacotherapeutics.

We gathered insights from the 2017 finalists of the Winning Pitch Challenge to learn how they began turning their ideas into reality. In a sidebar to this article, we also include comments from a mentor of the Challenge.

David Almeida, MD, MBA, PhD

- Erie Retina Surgery, Erie, Pennsylvania
- Innovation: CTX-1, a new therapeutic for dry AMD

Edwin Ryan, MD

- VitreoRetinal Surgery PA, St. Paul, Minnesota
- Innovation: Strip-based eye medication dispenser

Jeffrey S. Heier, MD (first place)

- Ophthalmic Consultants of Boston
- Innovation: iLoopes, assisted reality software as a low vision aid for smart glasses

How did you come up with your idea?

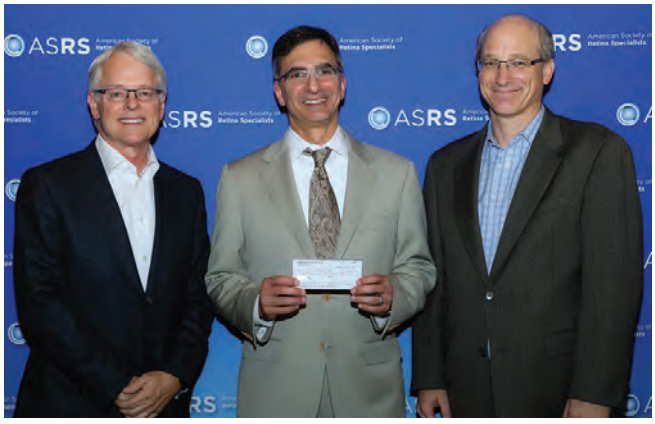
Dr. Almeida: Eric Chin, MD, (also a vitreoretinal surgeon) and I cofounded Citrus Therapeutics, a company centered around a pharmaceutical design philosophy of using multiple pharmacophores with multiple mechanisms of action to treat complex diseases such as dry AMD.

Dr. Ryan: I had noted when using fluorescein strips that the liquid I placed on the tip of the strip would often bead up as a droplet and wouldn't fall off the strip. This led to the idea of using a strip dispenser as a new way to administer eye drops.

Dr. Heier: I was approached by an entrepreneur, a patient of mine who knew I was heavily involved in retina research. He asked if I would help him

AT A GLANCE

- The Winning Pitch Challenge is an independent organization that empowers ophthalmology innovators with resources and support.
- Participants submit innovation concepts and are paired with experienced industry mentors who provide guidance.
- A total of $45,000 in prize money is awarded to the top three participants.



Dr. Heier, center, accepts the first-place prize during the 2017 Winning Pitch Challenge event. Joining him is David Williams, MD, at left, and John Pollack, MD, at right.

John Pollack, MD, flanked by the Winning Pitch Challenge panel, speaks to the audience during the 2017 presentation event.

develop a low vision device that could help patients. We began to work with a team to design such a device, and then we had low vision patients test it.

What prompted you to take time out of your schedule as a busy retina specialist to develop your idea?

Dr. Almeida: You have to derive satisfaction from the pursuit (pharmaceutical drug design), even if your ultimate destination (approved drug) is not reached. Just as important, having a cofounder like Eric who I trust and value makes the development journey and the associated investment of time a lot of fun.

Dr. Ryan: I have been a tinkerer for many years and have seen a number of inventions in the ophthalmology world become fairly successful, including the stiffening sleeve that Alcon uses to make 25- and 27-gauge tools stiffer. I like to solve problems.

Dr. Heier: My clinic was filled with patients who had vision loss from myriad diseases and who were desperate for any opportunity to improve their vision or their ability to function again. As we began to test our low vision device with patients, we began to realize that it could truly impact patients' ability to navigate the real world.

Fostering The Next Generation

Michael Fanning, CEO of Vortex Surgical and a long-time mentor for The Winning Pitch Challenge, offered feedback on his experiences with the organization:

What has your experience been like as a mentor for the Winning Pitch Challenge?

Mr. Fanning: It has been amazing. I have greatly enjoyed the innovator engagement component, helping inventors channel their enthusiasm and product concepts into commercialized solutions. Doing so has provided me with a greater appreciation for the bandwidth of innovators—and their insatiable commitment to problem solving, which is the root of most meaningful innovations.

What one piece of advice would you give to young, aspiring retina specialists interested in innovating new products?

Mr. Fanning: Approach any new product development as you would a startup business. Understand what problem you are solving and have an appreciation of how big a problem you are solving.

Was it worth it, and what is one lesson you learned from going through the process?

Dr. Almeida: I believe it was worth it, but I also realize there is a cost to any project, and this may not hold the same value for everyone. The process of design, development, and testing—win or lose—is enlightening, never for the answers you find but for the questions you raise and the connections you make along the way.

Dr. Ryan: I learned that getting a product through design, development, prototyping, and all the other steps is a lot more involved than simply coming up with an instrument design and going directly to a manufacturer with it. It is safe to say that this was a humbling experience in that regard.

Dr. Heier: It was a remarkably valuable experience. I am heavily involved in retina research and often help with fundraising, but not as a direct participant. In this case, I experienced firsthand what it is like to sell your concept to investors, to strive to convey the value of your work to those who can help to determine whether your idea is worthy.

How did the Winning Pitch Challenge assist you in your project?

Dr. Almeida: The Winning Pitch Challenge was valuable in terms of the "Shark Tank"–style feedback we received and the network we developed in the process. The cross-pollination that occurs at the intersections of medicine, research, marketing, and venture funding has been instrumental in refining our hypotheses and continues to drive us in the pursuit of a successful endpoint.

Dr. Ryan: Having to put together a convincing and compelling pitch that I would be presenting to colleagues and

knowledgeable business people without embarrassing myself really forced me to think through every aspect of my product and business model.

Dr. Heier: Winning the Winning Pitch Challenge provided validation of our concept and enabled us to better promote our concept to others. Potential collaborators and investors recognized that if such esteemed experts as the Winning Pitch Challenge panel believed our idea had merit, then they should as well.

TAKE THE PLUNGE

What should you do next with your bright idea? Ready to take the plunge? Submit your application for the Winning Pitch Challenge and take your first step toward translating your idea into a reality to help advance the field of retina. ■

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(Continued from page 28)

dose-limiting toxicities or drug-related serious AEs were reported. After a single injection, an increasing average improvement in BCVA of up to 7.5 letters was seen from day 1 to day 14. There was an average improvement in BCVA of 6.5 letters at day 90 following a single injection.[7]

Looking Forward

The phase 2 KALAHARI clinical trial (NCT03511898) began earlier this year and is recruiting approximately 122 patients with DME who are poor responders to anti-VEGF therapies. The first part of the study will assess the optimal dose from three dose levels of THR-149 injections. Part 2 will then evaluate the efficacy and safety of the selected optimal dose of THR-149 versus aflibercept (Eylea, Regeneron) for the treatment of DME.[8] Study completion is expected in 2022.

CONCLUSION

Modern treatments for macular edema and macular degenerations continue to evolve as new pathways of progression are discovered. The novel drugs outlined here show promise to give patients additional options to help preserve their vision. ■

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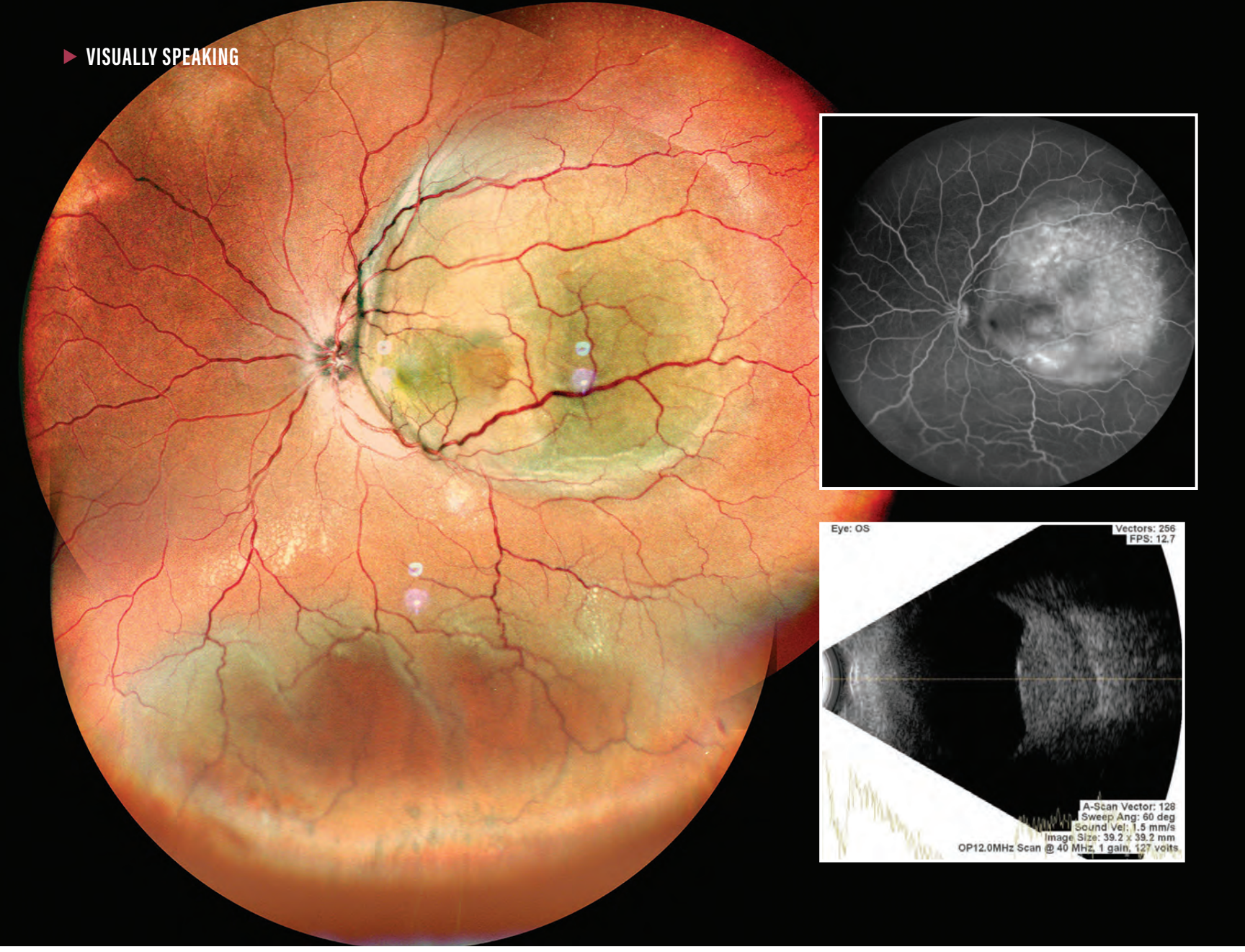


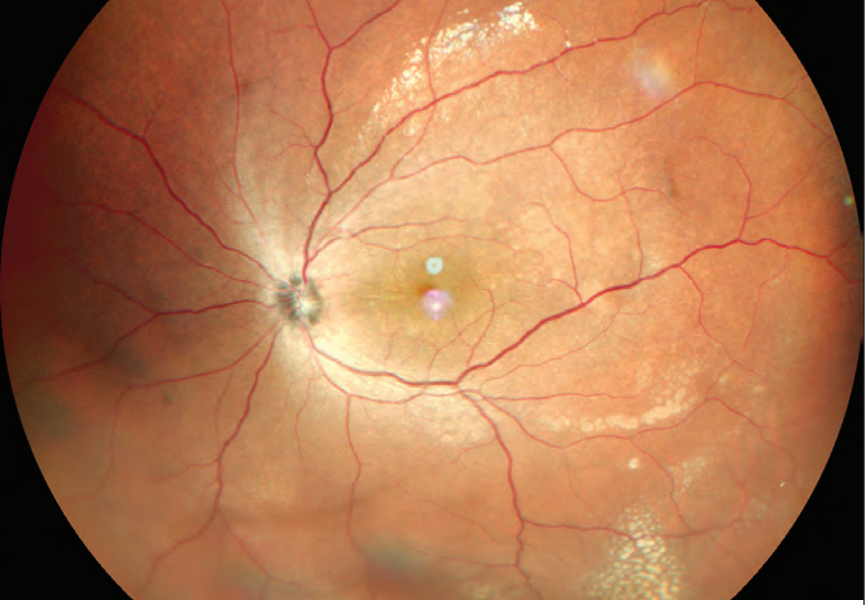
CHOROIDAL MASS: WADING THROUGH THE DIFFERENTIALS



BY SHAM TALATI, MBBS, DO; MANISH NAGPAL, MBBS, MS, FRCS; AND NAVNEET MEHROTRA, MBBS, DNB, FRF

A 17-year-old male patient presented with a chief complaint of a progressive, painless decrease in vision for the past 20 days. He reported no history of systemic illness. He had already undergone routine blood profiles and a chest x-ray, all of which were within normal limits.

The VA of the left eye was counting fingers at 3 m. The fundus examination showed a choroidal mass in the left eye involving the macula with inferior exudative detachment (Main Figure, above). Fluorescein angiography of the affected eye showed mottled hyperfluorescence



over the mass lesion (Inset, top). Ultrasonography captured the choroidal mass with moderate A-scan spikes (Inset, bottom).

A differential diagnosis of an inflammatory mass, metastasis, and melanoma was made, and we advised that the patient undergo an MRI of the brain and orbits to rule out pathology, as well as an abdominal ultrasound and a high-resolution CT of the chest to rule out the presence of any primary or secondary malignancy. We ordered intravenous 1 g methylprednisolone injections daily for 3 days followed by oral steroids.

The abdominal ultrasound and the CT were within normal limits, but the MRI showed a mild, bulky lacrimal gland, suggesting the possibility of an inflammatory etiology. The patient was subsequently diagnosed with posterior scleritis.

The patient returned the next week and reported that he was feeling better while on the steroid. Snellen distance VA had improved to 6/24 OS. Imaging of the left eye revealed a remarkably reduced elevation over the posterior pole with a reduction in the inferior exudative detachment (Figure, above).

We prescribed a slow steroid taper over 2 months and scheduled him for frequent monitoring. At the 1-month follow-up the patient continued to show improvement. ■

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If you have an image or images you would like to share, email Dr. Nagpal.
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BRIAN C. JOONDEPH, MD, MPS, FACS

You are the first 5Q interviewee in *Retina Today* since March, when COVID-19 took the wheel. How did the pandemic affect you personally and professionally? Based on your interactions with colleagues, would you say retina specialists are generally still interested in remaining up to date on new developments or that they are on COVID overload and need a break from coverage?

That's a perfect question for me as I have been affected both personally and professionally. My wife became very ill with COVID-19 in March and is still struggling with the aftereffects. I relearned much about critical care medicine and rehab during this time. I personally lost taste and smell with no other symptoms and now have antibodies along with the lingering question of "Why her and not me?"

Professionally, my practice was in the process of implementing LEAN processes when COVID-19 hit, making it easier to adapt to the new rules and practice patterns. We were assisted by federal relief money, did not have to eliminate any staff members, and came through as strong as ever.

Most of us are experiencing COVID-19 fatigue due to the ever-changing restrictions and constant mask use with no end in sight. Unfortunately, COVID-19 went from an infectious disease to a political issue, leading to sharpened opinions, skepticism, and ultimately COVID-19 overload.

What professional accomplishment are you most proud of?

I am most proud of developing a happy, efficient, and productive clinical team, along with having appreciative patients. That means more to me than papers or awards. But I also value my membership in the Macula Society and Retina Society, as well as the opportunity to publish and contribute to the field.

Why did you choose to pursue a master's degree in health care leadership? What do you plan to do with it, or how has it already benefited you?

When my youngest was in high school, I wanted a new challenge. The University of Denver was close by and offered classes one evening per week. After 3 years, I had my master's degree—and, if I'm allowed to brag, a 4.0 GPA, which is better than I had in college. What I learned has assisted me with leadership positions within my practice and refined my writing skills.

In terms of leadership, I'm more of an idea than a process person. And I have an aversion to meetings, so I have gravitated toward writing, converting my ideas to words.

One of my professors encouraged me to write an opinion piece on health care for a local business journal. The writing bug bit me hard, and I am now a columnist for *American Thinker*, *Rasmussen Reports*, and a local newspaper. I have published more than 700 opinion pieces about political issues, including health care, and I have given radio interviews on these subjects.

Figure. Dr. Joondeph and his wife Shirley in Geneva after the Retina Society meeting in London last year.

Because politics is a touchy subject, I have been called all manner of names by friends, relatives, and professional colleagues who have an aversion to viewpoints other than their own, but such is the nature of political discourse these days. I smile and keep writing, in awe of how consuming and divisive politics is to some.

What new technological advances do you find exciting?

I marvel at gadgets and devices, watches that tell me my heart rhythm and oxygen level, cars that drive themselves, and the world at my fingertips via the phone in my pocket. In retina, I am intrigued by gene therapy, creating a drug factory in the eye. I was honored to present on this subject at the recent Retina Society meeting.

You enjoy golfing and skiing. Did you do both as a child, or did you pick these sports up as an adult? Do any of your children share these interests?

I dabbled in both as a kid, but without lessons, I was just having fun with my friends. I waited until adulthood to take both seriously and try to reach a level of competence. Living on a golf course, I have ample opportunity to play. My wife and three kids all participate to varying degrees. The climate in Colorado is ideal for both sports, sometimes even on the same day. ■

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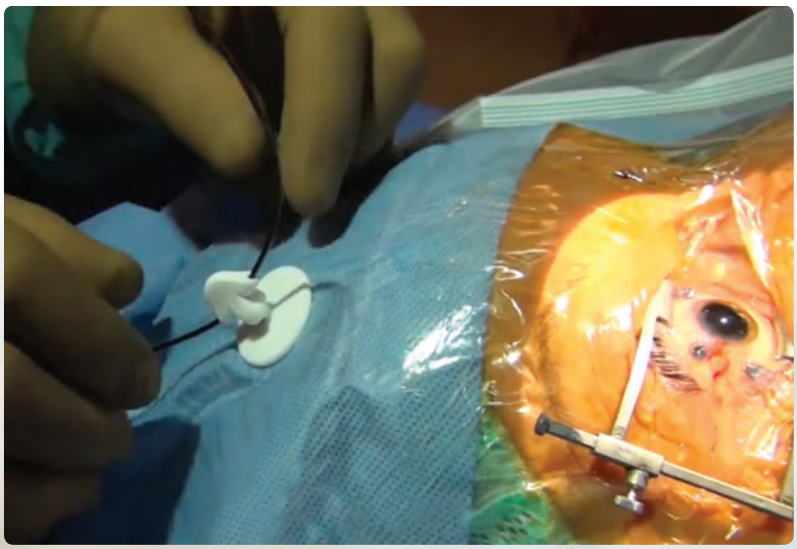

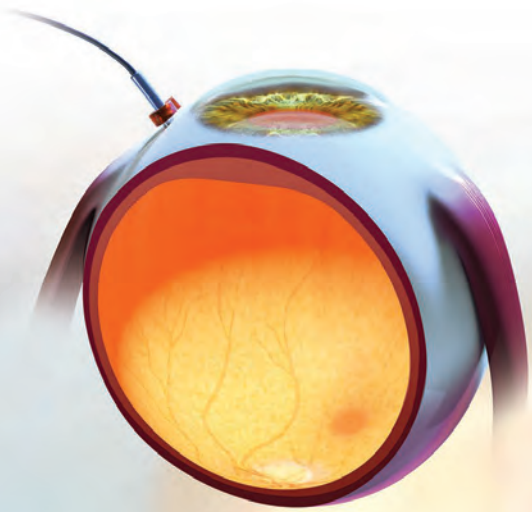

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