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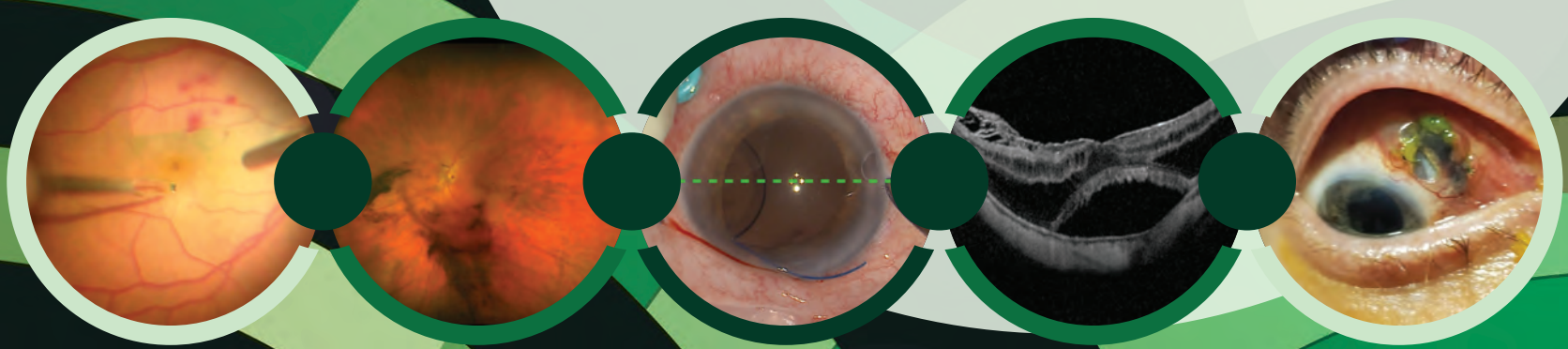
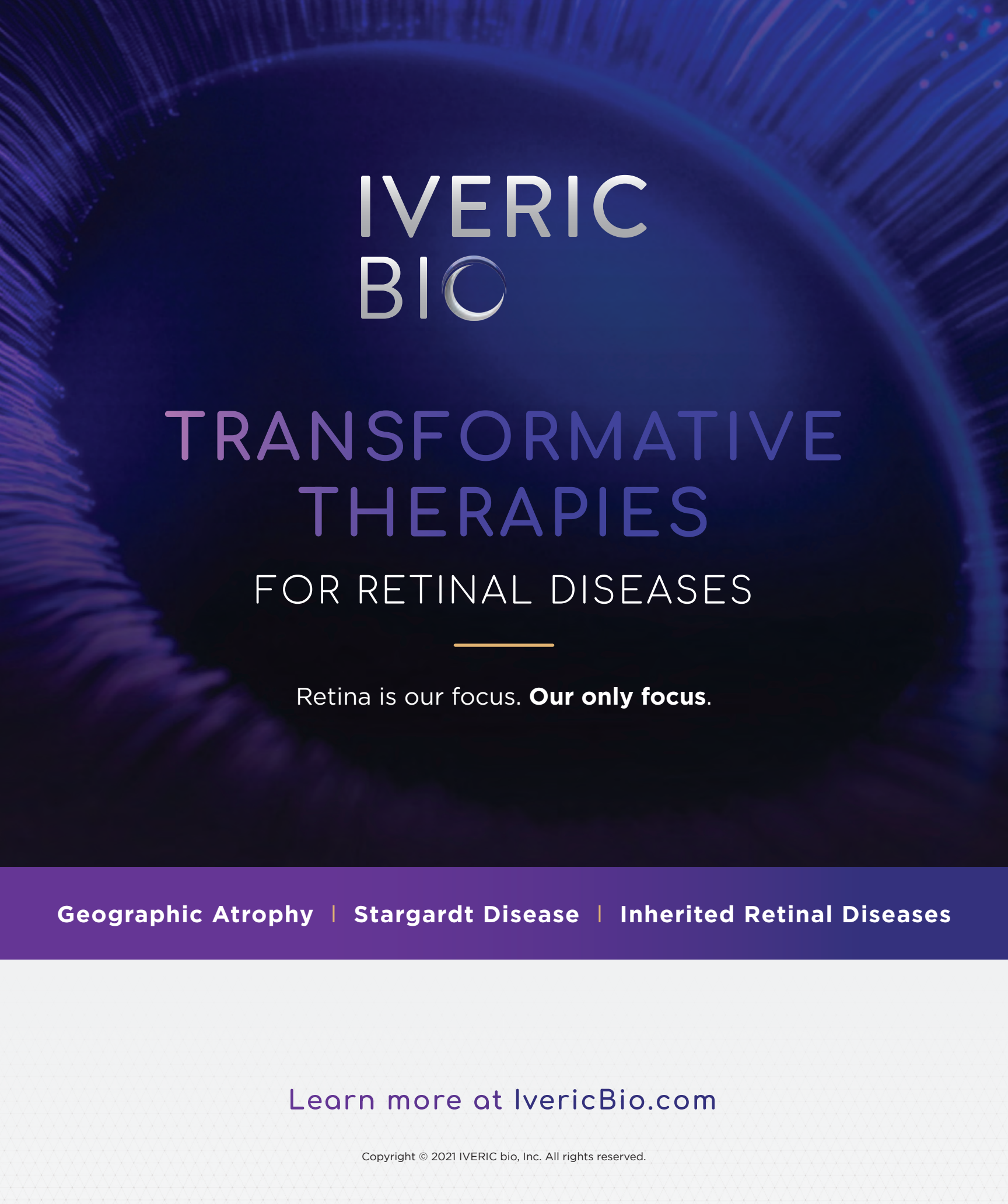
eyetube

RETINA SURGICAL ROUNDS



Experts share challenging cases and novel techniques in the OR.

DISSECTING, MASSAGING, AND PLUGGING MACULAR HOLES | CONTROVERSIES IN ILM PEELING | UNCONVENTIONAL BUCKLING TECHNIQUES



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RETINA: THE FINAL FRONTIER


The field of retina has often been likened to the Wild West by conference speakers, usually to convey the sense of expansion, discovery, and reinvention for which our field is known (we tend to ignore the unsavory traits that also defined America's Wild West of the 1800s).

We aren't out here gunslinging and robbing banks, so perhaps a more appropriate and tech-savvy analogy would be that of space exploration. Remember the first vitrectomy performed by the great Robert Machemer, MD, on April 20, 1970? That was 9 months, to the day, *after* we landed on the moon.[1,2] It took us longer to invent modern vitreoretinal surgery than it did to set foot on a space rock. To be fair, the first retinal detachment repair was back in 1929.[3]

In 2019, about 50 years after the moon landing, NASA provided the first look at a black hole, and in May of this year we got our first glimpse of the black hole at the center of our own Milky Way galaxy.[4]

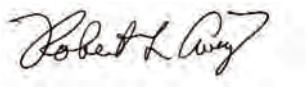
In the OR, we are forging ahead with our own discoveries, many of which are made possible by similar advances in imaging. Retina surgeons have 3D surgery, intraoperative OCT, and novel subretinal and suprachoroidal delivery approaches. We even have gene therapy, and researchers recently implanted a patch of stem cells to treat geographic atrophy.[5] It's the stuff science fiction is made of… and it's already in some of our ORs.

All of this is possible because retina specialists are explorers at heart. We love solving our patients' problems and saving their vision in the process. That mentality leads to *constant* innovation, whether that's for our tools, therapeutics, or surgical techniques. What's particularly fun about innovating in the retina space is that much of it happens as part of our day-to-day practice. Sure, we have a robust and ever-expanding pipeline of clinical research, but just as much is discovered by trying something new during a challenging surgical case.

This is why case presentations, lightning rounds, and surgical video contests are always well attended at retina meetings—and can get a bit raucous at times. Not everyone rolls in with a wriggling worm surgery (see last issue's Global Perspectives column to see what we mean, retinatoday.com/articles/2022-sept/a-serous-floater), but many still elicit gasps, oohs and ahhs, or applause from the audience. Others spark lively debates on the best approach and novel techniques that panelists and attendees have employed with success.

That's the kind of excitement for surgical innovation we wanted to capture within these pages. In this issue, our expert authors cover surgical approaches for everything from recurrent macular holes and secondary IOLs to non-diabetic vitreous hemorrhage, macular buckling, and an extruded scleral buckle in bad shape.

Whether you are new to practice or have been around the block a time or two, we hope these techniques, tips, and tricks broaden your expertise in the OR and give you new ways to solve the complex cases that roll in. We also hope they spark your own thirst for innovation because, like our friends at NASA and their interstellar exploration, we have much left to discover about the retina and our field as a whole. ■

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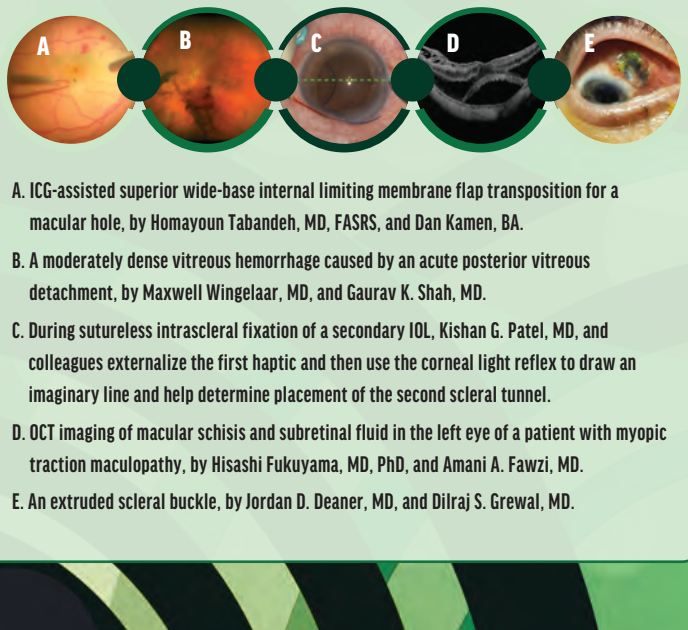
ASSOCIATE MEDICAL EDITOR

1. Blodi CF. David Kasner, MD, and the road to pars plana vitrectomy. *Ophthalmol Eye Dis*. 2016;8(Suppl 1):1-4.
2. Britannica. Apollo 11. www.britannica.com/topic/Apollo-11
3. Gonin J. Le traitement opératoire du décollement retinien. Conférence aux journées medicales de Bruxelles. *Bruxelles-Med*. 1930;23(17).
4. Event Horizon Telescope. Astronomers reveal first image of the black hole at the heart of our galaxy. May 12, 2022. Accessed September 15, 2022. eventhorizontelescope.org/blog/astronomers-reveal-first-image-black-hole-heart-our-galaxy
5. First US patient receives autologous stem cell therapy to treat dry AMD [press release]. September 2, 2022. Accessed September 15, 2022. eyewire.news/news/first-us-patient-receives-autologous-stem-cell-therapy-to-treat-dry-amd

ON THE COVER



A. ICG-assisted superior wide-base internal limiting membrane flap transposition for a macular hole, by Homayoun Tabandeh, MD, FASRS, and Dan Kamen, BA.

B. A moderately dense vitreous hemorrhage caused by an acute posterior vitreous detachment, by Maxwell Wingelaar, MD, and Gaurav K. Shah, MD.

C. During sutureless intrascleral fixation of a secondary IOL, Kishan G. Patel, MD, and colleagues externalize the first haptic and then use the corneal light reflex to draw an imaginary line and help determine placement of the second scleral tunnel.

D. OCT imaging of macular schisis and subretinal fluid in the left eye of a patient with myopic traction maculopathy, by Hisashi Fukuyama, MD, PhD, and Amani A. Fawzi, MD.

E. An extruded scleral buckle, by Jordan D. Deaner, MD, and Dilraj S. Grewal, MD.

0.18 mg
YUTIQ®
(fluocinolone acetonide intravitreal implant) 0.18 mg

Discover continuous calm in uveitis[1]

YUTIQ is designed to deliver a sustained release of fluocinolone for up to 36 months for patients with chronic non-infectious uveitis affecting the posterior segment of the eye[1]

- 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.
- Extended median time to first recurrence of uveitis[1,2]
  At 12 months–NE† for YUTIQ/92 days for sham in Study 1; NE for YUTIQ/187 days for sham in Study 2.
- Mean intraocular pressure (IOP) increase was comparable to sham[1,2]
  Study was not sized to detect statistically significant differences in mean IOP.

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

*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 non-infectious 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 non-infectious uveitis, or the need for rescue medications.

†NE=non-evaluable due to the low number of recurrences in the YUTIQ group.

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.

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.

Please see brief summary of full Prescribing Information on adjacent page.

References: 1. YUTIQ® (fluocinolone acetonide intravitreal implant) 0.18 mg full US Prescribing Information. EyePoint Pharmaceuticals, Inc. May 2021. **2.** Data on file.

EyePoint® Pharmaceuticals

480 Pleasant Street, Suite B300, Watertown, MA 02472
08/2021
US-YUT-2100061

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

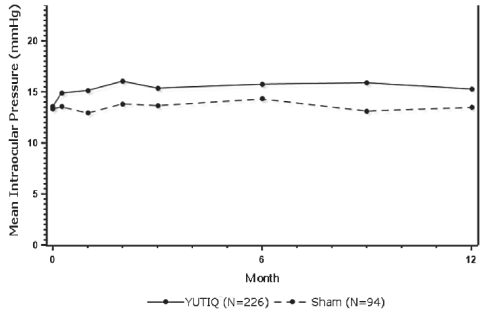
Ocular		
ADVERSE REACTIONS	**YUTIQ (N=226 Eyes) n (%)**	**Sham Injection (N=94 Eyes) n (%)**
Vitreous Hemorrhage	4 (2%)	0
Iridocyclitis	3 (1%)	7 (7%)
Eye Inflammation	3 (1%)	2 (2%)
Choroiditis	3 (1%)	1 (1%)
Eye Irritation	3 (1%)	1 (1%)
Visual Field Defect	3 (1%)	0
Lacrimation Increased	3 (1%)	0
Non-ocular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

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RT NEWS

OCTOBER 2022

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POSITIVE TOPLINE DATA FOR HIGH-DOSE AFLIBERCEPT

In two phase 3 clinical trials for diabetic macular edema (DME) and wet AMD, 8 mg aflibercept dosed on 12- and 16-week regimens met primary endpoints of noninferior visual gains compared with 2 mg aflibercept (Eylea, Regeneron) dosed on an 8-week regimen, according to a company press release last month.[1] In addition, the safety profile of the high-dose aflibercept was consistent with that of 2 mg aflibercept.

In the DME study (PHOTON, n = 658), the mean improvement in BCVA was 9.2 letters for the 2 mg aflibercept group, 8.8 letters for 8 mg aflibercept group dosed on a 12-week regimen ($P < .0001$), and 7.9 letters for 8 mg aflibercept group dosed every 16 weeks ($P < .0031$).

In the wet AMD study (PULSAR, n = 1,009), the mean BVCA improvement was 7.6 letters for the 2 mg aflibercept group, 6.7 letters for the high-dose group dosed every 12 weeks ($P = .0009$), and 6.2 letters for the high-dose group dosed every 16 weeks ($P = .0011$). Through week 48, 91% and 85% of DME patients and 79% and 77% of wet AMD patients treated with the high-dose aflibercept remained on 12- and 16-week dosing, respectively. There were no new safety signals for any group, nor any cases of retinal vasculitis, occlusive retinitis, or endophthalmitis.

These data represent a significant step forward in the effort to reduce the injection burden for patients with DME and wet AMD, while maintaining the same visual improvements as the standard regimen.

1. Aflibercept 8 mg meets primary endpoints in two global pivotal trials for DME and WAMD, with a vast majority of patients maintained on 12- and 16-week dosing intervals [press release]. Regeneron. September 8, 2022. Accessed September 15, 2022. investor.regeneron.com/news-releases/news-release-details/aflibercept-8-mg-meets-primary-endpoints-two-global-pivotal

IMAGING TECHNIQUE REVEALS CELLULAR ACTIVITY OF CHOROIDEREMIA

Researchers at the National Eye Institute (NEI) used adaptive optics combined with indocyanine green dye to observe for the first time the effects of choroideremia at the cellular level, including disruptions to photoreceptors, retinal pigment epithelium (RPE) cells, and choroidal blood vessels, according to a study published last month in *Communications Biology*.[1]

The researchers found that RPE cells are significantly enlarged in individuals with this X-linked retinal degenerative disease that affects men more than women. In both sexes, photoreceptors and blood vessels were less affected than RPE cells, suggesting that RPE disruption plays an important role in the disease process.[1]

Although useful for discovering this cellular activity in choroideremia, adaptive optics is not a part of routine diagnostic testing. However, according to Johnny Tam, PhD, head of the NEI Clinical and Translational Imaging Unit, the enlarged RPE cells can also be observed with a commercially available scanning laser ophthalmoscope combined with indocyanine green dye.[2] This way, the RPE layer may be evaluated using existing clinical tools, potentially allowing clinicians to better treat patients with this rare genetic disease.

1. Aguilera N, Liu T, Bower AJ, et al. Widespread subclinical cellular changes revealed across a neural-epithelial-vascular complex in choroideremia using adaptive optics. *Commun Biol*. 2022;5(1):893.
2. Novel imaging approach reveals important details about rare eye disease choroideremia [press release]. NIH. September 13, 2022. Accessed September 15, 2022. www.nih.gov/news-events/news-releases/novel-imaging-approach-reveals-important-details-about-rare-eye-disease-choroideremia

NOVEL THERAPY FOR GA MEETS PHASE 3 PRIMARY ENDPOINTS

Last month, Iveric Bio announced that its investigational C5 complement inhibitor, 2 mg avacincaptad pegol (Zimura) for the treatment of geographic atrophy (GA), met its 12-month primary endpoints in a phase 3 clinical trial.[1]

Data analysis revealed that patients in the investigative arm experienced a mean rate of GA growth of 1.745 mm, compared with a rate of 2.121 mm in the sham group ($P = .0039$).[1] Post-hoc analysis also showed significant efficacy at reducing the rate of GA growth. The investigative drug had a favorable safety profile compared with sham injections, with no events

of endophthalmitis, intraocular inflammation, or ischemic optic neuropathy with up to 12 months of follow-up.[1]

The need for a safe and effective therapy for GA continues to represent a critical gap in eye care. Iveric Bio plans to submit a new drug application to the FDA in the first quarter of 2023. If approved, avacincaptad pegol may offer a game-changing solution to reduce the growth of GA and manage this currently untreatable blinding disease.

1. Iveric Bio announces positive topline data from Zimura GATHER2 phase 3 clinical trial in geographic atrophy [press release]. Iveric Bio. September 6, 2022. Accessed September 15, 2022. www.businesswire.com/news/home/20220905005451/en/Iveric-Bio-Announces-Positive-Topline-Data-from-Zimura®-GATHER2-Phase-3-Clinical-Trial-in-Geographic-Atrophy

Updates From Eyewire+

- The first US patient has undergone surgery to be implanted with a retinal pigment epithelium (RPE) patch made with patient-derived induced pluripotent stem cells as part of a **National Institutes of Health** phase 1/2a clinical trial of an investigative therapy for geographic atrophy (GA). Each patch (2 x 4 mm) contains about 75,000 RPE cells and may work to reverse some of the damage caused by GA progression.
- Ophthalmologists can now seamlessly share clinical data and documentation between the **ModMed EMR** and **SamaCare's** free online prior authorization management platform. The goal of this integration is to improve practices' prior authorization management efficiency and alleviate some of the burden of administrative tasks, allowing providers to spend more time caring for patients.
- **Adverum Biotechnologies** announced that its LUNA phase 2 trial evaluating ixoberogene soroparvovec (Ixo-vec, formerly referred to as ADVM-022) dosed its first wet AMD patient. The trial will include up to 72 patients who will be randomized equally between a 2x10^11 vg/eye dose and lower 6x10^10 vg/eye dose and across four prophylactic steroid regimens.
- **Nanoscope Therapeutics** has completed enrollment of its phase 2 STARLIGHT clinical trial of MCO-010. The ambient-light activatable multi-characteristic opsin optogenetic monotherapy is designed to restore vision in patients blinded by Stargardt disease. The 6-month data are expected in the first half of 2023.
- Subgroup analysis of **Oculis'** DX-211 phase 2 trial of OCS-01 in patients with diabetic macular edema, presented at Euretina 2022, showed that patients with a baseline BCVA of ≤ 65 letters who were treated with the novel topical formulation of dexamethasone showed greater improvements in central macular thickness and BCVA at week 12.
- The European Commission approved faricimab (Vabysmo, **Genentech/Roche**) for the treatment of wet AMD and visual impairment due to diabetic macular edema. Faricimab is now approved in the European Union and nine other countries, including the United States, Japan, and the United Kingdom.

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NEW VIRTUAL CME EVENT FOCUSES ON DISPARITIES IN EYE CARE

The Association for Research in Vision and Ophthalmology (ARVO) is holding a new virtual conference, Envisioning Equity in Eye Care, on November 16–17, from 1:00 pm to 4:30 pm EST each day. The goal of the conference is to examine the social and environmental factors that lead to disparities in health and eye care and to develop solutions to address these disparities.[1]

The program will cover topics such as lessons learned from the COVID-19 pandemic about social inequities, using data to reveal health disparities, addressing disparities in health care, and increasing diversity among eye care professionals. Keynote speakers will include Marcella Nunez-Smith, MD, MHS; Michael F. Chiang, MD; and Eliseo J. Pérez-Stable, MD.[1]

ARVO has designated the activity for a maximum of 6.25 AMA PRA Category 1 credits. You can register for this event at www.arvo.org/education/2022-envisioning-equity.

1. Envisioning Equity in Eye Care virtual conference. ARVO. Accessed September 15, 2022. www.arvo.org/education/2022-envisioning-equity

NEW GENE THERAPY FOR LEBER CONGENITAL AMAUROSIS IN THE WORKS

Researchers at the NEI recently developed a new potential gene therapy for patients with Leber congenital amaurosis (LCA) due to mutations in the *NPHP5* gene.[1]

When studying stem cell samples from two patients with *NPHP5* deficiencies, the researchers found reduced levels of the NPHP5 protein within the patient-derived retinal organoid cells. They also noted reduced levels of the CEP-290 protein, which interacts with the NPHP5 and forms the primary cilium gate. *CEP-290* gene mutations are the most common cause of LCA. In the samples, photoreceptor outer segments in the retinal organoids were completely missing, and the opsin protein, usually localized to the outer segments, was found elsewhere in the photoreceptor cell body.

With this discovery in hand, the team introduced an adeno-associated viral vector containing a functional version of *NPHP5*, leading to the restoration of the opsin protein concentrated in the proper location in the outer segments. The findings also suggest that functional *NPHP5* may have the ability to stabilize the primary cilium gate.

"The findings not only shed light on the function of NPHP5 protein in the primary cilium, but also led to a potential treatment for this blinding condition," according to the press release. ■

1. Kruczek K, Qu Z, Welby E, et al. In vitro modeling and rescue of ciliopathy associated with IQCB1/NPHP5 mutations using patient-derived cells [Preprint published online August 27, 2022]. *Stem Cell Reports*.

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DEPARTMENTS

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A PEEK AT THE CLINICAL TRIALS AT THE SUMMIT

The latest research was on display at the 2nd annual CTS meeting at Lake Tahoe, Nevada.

BY AAMIR A. AZIZ, MSII

Clinical Trials at the Summit (CTS), the brainchild of Arshad M. Khanani, MD, MA, and Charles C. Wykoff, MD, PhD, is a new annual conference that brings together retina specialists and industry partners. This meeting focuses on the logistics of clinical research and showcases clinical trials for new treatments, devices, and breakthroughs. The second (first in-person) meeting covered everything from new imaging and functional biomarkers to trials investigating AMD, diabetic retinopathy, diabetic macular edema, delivery approaches, devices, and gene therapy. The unique panel format—four presenters, two panelists, and a moderator—created a fast-paced discussion that kept attendees on their toes.

Image courtesy of Tawnie Baranick, T Art Photos

Figure. The experts had much to discuss during the unique "Clinical Trial Failures: What Have We Learned?" panel at this year's CTS conference. Pictured here (left to right) are panelists Peter K. Kaiser, MD; Jeffrey S. Heier, MD; Carl D. Regillo, MD; David S. Boyer, MD; Charles C. Wykoff, MD, PhD; Arshad M. Khanani, MD, MA; and Christina Y. Weng, MD.

RESEARCH BEHIND THE SCENES

The first session focused on how to start and manage a successful clinical research department. Carl J. Danzig, MD, reminded new investigators to always consider logistics such as practice type, location, staffing, and equipment. Caesar K. Luo, MD, suggested eager researchers start with investigator-initiated trials to establish themselves in the field before conducting larger industry led trials.

IMAGING AND BIOMARKERS

During the second session, Frank G. Holz, MBBS, introduced photoreceptor laminae thickness and relative ellipsoid zone reflectivity as new efficacy biomarkers for the treatment of intermediate AMD and geographic atrophy (GA).

Karl G. Csaky, MD, PhD, provided an update on contrast sensitivity testing for clinical trials and discussed the utility of quantitative contrast sensitivity function as a testable parameter for patients with intermediate AMD.

Caroline R. Baumal, MD, presented on the use of OCT angiography as an endpoint for clinical trials, recognizing that while it's faster than fluorescein angiography, the lack of standardization and the difficulty it creates for some patients can be limiting. However, OCT angiography can determine the type of choroidal neovascularization (CNV), show vascularized drusen and quiescent macular neovascularization, and determine diabetic retinopathy stages, she said.

THE PIPELINE

In the next session, Julie Clark, MD, presented on results from the GATHER1 trial, which showed that treatment with avacincaptad pegol (Iveric Bio) reduced the growth of GA by 27% over 12 months and caused a reduced rate of conversion from incomplete retinal pigment epithelium (RPE) and outer retinal atrophy (iRORA) to complete RPE and outer retinal atrophy (cRORA) with no serious safety signals. *Editor's note: GATHER2 results were announced in September.*

Federico Grossi, MD, PhD, then discussed pegcetacoplan (Apellis Pharmaceuticals). The phase 3 OAKS trial met its primary endpoint, but the phase 3 DERBY did not. Reductions in GA progression were seen from months 6 to 18, at a rate reduction of 26% for patients with extrafoveal involvement and 13% for those with foveal involvement. Ninel Z. Gregori, MD, and SriniVas R. Sadda, MD, mentioned that they would use these drugs in patients at risk for foveal atrophy but that clinicians will have to consider the treatment burden and the

risks versus benefits.

Nikolas J.S. London, MD, presented on IONIS-FB-LRX (Ionis Pharmaceuticals), a subcutaneous antisense oligonucleotide injectable that degrades target RNA of complement factor B. The phase 1 study in young, healthy patients demonstrated safety and a dose-dependent level of plasma factor B. Dr. Gregori expressed concerns about the drug's risk for unwanted systemic effects for patients with comorbidities.

DELIVERY IS KEY

An exciting panel on surgical delivery and devices began with Steve Charles, MD, presenting on stem cells to treat GA with an iPSC-RPE patch.

Carlos Quezada Ruiz, MD, discussed the safety of the port delivery system with ranibizumab (Susvimo, Genentech/Roche). He noted that patients have experienced a variety of adverse events, but the safety profile has improved as the surgical technique evolves. Allen C. Ho, MD, suggested that the port delivery system may work best for diabetic patients who usually have decreased compliance, while Rahul N. Khurana, MD, stated that a permanent foreign body in the eye is a cause of concern in the average patient.

Sherri Van Everen, PharmD, presented on Regenxbio's subretinal gene therapy, RGX-314, for wet AMD and said that the drug seems safe while maintaining or improving visual outcomes in patients in the phase 1/2a trial.

Eduardo Uchiyama, MD, discussed the suprachoroidal triamcinolone acetonide (Xipere, Bausch + Lomb and Clearside Biomedical) and noted that only 13% of dosed patients required rescue treatment compared with 72% of control patients.

GENES UNDER ATTACK

The gene therapy session began with David S. Boyer, MD, who presented on Adverum's ADVM-022 (now called Ixo-vec) for wet AMD. Keeping neutralizing antibody titers below 1:125 maintains the generated aflibercept at optimal levels and shows no correlation with inflammation, he said. Dr. Boyer also presented on 4D Molecular Therapeutics' 4D-150, which uses dual inhibition with generated aflibercept and interfering RNA to inhibit all four VEGF family members, leading to 100% CNV inhibition without safety signals.

Peter A. Campochiaro, MD, discussed Regenxbio's suprachoroidal RGX-314, demonstrating a more than 70% reduction in treatment burden, with more than 30% of patients remaining injection free.

Susan Washer, MBA, presented on the X-linked retinitis pigmentosa gene therapy from Applied Genetic Technologies Corp, which demonstrated improvements in visual acuity for 12 months, with a 62.5% response rate in one cohort, without any serious adverse events.

Nadia K. Waheed, MD, presented on Gyroscope Therapeutics' GT005 for complement factor I production, which led to decreased vitreous levels of C3/complement Ba and a halved rate of lesion growth at 6 months, with only mild treatment-related adverse events.

WET AMD PALOOZA

During the wet AMD session, Carl D. Regillo, MD, presented on Kodiak Sciences' KSI-301; unfortunately, the phase 3 DAZZLE study did not meet its primary endpoint.

Joel Naor, MD, MSc, MBA, presented on Opthea's OPT-302, an adjunct treatment with ranibizumab (Lucentis, Genentech/Roche) to inhibit all four VEGF family members; in the phase 2b trial, the combination therapy demonstrated better visual acuity and decreased central retinal thickness (CRT) compared with ranibizumab monotherapy.

Dr. Khanani presented the real-world TRUCKEE study that is evaluating the safety and efficacy of faricimab (Vabysmo, Genentech/Roche) in wet AMD. New data show improved visual acuity and CRT after one injection, even for those switching from aflibercept (Eylea, Regeneron) to faricimab. He stated that he has been extending patient intervals if they return without fluid after their first treatment with faricimab.

Diana V. Do, MD, presented on the use of 8 mg aflibercept versus the normal 2 mg dose, noting that a higher proportion of patients demonstrated no fluid at week 16, with the trend dropping by week 44.

Marither S. Chuidian, MD, presented Graybug Vision's GB-102, which is entering a phase 2 study with an optimized formulation to establish durability and noninferiority.

Sophie J. Bakri, MD, discussed Eyepoint Pharmaceuticals' EYP-1901, which demonstrated safety and tolerability during the phase 1 study, as well as a 79% reduction in treatment burden at month 6, meeting all the efficacy objectives at month 8 for reduced treatment burden and stable CRT.

LEARN FROM OUR MISTAKES

The day concluded with a session on lessons learned from trial failures (Figure). Dr. Regillo expressed his disappointment with KSI-301, and Peter K. Kaiser, MD, suggested that 12-week intervals may be proof that the researchers were trying too hard to improve different parameters. Dr. Wykoff mentioned that drugs targeting other pathways, such as tyrosine kinase inhibitors, cannot sacrifice efficacy for the sake of durability.

STAY TUNED

CTS is already gearing up for the 2023 meeting, with plans to bring together more retina specialists and industry partners who are interested in moving retina research forward. ■

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ARDS 2022 NAMED LECTURES: TWO GREATS, TWO FRIENDS

Timothy G. Murray, MD, MBA, and H. Culver Boldt, MD, share their passions for oncology and surgical training.

BY REBECCA HEPP, EDITOR-IN-CHIEF

The 2022 Aspen Retinal Detachment Society (ARDS) meeting in Snowmass, Colorado—the 50th anniversary meeting—boasted named lectures that highlighted many significant changes in the field of retina. I was honored to present the Founders Award to H. Culver Boldt, MD, my close friend, who shared three decades of surgical training. I was also honored, and humbled, to be named the 2022 Taylor Smith & Victor Curtin Lecturer, and I chose to discuss my passion, advances in ocular oncology. I hope our peek into the past, present, and future sparks inspiration as you seek better ways to care for patients.

Registration is already open for ARDS 2023 set for March 4-8. Head to https://aspenretina.com for more information—and start digging out your ski gear.

– Timothy G. Murray, MD, MBA

FOUNDERS LECTURE

Dr. Boldt took to the stage to discuss surgical training and "what's changed, what hasn't, and maybe what we could do better" (Video 1). He first warned that there are many approaches to training, and some are better than others, but most are simply different. "Different trainees will learn better in certain environments, and different surgeons are probably better at training with different approaches," he explained.

What Hasn't Changed?

Surgeons still focus on the basics: anatomy, physiology, pathology, and pharmacology, as well as surgical indications, instrumentation, and techniques. Core vitrectomy remains a bread-and-butter procedure, according to Dr. Boldt, and while the basic techniques haven't changed much, the technology sure has. Back in 1990, Dr. Boldt was using the STORZ MVS vitrectomy system, "which raced along at 800 cuts per minute with 20-gauge cutters." The view was limited, 20° to 25°, and some ORs didn't use trocars, he said.

What Has Changed?

Scleral buckles are a good example of the shift in surgical training, Dr. Boldt said. They were common in the past, and "sometimes we got creative and even invented our own buckles," he admitted. "Detailed drawings were expected, you were expected to find all the breaks preoperatively, and draining subretinal fluid was an art—these are being lost." Today, it's challenging for a fellow to get enough experience with scleral buckles and draining subretinal fluid, he said.

In 1990, "we lasered everything," and he recounted lasering at least 300 choroidal neovascular membranes as a first-year fellow. "Now, people don't do as much of that. They just haven't had as much experience in some of these things because of anti-VEGF [therapy]."

In addition to the changing treatment landscape, Dr. Boldt touched on the training tools that were available decades ago. "We didn't have simulation that was worth a hill of beans, so you gained experience on patients," he said—without any real established guidelines for training.

Training on the latest vitrectomy systems is much safer, he said, and instruments are significantly smaller and more precise, leading to safer and faster surgeries and faster recovery times. When Dr. Boldt was training, the rate of iatrogenic breaks was approximately 4% in the first month of a fellow's time in the OR, he noted. Today's advances have changed fellowship training considerably, he said. "It has allowed us to have our fellows participate in surgeries that are more complex at an earlier time in their training."

As for visualization, widefield imaging is obviously the most significant game-changer, he said. "I don't think the junior people in the room could imagine fixing a giant retinal tear when you have a 20° lens as your maximum view." Surgeons relied on contact lenses to help them see the periphery and train fellows on peripheral pathology—still, those were tricky to use, Dr. Boldt recalled.

Other significant advances in visualization include intraoperative OCT, 3D heads-up displays, and vitreous staining, according to Dr. Boldt. These tools have been wonderful for

WATCH IT NOW

Video 1. Three Decades of Surgical Training

WATCH IT NOW

Video 2. Advances in Ocular Oncology

surgical training, and, for 3D visualization in particular, "it gives me more comfort in allowing my fellows to go further during surgery," he said.

Other important training tools available now include surgical simulators and model eyes that can help trainees become familiar with the instruments and simple techniques—all within a far less stressful environment. But one of the most important tools to help trainees is the proliferation of high-quality surgical training videos. "Fellows can watch these and can actually see surgeries and feel like they can almost do them afterward," Dr. Boldt said.

Another important change was the establishment of the Association of University Professors of Ophthalmology's Fellowship Compliance Committee (AUPO FCC), which outlined training guidelines with the help of the Retina Society, Macular Society, and the American Society of Retina Specialists. "There was no standardization in fellowships," according to Dr. Boldt. "Now, these are the surgical criteria that people can use. Programs are monitored on a yearly basis to make sure they're keeping up." The program is still voluntary with 60% of programs following the AUPO FCC guidelines, Dr. Boldt said.

Lasting Change

"We have had a ton of changes in our surgical indications and techniques over the last 30 years," Dr. Boldt concluded. "Many of things that have remained the same in teaching, the basics, are still as critical as ever. Still, the skillset to become a good vitreoretinal surgeon is quite different now than it was 30 years ago. Fellowships have become a little more standardized, but we still need more work."

TAYLOR SMITH & VICTOR CURTIN LECTURE

"Sometimes, when things happen over time, we lose track of where we were, where we are, and where we're going," Dr. Murray said to kick off his named lecture, which focused on advances in ocular oncology (Video 2).

Melanoma Pearls

In the 1980s, the standard treatment for melanoma was enucleation; then, charged-particle radiotherapy or brachytherapy was the go-to option until clinicians began noticing radiation-related complications. That led to a shift toward radiation-sparing techniques. Still, all of these are viable treatment options, according to Dr. Murray. "There is no procedure that we do not do," he emphasized.

The tumor control rate is an all-important statistic in oncology, Dr. Murray explained. That rate is 100% with enucleation, which is what drove the historical focus on the approach. But brachytherapy and charged-particle radiotherapy have phenomenal tumor control rates for the primary intraocular tumor, approaching 100%, he added.

A new approach to the management of small melanoma—a nanoparticle that is activated by photodynamic therapy—is showing a control rate in the 60% range. But Dr. Murray and many others strongly believe in the "fix it the first time" mantra, which has moved the field away from radiation-sparing techniques and back toward approaches with a control rate nearing 95%.

Dr. Murray shared a study of 2,374 patients who underwent treatment for uveal melanoma and retinoblastoma, with treatment trends broken down into decades: 1991 to 2001, 2002 to 2011, and 2012 to 2017. The data showed that enucleation rates dropped from 30% in the 90s to less than 5% between 2012 and 2017—an incredible shift.

Dr. Murray then combatted the age-old complaint that the field hasn't changed the mortality rate for ocular melanoma over the last 3 decades. First, patients are presenting for treatment earlier than ever before, he said. The mean apical height of tumors in that first decade was 5.9 mm compared with 4.7 mm in the last decade. Second, melanoma-specific mortality fell from 12.1% overall in this cohort to 9.5% in the last decade. Third, secondary enucleation fell from 6% in the earliest decades of the study to less than 1% by the last decade. His

(Continued on page 18)

ROP IN THE OR: WHEN LESS IS MORE

During surgery for advanced retinopathy of prematurity, removing all traction may not be the end goal.

BY ATCHARA AMPHORNPHRUET, MD

Retinopathy of prematurity (ROP) is one of the most common causes of preventable vision loss in children.[1,2] Despite the availability of various treatment approaches—and favorable results with timely intervention—many infants present for treatment only once they have reached the advanced stages of the disease.[2] This is due, in part, to the lack of access to pediatric ophthalmologists and retina specialists, particularly in developing countries (eg, South-East Asia).[3]

Although ROP screening protocols have improved, many infants still develop severe vision loss due to retinal folds and tractional retinal detachment (TRD), the most serious ROP complications leading to blindness.[4] With the advent of anti-VEGF therapy, the number of patients who develop TRDs has decreased.[3] Still, some patients will require surgical intervention for ROP. When they do, these clinical factors can help you understand when less is more in the OR.

STAGE 4

Surgery is indicated when ROP progresses to stage 4, whether stage 4A (macula-sparing TRD) or stage 4B (macula-involving TRD). The goal is to reattach as much of the retina as possible without introducing a retinal break. Although scleral buckling and/or vitrectomy are routine procedures in the hands of an experienced vitreoretinal surgeon, surgical intervention for these stages can quickly become complex if intraoperative complications arise. Each ROP-related TRD is unique with varying presentations, and even a tiny retinal tear can devastate the prognosis. Sen et al found that intraoperative breaks occurred in 19% of patients in their case series of 202 premature eyes.[4] Other complications included postoperative vitreous hemorrhage (28%), increased IOP (12.7%), and cataract progression (2.4%).[4]

More risk is involved with stage 4B ROP surgery because surgeons must peel the fibrovascular membranes to relieve traction and dissect all the preretinal fibrovascular membranes over the macula or around the equator. Thus, "less is more" for stage 4B surgery, more so than with stage 4A.

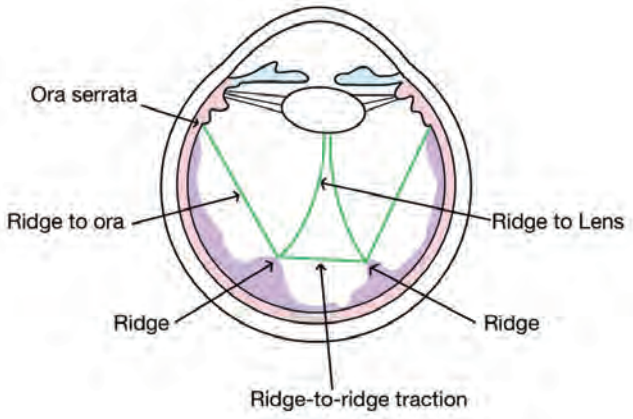

Image courtesy of Wararee sriyuttagral, MD

Figure 1. This diagram represents the beginning of a TRD due to various tractional forces in ROP. The traction must be released as much as possible with no complications. Some traction could be due to the vitreous and/or gross fibrovascular membranes.

The least risky surgical procedure to treat stage 4A ROP is scleral buckling, which I reserve for cases that present with a retinal tear or simple traction (ie, no fibrovascular membrane). To ensure success, surgeons must be careful to time the release of the silicone band properly, observe the IOP closely, and be mindful of the patient's refractive error. Scleral buckling should reduce the vascular activity and help to reattach the retina.

Thanks to today's advanced surgical tools, vitrectomy is another surgical approach that may help to release traction due to fibrovascular membranes with reasonable safety. In fact, some researchers have reported better surgical results with vitrectomy for ROP compared with scleral buckling.[5,6]

When performing surgery for stage 4 ROP, surgeons should follow two rules:

Rule no. 1: There is no need to induce a posterior vitreous detachment.

Rule no. 2: Try to relieve the traction in all directions (ie, ridge to ora serrata, ridge to ridge, and ridge to lens) while removing as few preretinal membranes and as little proliferative tissue as possible (Figure 1).[7,8]

Even if some traction remains, some areas of the retina will gradually reattach postoperatively, which is a better outcome than attempting to eradicate all traction and create a complication in the process, such as a retinal tear.

WHEN TO BE AGGRESSIVE

When the ridge-to-ridge traction is extensive and the surgeon does not feel that the retina will reattach, usually in stage 4B, a more aggressive approach is necessary to remove the fibrovascular membrane and trim the adhesive vitreous closely to the retina (Figure 2). I prefer to use smaller-gauge instruments, 25- or 23-gauge, without cannulas to allow easy access, better manipulation, and safer removal of fibrovascular tissue.[6] In the case of thick membranes that are difficult to cut (often stage 5 ROP), surgeons can use intraocular scissors, although these instruments require precision to avoid inducing a retinal break. Surgeons should watch for intraoperative bleeding, the telltale sign of a retina tear.

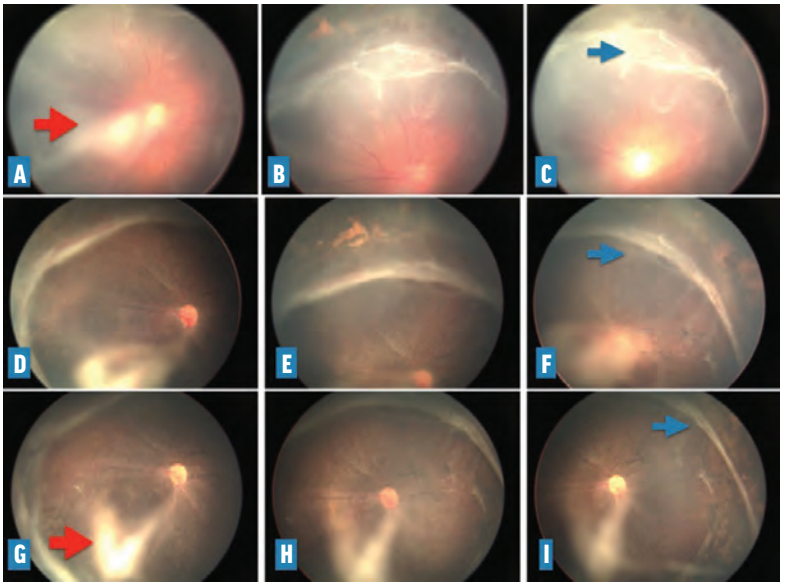

Figure 2. This patient, born at 28 weeks gestational age with a birth weight of 589 g, developed stage 3 ROP with plus in each eye. After treatment with laser indirect ophthalmoscope in each eye, the ROP progressed to stage 5C in the left eye and stage 5A the right eye. At 56 weeks postmenstrual age (PMA), the right eye demonstrated a total RD with a visible optic disc and a 360˚ ring of active TRD with no significant complex fibrovascular membranes or funnel (A-C). At 80 weeks PMA, the right eye presented with a spontaneously partially reattached retina without the need for surgery (D-F). At 3.6 years of age, fundus photography showed a reattached retina with spontaneously regressed ROP (G-I). Note the mature fibrovascular tissue regression in the vitreous from ridge traction (red arrows) and the regression of peripheral fibrovascular tissues (blue arrows).

STAGE 5

There is no consensus on the proper timing and type of surgery for stage 5 ROP, particularly given the poor anatomical and visual prognosis.[4] Stage 5 total RD is categorized into three configurations: stage 5A, in which the optic disc is visible by ophthalmoscopy (open-funnel detachment); stage 5B, in which the optic disc is not visible secondary to retrolental fibrovascular tissue (closed-funnel detachment); and stage 5C, in which stage 5B is accompanied by anterior segment abnormalities (eg, anterior lens displacement, marked anterior chamber shallowing, and iridocapsular adhesions).[9]

Surgeons must choose their stage 5 surgical cases carefully and impress upon parents the benefits of even light perception vision such interventions can provide. Research shows that surgical intervention for stage 5 ROP can lead to successful anatomical results in only 20% to 50% of cases.[2] Here are my typical approaches for each category of stage 5 ROP:

- **Stage 5A:** I often choose a conservative approach and may wait up to 6 months to see if the retina reattaches from spontaneous regression. If surgery is indicated, the goal of surgical intervention is to achieve at least partial reattachment because complete release of traction is extremely difficult.
- **Stage 5B:** I adhere to the "less is more" mantra during surgery and minimize my dissection of the fibrovascular membranes to open the funnels. The less vitreous that can be released during surgery, the more likely at least some of the retina will reattach. The less the surgeon manipulates the retina and globe, the better the chances of useful anatomical and functional outcomes.[2]
- **Stage 5C:** Selecting these cases is challenging. I do not recommend surgery for patients with severe corneal complications due to the poor surgical view for membrane dissection and subsequent risk of surgical failure, which can lead to phthisis bulbi. Stage 5C ROP with retrolental fibroplasia, more common than cases without retrolental fibroplasia, requires a lensectomy and deep dissection—a more technically challenging surgical approach.[2]

Preoperative ultrasonography can help surgeons verify the morphology of the stage 5 TRD and plan the best approach to improve the chances of a positive prognosis.

RDs that are closer to the lens with a narrower funnel provide the surgeons with poor visualization through cornea, which can limit the surgeon's precision when dissecting thin membranes; thus, these fibrovascular membranes should be manipulated as little as possible to avoid unintentional retinal tears.

Another challenge with these stage 5 cases is determining where to begin removing the sheath of vitreous that formed in a radial pattern and closed the funnel anteriorly. Often, the safest starting point is in the center, where surgeons can find the space and then dissect along the top of the retinal fold. Surgeons can be sure they have found the correct plane if they are able to safely dissect to the equator and further into the periphery.

ROP SURGERY QUICK TIPS

- Less is more.
- Surgeons should start ROP surgery with the goal of manipulating the tissues of the eye as little as possible to achieve the goal of an attached retina—even if only a partial reattachment.
- Vitrectomy in the setting of ROP aims to relieve the traction, eliminate the scaffold for further TRD progression, and remove excessive levels of VEGF. All are often enough to stop disease progression, accelerate disease regression, and decrease complications.

Failure to find the correct plane or distinguish between the thin fibrovascular membrane and the avascular retina may lead to unintentional retinal tears and surgical failure. Finally, how much of the fibrovascular membrane to remove depends on the circumstances of each case and requires careful preoperative and intraoperative consideration as the surgeon dissects.

FINAL GOAL

Vitrectomy for ROP-associated TRD is a complex procedure due to the risk of complications. Surgeons must judge carefully to determine how much of the fibrovascular membrane to remove to reduce the vitreous traction without inducing a retinal tear. More often than not, a successful surgery doesn't involve completely removing the traction; instead, partial reattachment of the retina may be the best possible outcome to avoid introducing complications that may further limit the patient's visual potential. When in doubt, I recommend surgeons remember that, when it comes to ROP surgery, less is more in complex TRD repair. ■

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■ Financial disclosure: None

(Continued from page 15)

fourth and final point was about change in visual acuity, and he noted that the mean VA in the retained globes was 20/100 in the first decade and 20/62 by the last decade.

But Dr. Murray is most excited about the management of very small tumors. In 2011, class 1A tumors came with a 2% mortality rate at 5 years and class 2 tumors had a 72% mortality rate associated with metastasis—stark numbers that didn't seem to play out in Dr. Murray's clinic. So, he looked at 100 patients with ocular melanoma with a mean entering VA of 20/80 and a mean tumor size of 1.9 mm. He and his team biopsied the tumors and managed the patients based on cytogenetic testing and the tumor classification.

At 79 months of follow-up, tumor height decreases to a mean of 1.4 mm, and VA improved from 20/80 at baseline to 20/40 by 6 months and 20/30 at 18 months. At the final endpoint, 92% of patients had a VA of 20/50 or better. "And what was the molecular classification in this small tumor series?" Dr. Murray queried the audience. "Twelve of these patients have a class 2 tumor." In total, cytogenetic testing showed that 12% of the patients had a class 2 tumor, 11% had a class 1B tumor, and 76% had a class 1A tumor.

The take-home message from Dr. Murray was simple: "Uveal melanoma treatment has undergone significant shifts, enhancing our ability to improve survival, enhance globe retention, and give patients eyes that are truly functional."

The Retinoblastoma Story

The standard care for retinoblastoma in the 1980s was also enucleation, which shifted to external beam radiotherapy (EBRT) in the 1990s. "EBRT did a phenomenal job of curing retinoblastoma, but our kids were dying from secondary malignancies, 10, 20, and even 30 years later," Dr. Murray said. Those concerns led to an abrupt shift to chemotherapy. However, aggressive systemic chemotherapy left kids sick and weak throughout the course of treatment. In comes intraarterial ophthalmic artery treatment, the real game-changer for these patients, according to Dr. Murray.

He shared select patient stories, beginning with a patient who presented with a complex retinal detachment and a vascular tumor. Today, that eye is 20/50, thanks to EBRT, he said.

In 2009, Dr. Murray used intraarterial chemotherapy for the first time to treat a child with retinoblastoma who now has a VA of 20/20 in that eye, he said—an eye that likely would have been enucleated at another institution.

"So, here's our treatment trend: enucleation has really come off the table, radiotherapy was replaced by chemotherapy, and we shifted to intraarterial chemotherapy," Dr. Murray summarized. Enucleation rates for primary retinoblastoma are almost gone, and secondary enucleation rates are down to below 5%.

"It's been an incredible 3 decades with major changes in our ability to take care of children with retinoblastoma and adults with melanoma," Dr. Murray concluded. ■

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- EYLEA is contraindicated in patients with ocular or periocular infections, active intraocular inflammation, or known hypersensitivity to aflibercept or to any of the excipients in EYLEA.

WARNINGS AND PRECAUTIONS

- Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately. Intraocular inflammation has been reported with the use of EYLEA.
- Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with VEGF inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately.
- There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA compared with 1.5% (9 out of 595) in patients treated with ranibizumab; through 96 weeks, the incidence was 3.3% (60 out of 1824) in the EYLEA group compared with 3.2% (19 out of 595) in the ranibizumab group. The incidence in the DME studies from baseline to week 52 was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

ADVERSE REACTIONS

- Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment.
- The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and intraocular pressure increased.
- Patients may experience temporary visual disturbances after an intravitreal injection with EYLEA and the associated eye examinations. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

INDICATIONS

EYLEA® (aflibercept) Injection 2 mg (0.05 mL) is indicated for the treatment of patients with Neovascular (Wet) Age-related Macular Degeneration (AMD), Macular Edema following Retinal Vein Occlusion (RVO), Diabetic Macular Edema (DME), and Diabetic Retinopathy (DR).

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

References: 1. EYLEA® (aflibercept) Injection full U.S. Prescribing Information. Regeneron Pharmaceuticals, Inc. June 2021. **2.** Data on file. Regeneron Pharmaceuticals, Inc.

REGENERON®

777 Old Saw Mill River Road, Tarrytown, NY 10591 06/2022 EYL.22.05.0005

EYLEA® (aflibercept) Injection
For Intravitreal Injection

BRIEF SUMMARY—Please see the EYLEA full Prescribing Information available on HCP.EYLEA.US for additional product information.

1 INDICATIONS AND USAGE
EYLEA is a vascular endothelial growth factor (VEGF) inhibitor indicated for the treatment of patients with:

Neovascular (Wet) Age-Related Macular Degeneration (AMD), Macular Edema Following Retinal Vein Occlusion (RVO), Diabetic Macular Edema (DME), Diabetic Retinopathy (DR).

4 CONTRAINDICATIONS

4.1 Ocular or Periocular Infections
EYLEA is contraindicated in patients with ocular or periocular infections.

4.2 Active Intraocular Inflammation
EYLEA is contraindicated in patients with active intraocular inflammation.

4.3 Hypersensitivity
EYLEA is contraindicated in patients with known hypersensitivity to aflibercept or any of the excipients in EYLEA. Hypersensitivity reactions may manifest as rash, pruritus, urticaria, severe anaphylactic/anaphylactoid reactions, or severe intraocular inflammation.

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis and Retinal Detachments
Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments [*see Adverse Reactions (6.1)*]. Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately [*see Patient Counseling Information (17)*].

5.2 Increase in Intraocular Pressure
Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA [*see Adverse Reactions (6.1)*]. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with vascular endothelial growth factor (VEGF) inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately.

5.3 Thromboembolic Events
There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA compared with 1.5% (9 out of 595) in patients treated with ranibizumab; through 96 weeks, the incidence was 3.3% (60 out of 1824) in the EYLEA group compared with 3.2% (19 out of 595) in the ranibizumab group. The incidence in the DME studies from baseline to week 52 was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

6 ADVERSE REACTIONS
The following potentially serious adverse reactions are described elsewhere in the labeling:
- Hypersensitivity [*see Contraindications (4.3)*]
- Endophthalmitis and retinal detachments [*see Warnings and Precautions (5.1)*]
- Increase in intraocular pressure [*see Warnings and Precautions (5.2)*]
- Thromboembolic events [*see Warnings and Precautions (5.3)*]

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in other clinical trials of the same or another drug and may not reflect the rates observed in practice.
A total of 2980 patients treated with EYLEA constituted the safety population in eight phase 3 studies. Among those, 2379 patients were treated with the recommended dose of 2 mg. Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment. The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and intraocular pressure increased.

Neovascular (Wet) Age-Related Macular Degeneration (AMD). The data described below reflect exposure to EYLEA in 1824 patients with wet AMD, including 1223 patients treated with the 2-mg dose, in 2 double-masked, controlled clinical studies (VIEW1 and VIEW2) for 24 months (with active control in year 1).
Safety data observed in the EYLEA group in a 52-week, double-masked, Phase 2 study were consistent with these results.

Table 1: Most Common Adverse Reactions (≥1%) in Wet AMD Studies

	Baseline to Week 52		Baseline to Week 96	
Adverse Reactions	EYLEA (N=1824)	Active Control (ranibizumab) (N=595)	EYLEA (N=1824)	Control (ranibizumab) (N=595)
Conjunctival hemorrhage	25%	28%	27%	30%
Eye pain	9%	9%	10%	10%
Cataract	7%	7%	13%	10%
Vitreous detachment	6%	6%	8%	8%
Vitreous floaters	6%	7%	8%	10%
Intraocular pressure increased	5%	7%	7%	11%
Ocular hyperemia	4%	8%	5%	10%
Corneal epithelium defect	4%	5%	5%	6%
Detachment of the retinal pigment epithelium	3%	3%	5%	5%
Injection site pain	3%	3%	3%	4%
Foreign body sensation in eyes	3%	4%	4%	4%
Lacrimation increased	3%	1%	4%	2%
Vision blurred	2%	2%	4%	3%
Intraocular inflammation	2%	3%	3%	4%
Retinal pigment epithelium tear	2%	1%	2%	2%
Injection site hemorrhage	1%	2%	2%	2%
Eyelid edema	1%	2%	2%	3%
Corneal edema	1%	1%	1%	1%
Retinal detachment	<1%	<1%	1%	1%

Less common serious adverse reactions reported in <1% of the patients treated with EYLEA were hypersensitivity, retinal tear, and endophthalmitis.

Macular Edema Following Retinal Vein Occlusion (RVO). The data described below reflect 6 months exposure to EYLEA with a monthly 2 mg dose in 218 patients following central retinal vein occlusion (CRVO) in 2 clinical studies (COPERNICUS and GALILEO) and 91 patients following branch retinal vein occlusion (BRVO) in one clinical study (VIBRANT).

Table 2: Most Common Adverse Reactions (≥1%) in RVO Studies

	CRVO		BRVO	
Adverse Reactions	EYLEA (N=218)	Control (N=142)	EYLEA (N=91)	Control (N=92)
Eye pain	13%	5%	4%	5%
Conjunctival hemorrhage	12%	11%	20%	4%
Intraocular pressure increased	8%	6%	2%	0%
Corneal epithelium defect	5%	4%	2%	0%
Vitreous floaters	5%	1%	1%	0%
Ocular hyperemia	5%	3%	2%	2%
Foreign body sensation in eyes	3%	5%	3%	0%
Vitreous detachment	3%	4%	2%	0%
Lacrimation increased	3%	4%	3%	0%
Injection site pain	3%	1%	1%	0%
Vision blurred	1%	<1%	1%	1%
Intraocular inflammation	1%	1%	0%	0%
Cataract	<1%	1%	5%	0%
Eyelid edema	<1%	1%	1%	0%

Less common adverse reactions reported in <1% of the patients treated with EYLEA in the CRVO studies were corneal edema, retinal tear, hypersensitivity, and endophthalmitis.

Diabetic Macular Edema (DME) and Diabetic Retinopathy (DR). The data described below reflect exposure to EYLEA in 578 patients with DME treated with the 2-mg dose in 2 double-masked, controlled clinical studies (VIVID and VISTA) from baseline to week 52 and from baseline to week 100.

Table 3: Most Common Adverse Reactions (≥1%) in DME Studies

	Baseline to Week 52		Baseline to Week 100	
Adverse Reactions	EYLEA (N=578)	Control (N=287)	EYLEA (N=578)	Control (N=287)
Conjunctival hemorrhage	28%	17%	31%	21%
Eye pain	9%	6%	11%	9%
Cataract	8%	9%	19%	17%
Vitreous floaters	6%	3%	8%	6%
Corneal epithelium defect	5%	3%	7%	5%
Intraocular pressure increased	5%	3%	9%	5%
Ocular hyperemia	5%	6%	5%	6%
Vitreous detachment	3%	3%	8%	6%
Foreign body sensation in eyes	3%	3%	3%	3%
Lacrimation increased	3%	2%	4%	2%
Vision blurred	2%	2%	3%	4%
Intraocular inflammation	2%	<1%	3%	1%
Injection site pain	2%	<1%	2%	<1%
Eyelid edema	<1%	1%	2%	1%

Less common adverse reactions reported in <1% of the patients treated with EYLEA were hypersensitivity, retinal detachment, retinal tear, corneal edema, and injection site hemorrhage.
Safety data observed in 269 patients with nonproliferative diabetic retinopathy (NPDR) through week 52 in the PANORAMA trial were consistent with those seen in the phase 3 VIVID and VISTA trials (see Table 3 above).

6.2 Immunogenicity
As with all therapeutic proteins, there is a potential for an immune response in patients treated with EYLEA. The immunogenicity of EYLEA was evaluated in serum samples. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to EYLEA in immunoassays. The detection of an immune response is highly dependent on the sensitivity and specificity of the assays used, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to EYLEA with the incidence of antibodies to other products may be misleading.
In the wet AMD, RVO, and DME studies, the pre-treatment incidence of immunoreactivity to EYLEA was approximately 1% to 3% across treatment groups. After dosing with EYLEA for 24-100 weeks, antibodies to EYLEA were detected in a similar percentage range of patients. There were no differences in efficacy or safety between patients with or without immunoreactivity.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Risk Summary
Adequate and well-controlled studies with EYLEA have not been conducted in pregnant women. Aflibercept produced adverse embryofetal effects in rabbits, including external, visceral, and skeletal malformations. A fetal No Observed Adverse Effect Level (NOAEL) was not identified. At the lowest dose shown to produce adverse embryofetal effects, systemic exposures (based on AUC for free aflibercept) were approximately 6 times higher than AUC values observed in humans after a single intravitreal treatment at the recommended clinical dose [*see Animal Data*].
Animal reproduction studies are not always predictive of human response, and it is not known whether EYLEA can cause fetal harm when administered to a pregnant woman. Based on the anti-VEGF mechanism of action for aflibercept, treatment with EYLEA may pose a risk to human embryofetal development. EYLEA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data
Animal Data
In two embryofetal development studies, aflibercept produced adverse embryofetal effects when administered every three days during organogenesis to pregnant rabbits at intravenous doses ≥3 mg per kg, or every six days during organogenesis at subcutaneous doses ≥0.1 mg per kg.
Adverse embryofetal effects included increased incidences of postimplantation loss and fetal malformations, including anasarca, umbilical hernia, diaphragmatic hernia, gastroschisis, cleft palate, ectrodactyly, intestinal atresia, spina bifida, encephalomeningocele, heart and major vessel defects, and skeletal malformations (fused vertebrae, sternebrae, and ribs; supernumerary vertebral arches and ribs; and incomplete ossification). The maternal No Observed Adverse Effect Level (NOAEL) in these studies was 3 mg per kg. Aflibercept produced fetal malformations at all doses assessed in rabbits and the fetal NOAEL was not identified. At the lowest dose shown to produce adverse embryofetal effects in rabbits (0.1 mg per kg), systemic exposure (AUC) of free aflibercept was approximately 6 times higher than systemic exposure (AUC) observed in humans after a single intravitreal dose of 2 mg.

8.2 Lactation
Risk Summary
There is no information regarding the presence of aflibercept in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production/excretion. Because many drugs are excreted in human milk, and because the potential for absorption and harm to infant growth and development exists, EYLEA is not recommended during breastfeeding.
The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for EYLEA and any potential adverse effects on the breastfed child from EYLEA.

8.3 Females and Males of Reproductive Potential
Contraception
Females of reproductive potential are advised to use effective contraception prior to the initial dose, during treatment, and for at least 3 months after the last intravitreal injection of EYLEA.

Infertility
There are no data regarding the effects of EYLEA on human fertility. Aflibercept adversely affected female and male reproductive systems in cynomolgus monkeys when administered by intravenous injection at a dose approximately 1500 times higher than the systemic level observed humans with an intravitreal dose of 2 mg. A No Observed Adverse Effect Level (NOAEL) was not identified. These findings were reversible within 20 weeks after cessation of treatment.

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

8.5 Geriatric Use
In the clinical studies, approximately 76% (2049/2701) of patients randomized to treatment with EYLEA were ≥65 years of age and approximately 46% (1250/2701) were ≥75 years of age. No significant differences in efficacy or safety were seen with increasing age in these studies.

17 PATIENT COUNSELING INFORMATION
In the days following EYLEA administration, patients are at risk of developing endophthalmitis or retinal detachment. If the eye becomes red, sensitive to light, painful, or develops a change in vision, advise patients to seek immediate care from an ophthalmologist [*see Warnings and Precautions (5.1)*].
Patients may experience temporary visual disturbances after an intravitreal injection with EYLEA and the associated eye examinations [*see Adverse Reactions (6)*]. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

REGENERON

Manufactured by:
Regeneron Pharmaceuticals, Inc.
777 Old Saw Mill River Road
Tarrytown, NY 10591

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Based on the August 2019 EYLEA® (aflibercept) Injection full Prescribing Information.

EYL.20.09.0052

VITREORETINAL SURGERY ONLINE


A free digital guide to surgical techniques, complete with instructional videos and pearls from experienced surgeons around the world.

BY NIMESH A. PATEL, MD, AND ADRIAN T. FUNG, MBBS, MMED, FRANZCO

While training for vitreoretinal surgery, fellows have a lot to master, including new surgical skills and a deep-seated understanding of the underlying principles. Volumes of textbooks, often given as suggested reading, can help fellows cover this information comprehensively. There are, however, more demands on their time now; for example, they must answer patient communications via instant EHR messaging for clinics that can see up to 90 patients a day—all while building a curriculum vitae to meet the standard of their peers.

Further barriers to education exist, including mounting financial pressures due to the ballooning cost and duration of medical subspecialty training and, perhaps most important, rapid innovation in the field of retina. Although many of the core principals remain steady, there are novel surgical techniques with evolving instrumentation, driven by our field's connection with the surgical device industry. It is difficult for print materials to remain current and generalizable in this ever-changing landscape.

Consequently, there exists a need for a modern online surgical textbook that is accessible, digestible, affordable, and malleable. Here's how we made that vision a reality.

IMPLEMENTATION AND COLLABORATION

The task of building a high-quality retinal surgery guide requires many willing international contributors. The first step was to find a group of authors for each chapter. The goal was to have global leaders in the field record their expertise, ideas, and illustrative clinical images in one location, and we solicited those with a particular area of focus from top institutions (Figures 1-3). We provided each author a guide to help them draft their sections in a "cookbook style" to ensure their content was digestible, especially for readers restricted in time and attention span. A favorable factor was the diversity of the senior editorial group, which includes Raymond Guan, MD, BSc; Nicolas Yannuzzi, MD; Sebastian M. Waldstein, MD, PHD; and Kenneth Rohan Lee, MBBS, M.Ophthal, and we both contributed as well.

Although planning conference calls to accommodate all the senior editors' time zones in Australia, the United States, Austria, and Malaysia was a significant challenge,

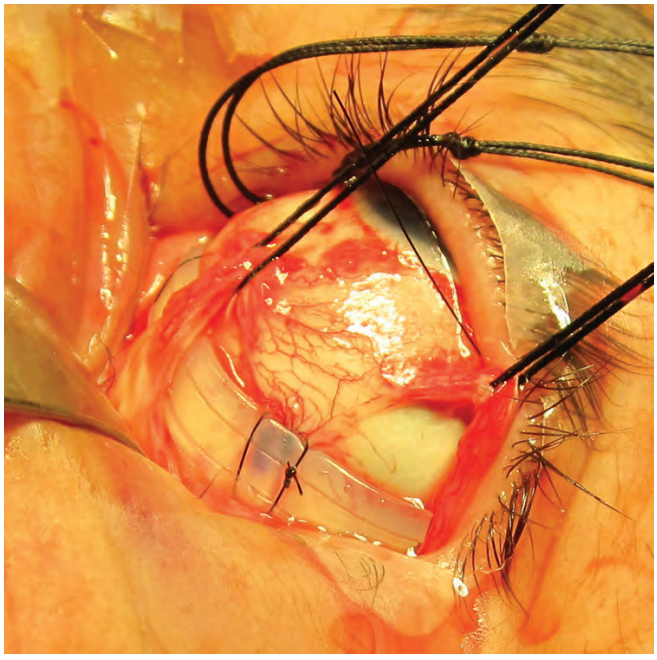

Image courtesy of Adrian T. Fung, MBBS, MMED, FRANZCO, and William Ross, MD

Figure 1. The scleral buckle section walks readers through every step, including the proper way to tie the nylon sutures.

Figure 2. Retinal detachment in a patient with retinopathy of prematurity.

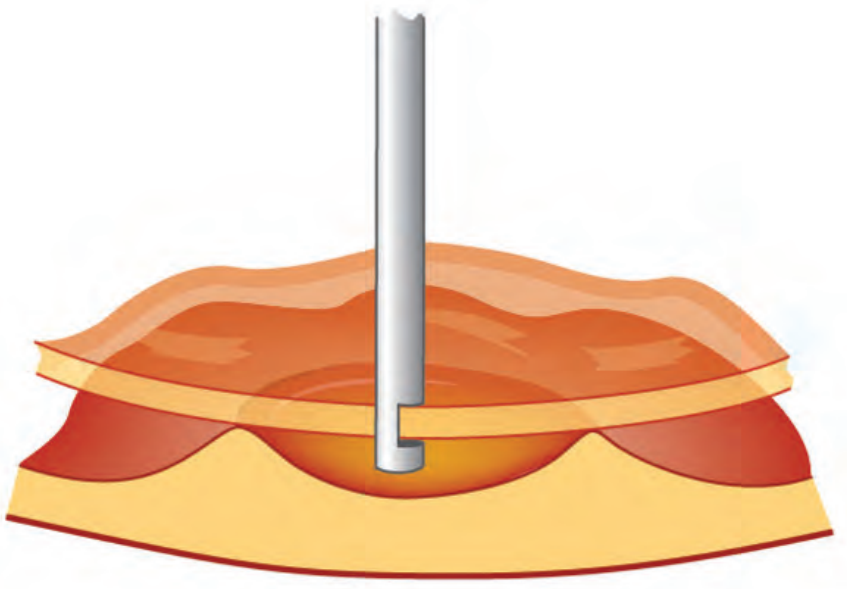

Image courtesy of Abhilasha Alone Patil, MBBS, DNB, FICO(UK), FLVPEI; Jay Chhablani, MD; and Adrian T. Fung, MBBS, MMED, FRANZCO

Figure 3. The vitreoretinal surgery textbook also includes schematics to help demonstrate the ways in which various surgical techniques affect membranes. This illustration depicts segmentation, which involves cutting membranes between focal retinal adhesions.

the group was able to recruit from unique networks and ultimately assemble a total of 93 authors. There were also partnerships forged with shared content from other prominent online educational platforms, including BascomPalmerLearn, CataractCoach, and EyeGuru.

Once the source documents were collected, the next step was to collaborate with a website developer to make the textbook readily available online with a user-friendly interface. The entire surgical guide was created to be searchable by key words, and the individual chapters (35 total so far) were outfitted with quick links to jump to sections of interest. Perhaps the most important development was the upgrade to mobile capability with a one-time sign on. With this feature, the textbook became reachable anytime from anywhere.

THE MISSING PIECE

As the first chapters were being submitted, it became apparent that there was a missing ingredient to bring the manual to life—surgical videos. A clear graphic demonstration is an element absent from many resources, but one that can go a long way in relating to the next generation of learners.

With the ready availability of high-definition recording equipment and editing software, it was possible to make videos a part of all relevant chapters. Although one can find certain video examples on other platforms, such as Eyetube or YouTube, it can be difficult to rapidly locate those relating to subspecialty topics. Numerous videos were contributed, and fortunately, most chapters have a variety of techniques exemplified. The formatting was standardized in terms of length and presence of subtitles. The objective was to ensure that the video could stand alone as a demonstration, with the associated text from the guide available as supplementary material if desired, or vice versa, depending on the learning preferences of the user.

INITIAL RECEPTION

The initial reception has exceeded expectations. In the first 6 weeks after launch, there were 22,000 website hits from 65 countries. The usage was split evenly between desktop and mobile devices. Although it is unknown how successful a printed book version would have been, our new virtual guide does seem to have greater potential for rapid access and dissemination.

FUTURE DIRECTION

The hope is to create lasting value as a free, open-access educational tool to serve current and future vitreoretinal surgeons globally. To achieve this goal, we are continually soliciting ideas for new chapters to add, at least on an annual basis. In addition to keeping up with the fluid subject material, is essential to be mindful of trends in media platforms. This idea began as a book, has since evolved to a website, and could one day transition into a smartphone application, or even a 3D virtual reality learning experience. ■

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Check out the full textbook at vrsurgeryonline.com.

RT Retina Today ONE TO Watch

NIMESH A. PATEL, MD

Please share with us your background.

I was born in New Zealand and was mostly interested in becoming a professional rugby player for the national team. After realizing that I lacked the physical attributes for this career, and my family moving to United States, I pursued science and biomedical engineering at the University of Connecticut. I enjoyed the rationality of physics, problem solving, and the creativity associated with design. The missing elements were seeing the final application of devices and the human component. This is why medicine was a better fit for me, having all these factors in combination.

When did you know that you wanted to be a retina specialist?

The Bascom Palmer Eye Institute, where I trained for residency, has a deep history in retinal surgery. My interest was sparked when visiting the lab of Jean-Marie Parel, Ing.ETS-G, PhD, FARVO, during my first year and hearing a first-hand account of the vitrectomy origin story. Throughout training, Basil K. Williams Jr, MD, reinforced my curiosity by often pointing out that retina specialists can handle most parts of the eye and the complications. I liked the thought of being as comprehensive as possible in an already specialized field. Staying at Bascom Palmer for my fellowship allowed me to become a chief resident, teach others, and gain experience in a leadership role while still in training.

Who are your mentors?

My father and older sister guided me, as they are both in medicine. It was clear from watching them that if you enjoy what you do, you are never quite working. In terms of ophthalmology and retina, there are too many important influences to name. Audina M. Berrocal, MD, steered me towards pediatric retina and showed me the potential effect I could have due to the significant need coupled with the quantity of unanswered research questions. Watching her tackle testing surgeries and mystery cases made it clear that there would be few dull moments if I chose to follow in her footsteps. We are still in touch, mainly when I call in a panic about cases, but also with ongoing collaborative projects. On a personal level, she also demonstrated how to act with exceptional kindness and honesty with trainees and staff. She treated us to dinners and sent gifts for the holidays, to name a few things. I work to emulate this approach in my own career, and she has now become one of my closest friends.

Describe your current position.

I am an adult and pediatric retinal specialist at Massachusetts Eye and Ear and Boston Children's Hospital, which are affiliated with Harvard Medical school. I see a variety of pathology, including some oncology and uveitis. The practice is approximately 80% adult patients, and I spend nearly 80% of my time in the clinic. I appreciate working with very intelligent residents and fellows, as well as a group of distinguished faculty who motivate and guide me. I mentor a research fellow, Sandra Hoyek, MD, who helps on research projects on retinopathy of prematurity and Coats disease.

What has been a memorable experience in your career?

We are lucky in ophthalmology to have daily chances to help patients, which creates many memorable moments. The one that comes to mind first is when Anne Kunkler, MD, saw a patient in the emergency department with long-standing vision loss and found a worm accompanying unilateral retinal atrophy. Laser was unsuccessful due to the mobility of the target. During surgery, I staffed Nathan Scott, MD, while he removed the villainous nematode from underneath the hyaloid. After extracting, we could visualize the parasite alive in the syringe. It was likely a once-in-a-lifetime experience. I still watch the surgical video like a rerun of a favorite sitcom.

What advice can you offer to individuals who are just now choosing their career paths after finishing fellowship?

Ask for help! Almost everything good that has happened to me has been based on advice from others. There are many difficult subjects that are not broached in training, including contract negotiation, managing complications, optimizing clinical templates, attaining research funding, and collaborating with industry. Those who have already been through it are the best resources. It is okay if some advice is conflicting; all that usually means is that there is no clear correct answer. We have a great community willing to assist if called upon. ■

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SECONDARY IOLS FOUR WAYS

These surgical pearls can help you succeed with whichever technique you choose.

BY KISHAN G. PATEL, MD; PARTH SHAH, DO; ARSHAM SHEYBANI, MD; AND RAJENDRA S. APTE, MD, PHD

Despite numerous surgical advances to address a cataractous crystalline lens, many challenges remain to address IOL placement in the presence of inadequate capsular support. Multiple techniques have been developed to address aphakia in the presence of poor capsular support, each with unique advantages and disadvantages.[1]

This article discusses some of the challenges associated with secondary IOL surgery and provides surgical pearls for various techniques.

ANTERIOR CHAMBER IOLS

The anterior chamber IOLs (ACIOLs) for aphakia currently available in the United States have open-looped haptics that rest in the angle. When sizing for these IOLs, surgeons often add 1 mm to the white-to-white (WTW) distance, but pannus and previous conjunctival surgery can affect the subjective WTW measurement. Because this technique requires estimation of the true angle-to-angle distance, surgeons can adjust the calipers slightly to account for the anatomic appearance of the external and internal structures. If the angle measurement falls between available ACIOL sizes, the lens can be rotated along a different meridian to facilitate suitable placement. We tend to choose a smaller size if the decision is equivocal because a smaller ACIOL can be rotated vertically (if initially placed horizontally) to achieve a tighter fit or later secured to the iris using 10-0 polypropylene sutures.[2]

We inject a miotic agent before placing the ACIOL to create a scaffold for the viscoelastic and the IOL and make it easier to perform a peripheral iridotomy (PI). A glide-sheet can help guide the ACIOL but can also gape the wound and lead to iatrogenic injury. We prefer to use Kelman-McPherson forceps to grasp and deliver the ACIOL into the distal angle and then use a second instrument to push the externalized haptic into the subincision angle (Figure 1). We find that temporarily clamping any posterior infusion during ACIOL insertion can help mitigate iris prolapse. Once the ACIOL is placed, it can be rotated using a second instrument. We recommend lifting each haptic centrally and anteriorly to ensure there is no iris tuck or capture.

Current PMMA ACIOL models must be implanted through a large (approximately 6 mm) scleral tunnel or clear corneal wound. We perform clear corneal incisions and operate on the steep axis of the cornea to reduce astigmatism. We close the wound with a single 10-0 nylon suture in a cross-stitch pattern to spread out the radial forces and reduce surgically induced astigmatism (Figure 2). We recommend waiting at least 6 to 8 weeks before removing a suture for this size incision.

AT A GLANCE

- Many techniques have been developed to address aphakia in the presence of poor capsular support, each with advantages and disadvantages.
- Current anterior chamber IOL models must be implanted through a large (approximately 6 mm) scleral tunnel or clear corneal wound.
- During sutureless intrascleral fixation, minimizing the manipulation of the haptics is important because breakage or kinking can lead to IOL tilt and dislocation.
- The choice of technique depends on many factors, and surgeons should perform the procedure with which they are the most comfortable.

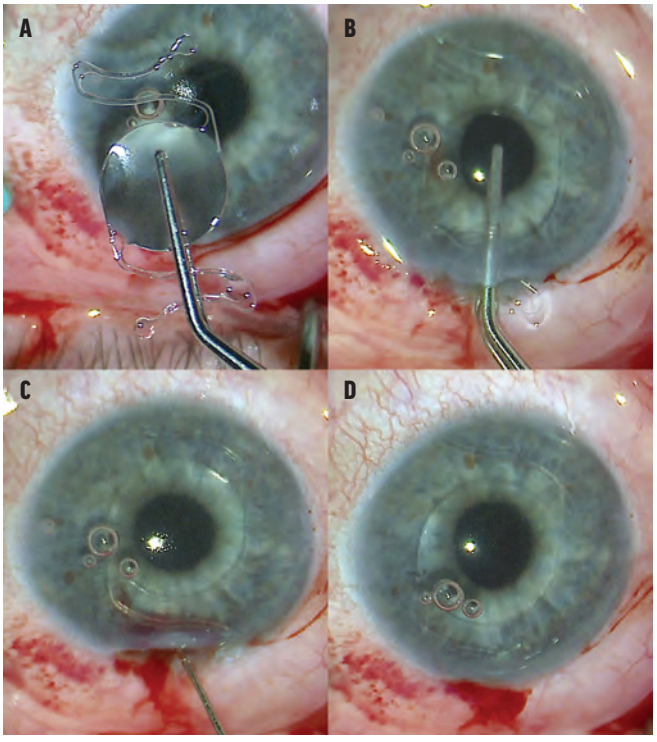

Figure 1. When inserting an ACIOL, we first grasp the IOL lengthwise across the optic using Kelman-McPherson forceps (A). We then insert the ACIOL into the eye and place the leading haptic directly into the distal angle (B). We use a second instrument to push the trailing haptic (C), which compresses the ACIOL and allows it to be fully inserted into the eye (D).

SUTURELESS INTRASCLERAL FIXATION

A bent 27- or thin-walled 30-gauge needle is used to create a scleral tunnel through which a three-piece IOL haptic is docked into the needle and then externalized.[3] The technique can be modified by using trocars to create the scleral tunnel and microforceps to grasp and externalize the haptics.[4-6] Cauterizing the tip of the externalized haptic to create a flange can help prevent subsequent dislocation of most three-piece IOLs.[3,4] The haptic should be buried in the scleral tunnel opening, and the conjunctiva is retracted to prevent haptic exposure. In eyes that have undergone prior conjunctival surgery or have scarring, we often perform a small peritomy to expose the site of the scleral tunnel so that the conjunctiva and Tenon's capsule can later be retracted over the haptic flange for adequate coverage.

Minimizing the manipulation of the haptics is important because breakage or kinking can lead to IOL tilt and dislocation. We have found that polyvinylidene fluoride haptics are more forgiving than PMMA haptics; thus, we almost exclusively use IOLs with polyvinylidene fluoride haptics for this technique (Video). We mark scleral tunnels 2 mm posterior to the limbus to approximate the zonular plane; however, most three-piece IOLs are 13 mm in width, placing the haptics on stretch. Caution should be taken in myopic eyes and those with a large WTW distance because tension on the haptics may be greater than in smaller eyes, which can lead to complications such as IOL dislocation or malpositioning. Scleral tunnels can be marked 14 mm apart to minimize haptic stretch, but care should be taken to avoid incising the ciliary body or angle structures.

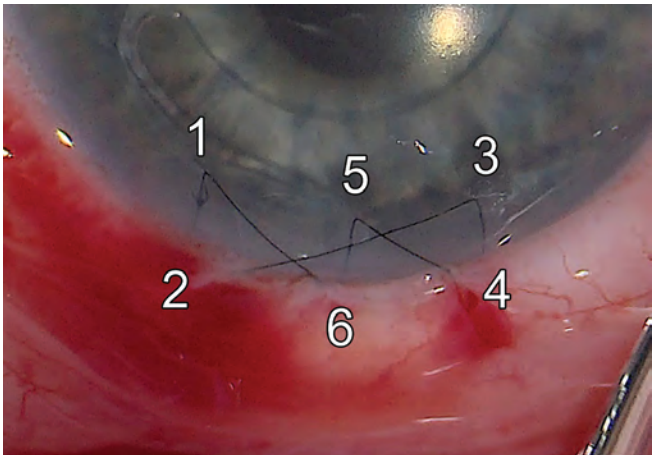

Figure 2. To create a cross-stitch pattern for large corneal wound closure, we pass a single 10-0 nylon suture from point 1 to 2, 3 to 4, and 5 to 6. We tie the loose ends (points 1 and 6) together and rotate the suture to bury the knot.

If an existing three-piece IOL is being rescued, the surgeon must take care not to damage the haptics when removing residual capsule or lens material. Bringing the IOL into the anterior chamber, avoiding a 23-gauge vitrector, or employing a bimanual posterior chamber technique can help to minimize IOL damage. A large single-surgeon series using trocar-based fixation found increased rates of subsequent dislocation after the rescue of an existing IOL, suggesting that surgeons should have a low threshold for IOL exchange if there is significant manipulation of the existing IOL.[4]

Reverse pupillary block (RPB) is an uncommon complication that can lead to elevated IOP, iris-optic capture, IOL instability, and refractive change. The

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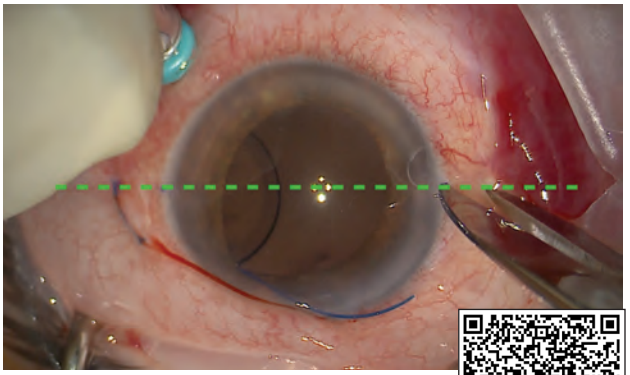

Video. Sutureless Intrascleral Fixation of a Secondary IOL: Modified Yamane Technique

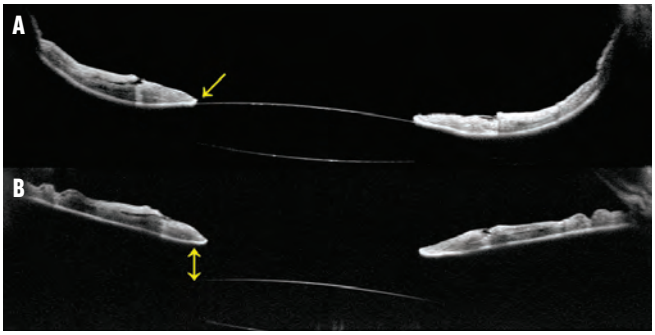

Figure 3. This patient with a sutureless intrascleral-fixated three-piece IOL presents with elevated IOP and RPB. The anterior segment OCT shows a hyperdeep anterior chamber with IOL touch (single arrow) from a posteriorly bowed iris (A). Immediately following outpatient PI, OCT imaging shows release of the IOL touch (double arrow) and flattening of the iris (B).

mechanism of RPB is unclear, but a flaccid iris may prevent aqueous humor flow and cause a reverse pressure gradient.[7,8] In patients without an existing PI who develop RPB during the postoperative period, an outpatient laser PI can be performed to break the RPB and reestablish the proper IOP gradient (Figure 3). Patel et al demonstrated that the rate of RPB decreased from 3% to 0.4% with intraoperative PI, and they recommended performing a prophylactic PI in all cases of sutureless intrascleral fixation.[4]

IOL tilt and decentration can occur with asymmetric, short, or obliquely placed scleral tunnels. When creating scleral tunnels, we use a relatively flat approach of approximately 15º to 30º from the scleral surface to ensure that the needle does not enter the eye prematurely and then advance the needle to create a tunnel that is 2 mm to 3 mm in length. Before rotating the needle completely into the eye, we gently tilt the needle to indent the sclera. If we do not see the sclera indent or buckle, we assume that the pass is too short and recreate the tunnel.

We favor externalizing a single haptic at a time so that the needles are not left unattended in the eye. Creating the main wound centrally or slightly to the left can help dock the trailing haptic. Once the first haptic has been externalized, we use the corneal light reflex to draw an imaginary line and help determine placement of the second scleral tunnel. If there is IOL tilt, it should be addressed at the time of surgery because the IOL positioning is unlikely to change significantly postoperatively. If a flange has been created, it can be trimmed to revise the haptic and scleral tunnel; however, the IOL should be exchanged if a significant amount of the haptic requires trimming.

SCLERAL SUTURE FIXATION

IOLs are scleral fixated using a polypropylene or PTFE (Gore-Tex, W.L. Gore) suture with a knot (typically), or a knotless double-flanged technique using a 5-0 polypropylene suture.[9] Various IOLs with eyelets, including the CZ70BD

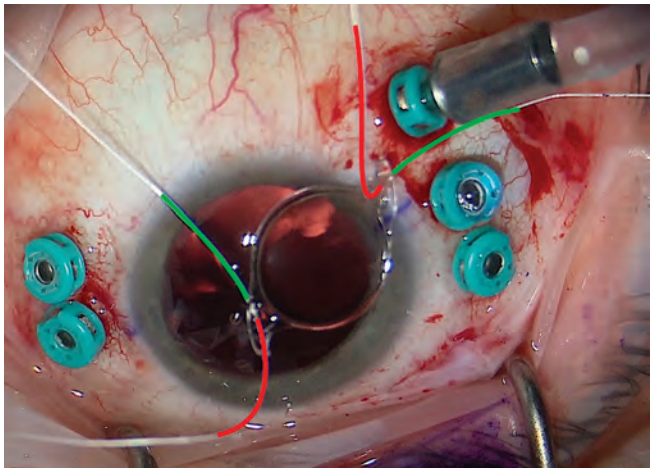

Figure 4. During this Gore-Tex suture fixation of an MX60E IOL, the haptics are trimmed, and the Gore-Tex suture is passed through each eyelet in opposite orientation to allow a pseudo-four-point fixation. The red lines denote the sutures anterior to the IOL, and the green lines denote sutures posterior to the IOL.

(Alcon), Akreos AO60 (Bausch + Lomb), and enVista MX60E (Bausch + Lomb), facilitate suture fixation. We tend to use the hydrophobic acrylic MX60E with a pseudo-four-point fixation, which avoids the large incision required for the CZ70BD and the risk of opacification with gas tamponade or air during corneal surgery reported with the hydrophilic acrylic AO60.[10-12]

A conjunctival peritomy is performed, and paired stab incisions are made approximately 2 mm posterior to the limbus and 2 mm to 3 mm apart. The sclerotomy sites must be symmetrically placed to avoid IOL tilt. Although a 20-gauge microvitreoretinal blade can be used to create the stab incisions, smaller-gauge incisions such as those made with the trocar inserter blade may reduce the risk of postoperative transient hypotony. Larger sclerotomies can be closed using a dissolvable suture, but care must be taken to avoid cutting the fixation suture.

We prefer to use a 7-0 Gore-Tex suture because we find it causes minimal inflammation and has excellent tensile strength, minimal memory, and high visibility. Slipknots should be employed to help titrate the knot tension; overtightening the sutures can result in complications such as eyelet fracture.[13] To minimize the risk of suture erosion through the conjunctiva, we make a partial-thickness, one-third depth scleral groove between the adjacent sclerotomies so that the suture can rest flush against the sclera. Care should be taken to rotate the knot into the eye to avoid conjunctival erosion.

For the MX60E, we pass the sutures through the eyelets externally, and we sometimes mark the Gore-Tex sutures to assist with orientation (Figure 4). The sutures are then passed through the corresponding sclerotomies, and the IOL is manually folded and delivered into the eye. Flipping the suture orientation during surgery can result in significant IOL

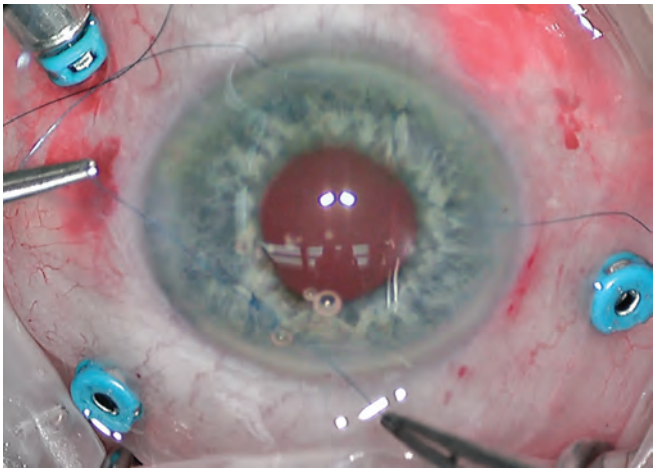

Figure 5. This three-piece IOL is iris fixated using 10-0 polypropylene sutures.

tilt and subsequent iris chafing. We trim the haptics to avoid entanglement of the sutures during surgery and minimize the risk of iris chafing if there is mild IOL tilt.

IRIS FIXATION

In patients with some capsular support but who are at risk of IOL decentration or dislocation due to capsular defects, we often opt to place a three-piece IOL in the sulcus and use 10-0 polypropylene sutures for iris fixation (Figure 5). Before suturing, we capture the IOL optic and leave the haptics in the sulcus space. This maneuver helps to stabilize the IOL while the haptics slightly indent the iris and allow visualization for suture placement. We use a Siepser sliding knot to secure the haptics to the midperipheral or peripheral iris and use microforceps to pull the pupil centrally to mitigate any corectopia before locking the knot. Once the knot has been locked, correcting an ovoid pupil without cutting the knots can become difficult.

CHOOSING THE RIGHT TECHNIQUE

There is no consensus on which secondary IOL technique is superior.[1] Interest in scleral-fixated IOLs is growing, but studies have demonstrated a comparable safety profile, including a similar rate of corneal decompensation between ACIOL and posterior-fixation techniques.[1,14,15]

In older patients and those who require a large incision to remove rigid implants, we often select an ACIOL. In younger patients, those with anterior segment pathology, and those who do not require large sclerocorneal incisions, we prefer an acrylic lens with scleral fixation that can be performed using minimally invasive techniques. In patients with myopia and those with large WTW distances, we tend to avoid sutureless intrascleral fixation because the IOL haptics are on greater stretch than in smaller eyes; instead, we opt for Gore-Tex suture fixation or an ACIOL. In patients with partial capsular support, we prefer to place the lens within the ciliary sulcus with iris fixation.

Our choice of technique depends on multiple factors, and surgeons should perform the procedure with which they are the most comfortable. ■

Disclaimer: The use of implants and techniques, including Gore-Tex sutures, described in this article are off-label and not approved by the US FDA.

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DISSECTING, MASSAGING, AND PLUGGING MACULAR HOLES

These adjunctive techniques can be useful for large and refractory holes.

BY ADITYA S. RALI, MD, AND MOHSIN H. ALI, MD


Modern vitreoretinal surgical techniques, such as pars plana vitrectomy (PPV) with gas tamponade with or without internal limiting membrane (ILM) peeling, have resulted in high single-operation success rates for macular hole (MH) closure. However, refractory idiopathic MHs and complex secondary MHs (ie, those that are complicated by coexisting pathology such as proliferative vitreoretinopathy [PVR], tractional retinal detachment [RD], pathologic myopia, or macular telangiectasia type 2) remain a challenge. A more advanced technique or a combination of various advanced maneuvers is often required to manage these atypical scenarios.

Two cases illustrate how a combination of maneuvers—such as hydrodissection, lysis of retina–retinal pigment epithelium (RPE) adhesions, flexible nitinol loop (eg, Finesse Flex Loop [Alcon]) massage, and placement of an amniotic membrane (AM) graft—can help to close complex MHs.[1-3]

REAL-WORLD EXAMPLES

Case No. 1: A woman in her 30s with type 1 diabetes and severe nonproliferative diabetic retinopathy who developed vitreomacular traction and an epiretinal membrane (ERM) underwent PPV with ERM and ILM peeling and gas tamponade. After surgery, she developed a large full-thickness MH for which she underwent a second PPV with additional ILM peeling and gas tamponade. The MH failed to close, and she was referred to us for a second opinion (Figure 1A). At initial presentation to our clinic, her VA was counting fingers. We performed MH hydrodissection, MH massage, subretinal AM placement, and SF_6 gas. Her VA improved to 20/100 approximately 9 months postoperatively (Figure 1B).

Case No. 2: A man in his 30s with high myopia (axial length approximately 30 mm) and a history of a giant retinal tear-associated RD experienced multiple recurrent RDs secondary to PVR and subsequent MH formation. The MH persisted despite a prior PPV with ERM and ILM peeling. The patient was referred to us for a second opinion and presented with a MH measuring approximately 1,250 µm at the narrowest inner aperture (Figure 2A). His preoperative VA was counting fingers.

He underwent PPV, peeling of residual vitreoschisis, ERM and ILM peeling, subretinal AM placement, and C_3F_8 gas tamponade (Figure 2B).

PREOPERATIVE OCT GUIDES SURGICAL MANAGEMENT

In cases of refractory MHs, preoperative OCT can facilitate the detection of a residual ERM and the assessment of the configuration and size of the MH (especially the narrowest inner retinal aperture). Preoperative OCT can also aid in the identification of other possible causes of poor visual potential such as a thin or absent retinal nerve fiber layer that may suggest optic neuropathy.

Preoperative OCT imaging for the patient in the first case showed a large irregular MH measuring approximately 1,300 µm at the narrowest inner diameter. Importantly, the hole had a flat-open configuration, as opposed to the anvil configuration typically seen with acute idiopathic MHs in which the MH edges (often with cystic changes) are slightly

AT A GLANCE

- In complex macular hole cases, surgeons often need to employ advanced techniques or a combination of advanced maneuvers.
- Preoperative OCT imaging can help guide surgical decision making.
- Hydrodissection, lysis of retina–retinal pigment epithelium adhesions, flexible nitinol loop massage, and amniotic membrane placement can be employed to close complex macular holes.

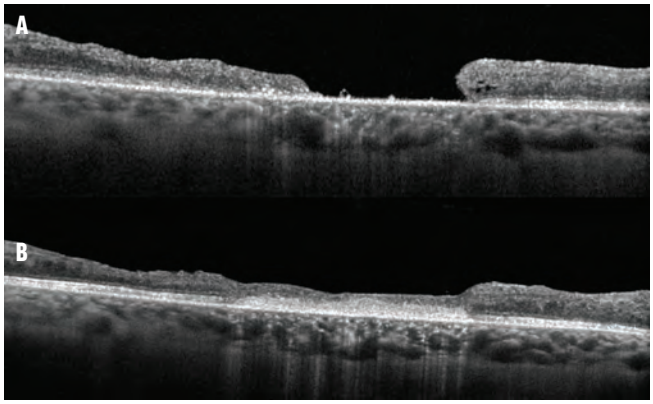

Figure 1. Preoperative OCT imaging shows a large MH measuring approximately 1,300 µm with a flat-open configuration (A). OCT imaging obtained 9 months after PPV, MH hydrodissection, MH massage, subretinal AM placement, and SF_6 gas shows closure of the hole (B).

elevated by a cuff of subretinal fluid. Th flat-open configuration may indicate the presence of retina–RPE adhesions and may alert the surgeon that, for the edges to mobilize, hydrodissection or blunt dissection may be helpful. The same may be necessary for an AM to be easily positioned subretinally and anchored under the MH's edges. In the first case, lysis of the adhesions was required before an AM could be introduced into the subretinal space.

In contrast, the MH in the second case had an anvil configuration with slight elevation and cystic changes of the edges. In general, this configuration suggests that there may not be significant adhesions at the MH edges. In this case, an AM was easily inserted under the edges without the necessity of first lysing adhesions.

ADDITIONAL PEELING

It is generally helpful to restain the macular surface with brilliant blue or indocyanine green dyes (with or without triamcinolone acetonide) and check for the presence of residual vitreoschisis, ERM, and ILM. It is not unusual to encounter these, even if the prior operative report states that the ILM was peeled. Anecdotally, this appears to be more likely in patients with high myopia (especially vitreoschisis) or those with a blonde fundus because the ILM stain is more difficult to appreciate. If additional membranes are encountered, they should be peeled to the greatest extent possible (eg, from the superotemporal to the inferotemporal vascular arcade).[4,5] It is also possible to harvest residual ILM for an inverted, rotational, or free ILM flap to cover the MH and serve as a scaffold for closure.

ADDRESSING ADHESIONS

As discussed above, retina–RPE adhesions at the MH edges may limit mobilization of these edges for successful closure. In these cases, it may be helpful to perform MH hydrodissection. This technique can be performed in a variety of ways, including refluxing fluid (balanced salt solution) via a backflush or soft tip directly through the MH, creating subretinal fluid blebs that extend to the hole with a subretinal cannula,[6,7] or using a soft-tipped cannula to reflux fluid transretinally in an area of peeled ILM.[8] Another method of lysing retina–RPE adhesions is to use a blunt delamination spatula or even a lighted pick. These instruments can be inserted under the MH edges and used to lift and separate the retina–RPE adhesions. These techniques come with the risk of trauma to the outer retina and the RPE and must be performed with care.

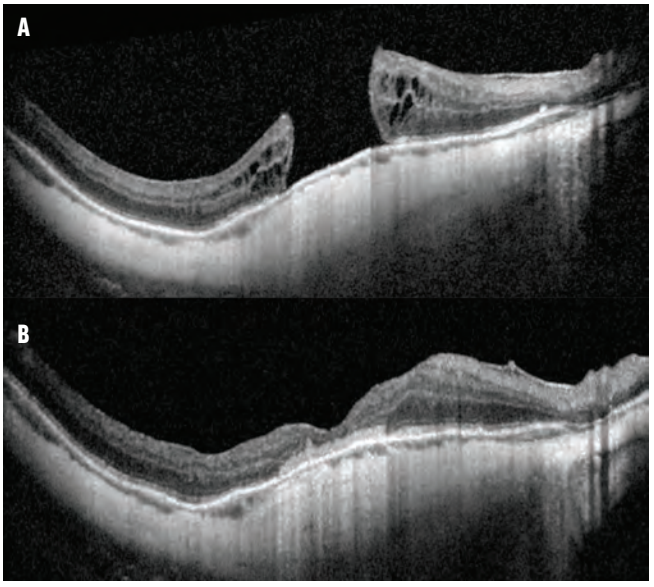

Figure 2. Preoperative OCT imaging shows a large MH measuring approximately 1,250 µm (A). Postoperative OCT imaging shows MH closure after PPV, peeling of the residual vitreoschisis, peeling of the ERM and ILM, subretinal AM placement, and C_3F_8 gas (B).

Another method of mobilizing the retina is to massage the edges of the hole with a flexible nitinol loop. In many instances, the MH diameter visibly decreases intraoperatively with this maneuver. However, this technique also carries the risk of damage to the inner retina if not performed carefully.

AMNIOTIC MEMBRANE

We prefer to use a cryopreserved AM (AmnioGraft, BioTissue), but the use of a dehydrated AM is another option.[9] The membrane can be cut to the appropriate size with a circular biopsy punch or scissors.

Staining the surface of the AM with brilliant blue dye can make it easier to identify the basement membrane surface. The AM is then peeled from the carrier paper using forceps and introduced into the vitreous cavity through 23- or 25-gauge cannulas. If the surgeon loses the orientation of the membrane in the vitreous cavity and cannot identify the basement membrane side from the stromal side, brilliant blue dye can help. Moreover, the stromal side is stickier and will be more adherent to the forceps. In some situations, the use of

(Continued on page 36)

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

Neovascular (wet) age-related macular degeneration

- The ATE rate in the 3 controlled neovascular AMD studies during the first year was 1.9% (17 of 874) in the combined group of patients treated with 0.3 mg or 0.5 mg ranibizumab compared with 1.1% (5 of 441) in patients from the control arms. In the second year of Studies AMD-1 and AMD-2, the ATE rate was 2.6% (19 of 721) in the combined group of ranibizumab-treated patients compared with 2.9% (10 of 344) in patients from the control arms. In Study AMD-4, the ATE rates observed in the 0.5 mg arms during the first and second year were similar to rates observed in Studies AMD-1, AMD-2, and AMD-3
- In a pooled analysis of 2-year controlled studies (AMD-1, AMD-2, and a study of ranibizumab used adjunctively with verteporfin photodynamic therapy), the stroke rate (including both ischemic and hemorrhagic stroke) was 2.7% (13 of 484) in patients treated with 0.5 mg ranibizumab compared to 1.1% (5 of 435) in patients in the control arms (odds ratio 2.2 [95% confidence interval (0.8-7.1)])

Macular edema following retinal vein occlusion

- The ATE rate in the 2 controlled RVO studies during the first 6 months was 0.8% in both the ranibizumab and control arms of the studies (4 of 525 in the combined group of patients treated with 0.3 mg or 0.5 mg ranibizumab and 2 of 260 in the control arms). The stroke rate was 0.2% (1 of 525) in the combined group of ranibizumab-treated patients compared to 0.4% (1 of 260) in the control arms

Diabetic macular edema and Diabetic Retinopathy

- In a pooled analysis of Studies D-1 and D-2, the ATE rate at 2 years was 7.2% (18 of 250) with 0.5 mg ranibizumab, 5.6% (14 of 250) with 0.3 mg ranibizumab, and 5.2% (13 of 250) with control. The stroke rate

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at 2 years was 3.2% (8 of 250) with 0.5 mg ranibizumab, 1.2% (3 of 250) with 0.3 mg ranibizumab, and 1.6% (4 of 250) with control. At 3 years, the ATE rate was 10.4% (26 of 249) with 0.5 mg ranibizumab and 10.8% (27 of 250) with 0.3 mg ranibizumab; the stroke rate was 4.8% (12 of 249) with 0.5 mg ranibizumab and 2.0% (5 of 250) with 0.3 mg ranibizumab

- **Fatal events in patients with diabetic macular edema and diabetic retinopathy at baseline:** A pooled analysis of Studies D-1 and D-2 showed that fatalities in the first 2 years occurred in 4.4% (11 of 250) of patients treated with 0.5 mg ranibizumab, in 2.8% (7 of 250) of patients treated with 0.3 mg ranibizumab, and in 1.2% (3 of 250) of control patients. Over 3 years, fatalities occurred in 6.4% (16 of 249) of patients treated with 0.5 mg ranibizumab and in 4.4% (11 of 250) of patients treated with 0.3 mg ranibizumab. Although the rate of fatal events was low and included causes of death typical of patients with advanced diabetic complications, a potential relationship between these events and intravitreal use of VEGF inhibitors cannot be excluded

ADVERSE REACTIONS

- Serious adverse events related to the injection procedure have occurred in <0.1% of intravitreal injections, including endophthalmitis, rhegmatogenous retinal detachment, and iatrogenic traumatic cataract
- In ranibizumab-treated patients compared with the control group, the most common ocular side effects included conjunctival hemorrhage, eye pain, vitreous floaters, and intraocular pressure. The most common non-ocular side effects included nasopharyngitis, anemia, nausea, and cough
- As with all therapeutic proteins, there is the potential for an immune response in patients treated with ranibizumab products. The clinical significance of immunoreactivity to ranibizumab products is unclear at this time

Postmarketing Experience

The following adverse reaction has been identified during post-approval use of ranibizumab products:

- Ocular: Tear of retinal pigment epithelium among patients with neovascular AMD

*An interchangeable product (IP) is a biological product that is approved based on data demonstrating that it is highly similar to an FDA-approved reference product (RP) and that there are no clinically meaningful differences between the products; it can be expected to produce the same clinical result as the RP in any given patient; and if administered more than once to a patient, the risk in terms of safety or diminished efficacy from alternating or switching between use of the RP and IP is not greater than that from the RP without such alternation or switch. Interchangeability of CIMERLI™ has been demonstrated for the condition(s) of use, strength(s), dosage form(s), and route(s) of administration described in its Full Prescribing Information

References: 1. CIMERLI™ (ranibizumab-eqrn) prescribing information. Redwood City, CA: Coherus BioSciences, Inc. **2.** Data on file. Coherus BioSciences, Inc.

To report SUSPECTED ADVERSE REACTIONS, contact Coherus BioSciences at 1-800-483-3692 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see additional Important Safety Information and Brief Summary of Full Prescribing Information on the following page.

CIMERLI™
(ranibizumab-eqrn) injection

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CIMERLI™ (ranibizumab-eqrn) injection, for intravitreal use

CIMERLI™
(ranibizumab-eqrn) injection

BRIEF SUMMARY—please review the full Prescribing Information prior to prescribing CIMERLI™. CIMERLI™ is interchangeable with LUCENTIS® (ranibizumab injection).

1 INDICATIONS AND USAGE

CIMERLI is indicated for the treatment of patients with:

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

1.2 Macular Edema Following Retinal Vein Occlusion (RVO)

1.3 Diabetic Macular Edema (DME)

1.4 Diabetic Retinopathy (DR)

1.5 Myopic Choroidal Neovascularization (mCNV)

4 CONTRAINDICATIONS

4.1 Ocular or Periocular Infections

CIMERLI is contraindicated in patients with ocular or periocular infections.

4.2 Hypersensitivity

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

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis and Retinal Detachments

Intravitreal injections, including those with ranibizumab products, have been associated with endophthalmitis and retinal detachments. Proper aseptic injection technique should always be used when administering CIMERLI. In addition, patients should be monitored following the injection to permit early treatment should an infection occur [*see Dosage and Administration (2.6, 2.7) in the Full Prescribing Information*].

5.2 Increases in Intraocular Pressure

Increases in intraocular pressure have been noted both pre-injection and post-injection (at 60 minutes) while being treated with ranibizumab products. Monitor intraocular pressure prior to and following intravitreal injection with CIMERLI and manage appropriately [*see Dosage and Administration (2.7) in the Full Prescribing Information*].

5.3 Thromboembolic Events

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

Neovascular (Wet) Age-Related Macular Degeneration

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

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

Macular Edema Following Retinal Vein Occlusion

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

Diabetic Macular Edema and Diabetic Retinopathy

Safety data are derived from studies D-1 and D-2. All enrolled patients had DME and DR at baseline [*see Clinical Studies (14.3, 14.4)*].

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

5.4 Fatal Events in Patients with Diabetic Macular Edema and Diabetic Retinopathy at Baseline

Diabetic Macular Edema and Diabetic Retinopathy

Safety data are derived from studies D-1 and D-2. All enrolled patients had DME and DR at baseline [*see Clinical Studies (14.3, 14.4)*].

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

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the label:

- Endophthalmitis and Retinal Detachments [*see Warnings and Precautions (5.1)*]
- Increases in Intraocular Pressure [*see Warnings and Precautions (5.2)*]
- Thromboembolic Events [*see Warnings and Precautions (5.3)*]
- Fatal Events in patients with DME and DR at baseline [*see Warnings and Precautions (5.4)*]

6.1 Injection Procedure

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

6.2 Clinical Trials Experience

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

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

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

Ocular Reactions

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

Table 1

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

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

Non-Ocular Reactions

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

Table 2

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

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

6.3 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or to other ranibizumab products may be misleading.

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

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

6.4 Postmarketing Experience

The following adverse reaction has been identified during post-approval use of ranibizumab products. Because this reaction was reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure.

• Ocular: Tear of retinal pigment epithelium among patients with neovascular AMD

7 DRUG INTERACTIONS

Drug interaction studies have not been conducted with ranibizumab products.

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate and well-controlled studies of ranibizumab products administered in pregnant women.

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

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

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

Data

Animal Data

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

8.2 Lactation

Risk Summary

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

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

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

8.3 Females and Males of Reproductive Potential

Infertility

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

8.4 Pediatric Use

The safety and effectiveness of ranibizumab products in pediatric patients have not been established.

8.5 Geriatric Use

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

10 OVERDOSAGE

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

17 PATIENT COUNSELING INFORMATION

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

Manufactured by:
Coherus BioSciences, Inc.
Redwood City, CA, USA 94065-1442

US Lisence No. 2023

UNCONVENTIONAL BUCKLING TECHNIQUES: CONTROLLING MTM

When faced with myopic traction maculopathy, consider using a macular buckle.

BY HISASHI FUKUYAMA, MD, PHD, AND AMANI A. FAWZI, MD


Scleral buckling is generally used to support peripheral retinal breaks to allow permanent closure, reduce vitreoretinal traction, and promote long-lasting chorioretinal adhesion. The buckling technique achieves these effects by bringing the retinal pigment epithelium (RPE) closer to the retina, which allows the subretinal fluid to be reabsorbed and leads to retinal reattachment.[1]

Scleral buckling techniques evolved from scleral resection, a procedure initially developed to reduce the size of the eyeball or strengthen the sclera and prevent stretching.[2] In response to the complications associated with this approach, in 1949, Ernst Custodis designed an exoplant to produce a buckling effect for retinal detachment (RD) repair.[3] Since then, many buckling techniques have been developed to treat RD.[4]

The volume of scleral buckling procedures has decreased as vitreoretinal surgeons, especially those who are young, increasingly perform pars plana vitrectomy (PPV) to repair primary rhegmatogenous RDs.[5,6] However, scleral buckling has applications for many retinal conditions, including the treatment of myopic traction maculopathy (MTM). Macular buckling is a modified scleral buckling technique in which the buckle is placed in the posterior pole to provide scleral indentation in the area of the macula.

MYOPIC TRACTION MACULOPATHY

MTM refers to a broad clinical spectrum of conditions estimated to affect between 9% and 34% of eyes with pathologic myopia.[7-9] MTM-inducing forces can lead to macular pathologies, such as macular schisis and macular detachment, inner lamellar macular hole, and full-thickness macular hole (Figure 1).[10]

There are several classifications for MTM. Shimada et al described retinoschisis in five stages and progression from macular retinoschisis to RD.[11,12] Ruiz-Moreno et al proposed a classification and grading system for myopic maculopathy (ATN classification) that includes MTM.[13] Parolini et al recently proposed a comprehensive OCT-based classification of MTM.[10] These classifications are based on the progressive nature of MTM, with progressively decreasing vision.[10,12,14]

SURGICAL MANAGEMENT

The best surgical approach to MTM is a subject of debate. Though some researchers suggest that early-stage MTM can be observed because spontaneous improvement may occur,[12,15] most ophthalmologists agree that surgery should be performed when patients' visual acuity decreases and when they enter severe, sight-threatening stages of MTM, such as foveal detachment and macular hole RD (MHRD).[16-18]

Schepens described the macular buckling technique for the first time in 1957,[19] and other researchers later reported the efficacy of this treatment in eyes with MHRD.[20,21]

PPV wasn't introduced as a treatment for MHRD until the 1980s.[22,23] Different types of intravitreal tamponades (eg, gas, silicone oil) and surgical techniques (internal limiting membrane [ILM] peeling and laser treatment) have been proposed for PPV for MHRD. However, anatomic results showed limited primary success rates for vitrectomy in highly

AT A GLANCE

- Scleral buckling has applications beyond primary rhegmatogenous retinal detachment, including for the treatment of myopic traction maculopathy.
- A review showed that resolution of foveoschisis, retinal reattachment, and macular hole closure were achieved more frequently with macular buckling than with vitrectomy.
- Intraoperative OCT may prove useful for confirming the accurate positioning of a macular buckle.

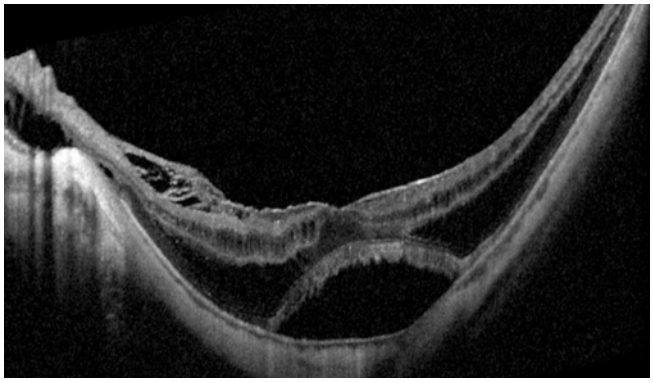

Figure 1. OCT imaging demonstrates macular schisis and subretinal fluid in the left eye of a patient with MTM. A high-density OCT scan through the fovea should be used to identify a small macular hole.

myopic eyes.[24] In addition, postoperative recurrence and postoperative macular hole recurrence have been reported in patients who undergo vitrectomy.[25] These postoperative events may be related to the extended axial length and the persistent tangential traction on the retinal surface, related to posterior staphyloma, that remain after vitrectomy.

Modified vitrectomy approaches, such as foveal-sparing ILM peeling and inverted flaps, were recently proposed to improve anatomic outcomes, but the role of these approaches in MTM remains unclear. Furthermore, a review of 31 articles published over the course of 16 years comparing macular buckling with PPV for the treatment of MTM suggested that complete resolution of foveoschisis, retinal reattachment, and macular hole closure were achieved more frequently with macular buckling than with PPV.[26] A recent randomized controlled study showed that macular buckling was superior to vitrectomy with ILM peeling plus gas tamponade for the surgical treatment of macular schisis and associated MHRD in high myopia.[27] These studies have renewed researchers' and clinicians' interest in the macular buckling technique.

Macular Buckle Updates

The centrifugal MTM-inducing forces are both perpendicular and tangential to the retinal plane. The goal of macular buckling is to support the posterior staphyloma area by reducing various shearing forces and stretching and help to prevent the eventual failure of internal retinal structures, all of which are thought to induce MTM (Figure 2). The options for macular buckling include an ab externo approach with silicone bands or macular plombs. To date, the commercially available macular buckles are as follows:

- Ando Plombe (Ondeko)
- T-shaped scleral buckle (FCI, a Carl Zeiss Meditec Company)
- NPB macular buckle (AJL Ophthalmic)
- Adjustable MB (Micromed)

In the 2000s, macular buckling with a sponge and a solid

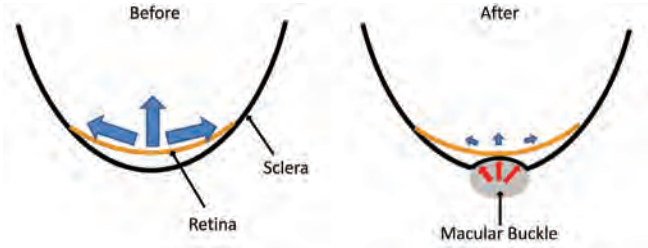

Figure 2. This schematic represents the forces before and after macular buckling for MTM.

silicone implant provided high reattachment rates for myopic MHRD,[28,29] although it is a technically challenging procedure. Several updates to the buckle designs aimed to improve the surgical technique. For example, a T-shaped, semirigid, silicon rod-exoplant reinforced with titanium wires with an indenting head was proposed as an approach to MHRD in 2005.[28] An L-shaped buckle with a titanium stent inserted into a silicon stent, allowing a macular indentation and anterior suture, was proposed to support a posterior staphyloma.[30] Suprachoroidal buckling has also been proposed for MTM. In one technique, a catheter is used to deliver long-lasting hyaluronic acid into the suprachoroidal space in the area of the staphyloma in patients with MTM.[31]

VISUALIZATION OPTIONS

Despite the innovations described earlier, macular buckling remains a challenging surgery. One of the principal challenges is optimal positioning of the buckle. Some researchers reported using external posterior landmarks and adjustable macular buckles to facilitate better positioning of the indenting head, but this was associated with potential injury to the extraocular muscle.[32,33] To avoid this problem and enhance visualization, Mateo et al proposed the insertion of an optical fiber coupled to an Ando Plombe, which allowed better visualization and positioning of the exoplant with an internal chandelier-assisted technique.[34] A few recent case reports also showed the efficacy of internal chandelier-assisted techniques using a widefield contact lens system to repair myopic macular holes.[35,36]

Intraoperative OCT allows real-time visualization of the retinal layers and could provide important guidance for surgical decision making.[37] Intraoperative OCT may prove useful for confirming the accurate positioning of a macular buckle. This technology may help surgeons overcome potential causes of surgical failure, such as excessive or insufficient posterior indentation, by allowing them to diagnose and address problems intraoperatively.

RETHINKING THE MACULAR BUCKLE

The macular buckling technique offers significant benefits for the treatment of MTM. Future advanced techniques and technologies may one day allow ophthalmologists to achieve even better surgical outcomes and wider clinical utility. ■

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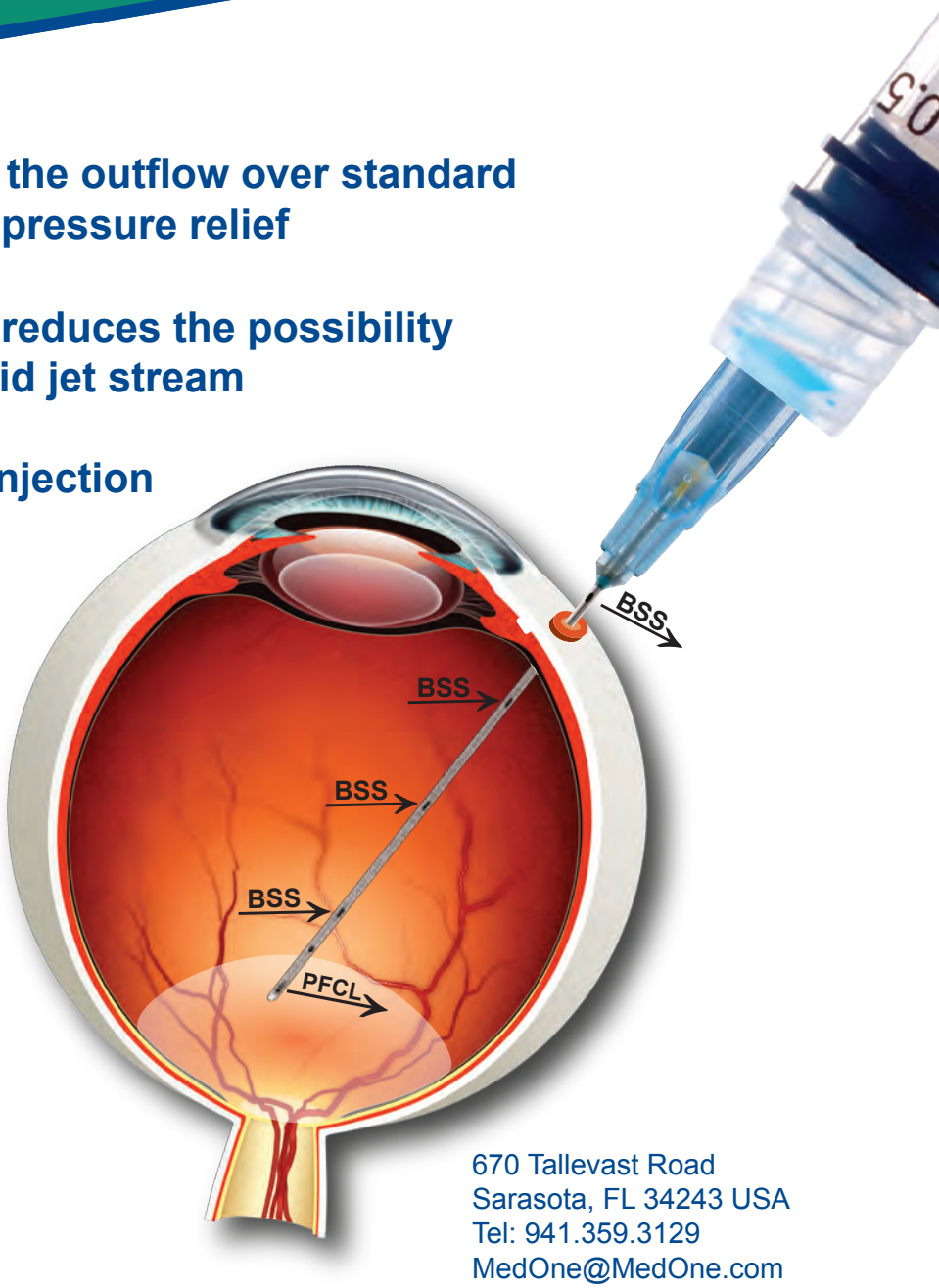

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(Continued from page 29)

a bimanual technique with chandelier illumination can allow the use of two instruments to help manipulate the AM.

The goal is to place the stromal side against the exposed RPE inside the MH. With forceps or a blunt delamination spatula, the AM is pushed underneath the edges of the hole. The membrane should lie as flat as possible; otherwise, it may bunch up in the center of the MH postoperatively and block apposition of the edges, as opposed to lying as a flat disk over which the retinal layers can reapproximate. Surgery concludes with whichever tamponade the surgeon prefers, including short-acting agents such as air or SF_6.[10]

ALTERNATIVES

Numerous alternative techniques exist for addressing refractory or complex MHs. This article highlights only a few of the adjunctive techniques that may be useful with subretinal AM placement, but they should not be used in every case; careful consideration should be given to other techniques such as autologous retinal transplantation.[11] While further research may suggest that this technique may yield better visual acuity results, it is technically more challenging, typically requires more than one surgery (for removal of the PFO liquid or silicone oil), and may carry a greater risk of complications. In our experience, many patients with refractory MHs are wary of additional surgery and are thus drawn to AM placement. ■

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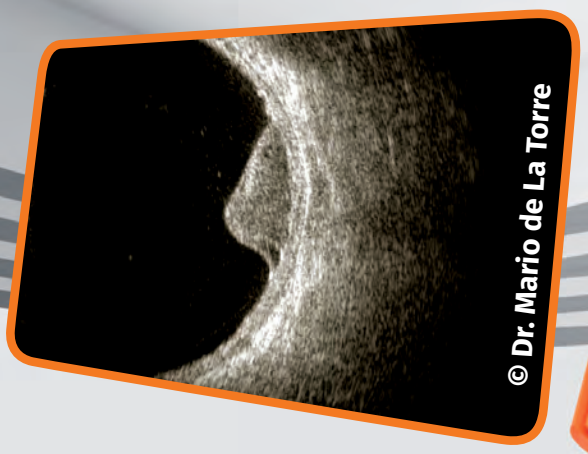

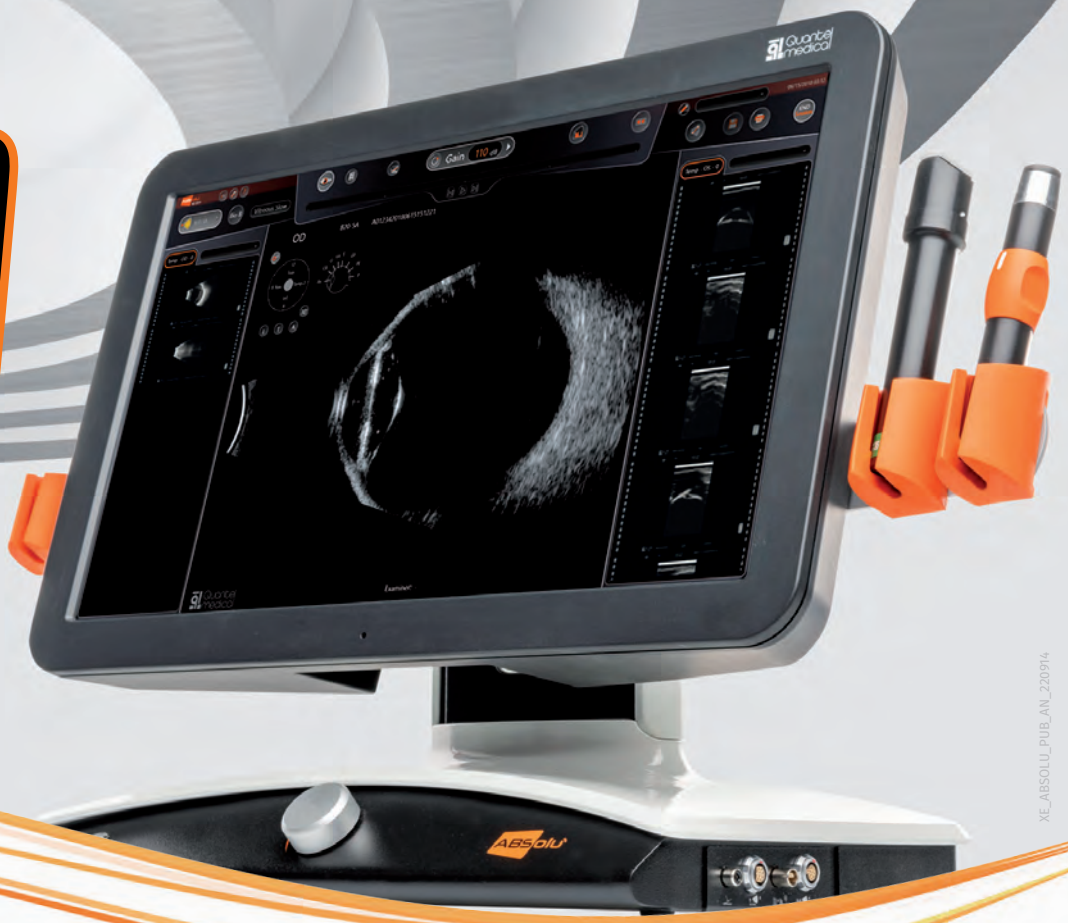

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A SWIFT APPROACH TO MACULAR HOLES

When faced with a challenging case that just won't close, consider this surgical technique.

BY HOMAYOUN TABANDEH, MD, FASRS, AND DAN KAMEN, BA


Idiopathic macular holes (MHs) were considered untreatable until the 1990s when Kelly and Wendell reported that pars plana vitrectomy (PPV) and gas tamponade with face-down positioning resulted in the resolution of subretinal fluid associated with MH. In 30 (58%) of 52 eyes, they found that visual acuity improved by 2 or more lines in 78% of eyes.[1]

Since that initial report, advances in vitreoretinal surgery—including instrumentation, intraoperative visualization, and dye-assisted removal of the internal limiting membrane (ILM)—have led to improved surgical outcomes. Currently, PPV with the removal of the ILM and gas tamponade is the standard treatment for primary idiopathic MHs. The procedure is associated with an 85% to 95% closure rate.[2-8]

However, the surgical success rate is significantly lower (between 45% and 70%) for MHs with certain characteristics, such as large size, chronicity, refractory status, and myopic in nature.[9,10] Many surgical techniques and modifications can help to improve the closure rate, including prolonged positioning and tamponade, retina tissue manipulation, and ILM flap techniques. In addition, lens capsule, autologous retinal transplant, and amniotic membrane grafts have been used in cases where the ILM may not be available for flap formation.[11-22]

Michalewska et al first reported on an inverted ILM flap technique that involved peeling of the ILM and leaving the base of the flap attached to the MH rim. The ILM flap was trimmed and folded to cover the MH. Several modifications to this technique have been described, including limiting the ILM peel to the temporal area and tucking the ILM into the MH. Numerous studies reported improved anatomic outcomes for the inverted ILM flap technique compared with ILM peel and removal, particularly for large and myopic MHs.[11,12,23]

WHEN THE MACULAR HOLE WON'T CLOSE

Conventional rim-based ILM flap techniques are not feasible in eyes with a persistent MH and previously removed ILM, and these cases continue to present a surgical challenge. Distal ILM flap techniques—including free ILM patch grafts and pedicle ILM flaps—and lens capsule free grafts have been described for the management of persistent MH with previously removed ILM. However, free flaps are unstable

AT A GLANCE

- Many surgical techniques and modifications can help to improve the macular hole closure rate, including prolonged positioning and tamponade, retina tissue manipulation, and internal limiting membrane (ILM) flap techniques.
- The superior wide-base ILM flap transposition (SWIFT) technique is a non-rim-based distal ILM flap technique that involves harvesting a flap from the residual ILM.
- Postoperative evaluation of the flap status using indocyanine green fluorescence imaging helps to refine the surgical technique and improve outcomes.
- The SWIFT technique is a valuable approach for the management of refractory macular holes with previously removed ILM and for cases at high risk of non-closure.

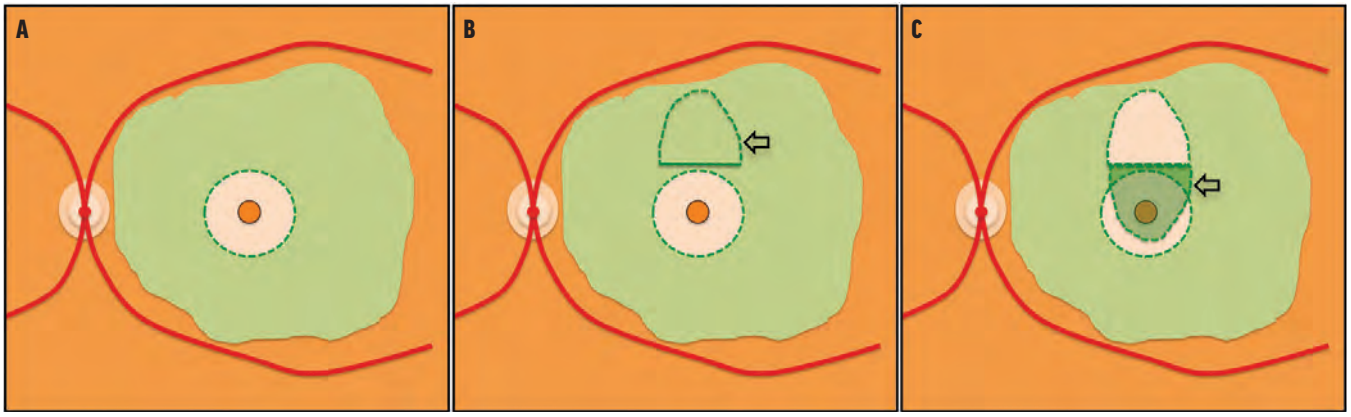

Figure 1. During the SWIFT technique, the ILM has been removed during a previous surgery or is removed at the time of the SWIFT procedure (A). An ILM flap is harvested from the superior residual ILM, leaving a narrow base that is preferably oriented horizontally (B). The ILM flap is inverted and manipulated to drape over the MH (C).

intraoperatively and postoperatively and are prone to displacement. Furthermore, the graft is frequently caught up within the surgical instruments.

Adjunct tools such as viscoelastics, perfluorocarbon liquid, and autologous serum or blood may help with positioning of the flap over the MH. Distal pedicle ILM flaps, although they remain attached to the retina at the base, are also prone to rotation and displacement by intraocular fluid currents.

The superior wide-base ILM flap transposition (SWIFT) technique is a non-rim-based distal ILM flap technique that involves harvesting a flap from the residual ILM (Video).[18] During the procedure, a wide-base ILM flap is fashioned from the residual ILM, preferably superiorly (Figure 1).

Other locations, such as the temporal macula, may be considered if the superior residual ILM is not accessible. The wide base confers some degree of flap stability, the superior location takes advantage of gravity to keep the flap in good position, and the wide width allows continued coverage of the MH in the case of flap rotation.

SWIFT TECHNIQUE

Following PPV, brilliant blue G or ICG tissue dye is administered to improve the visualization of the ILM (Figure 2). If the ILM was removed during a previous surgery, a wide-based flap is harvested from the residual ILM over the superior part of macula and inverted to cover the MH.[18] If residual ILM is not available superiorly, the flap is harvested from the temporal or other areas. The base of the flap is preferably orientated horizontally. When the ILM is intact, it is removed 1 to 2 disc diameters around the MH, before or after harvesting the flap. Intraocular ILM forceps and loop membrane scrapers (ie, the Finesse Flex Loop [Alcon/Grieshaber]) are used to initiate and manipulate the flap.

The ILM flap is inverted and positioned over the MH and a fluid-air exchange is performed. The infusion line is cleared of fluid by minimal fluid-air exchange prior to positioning the flap over the MH to minimize the chance of flap displacement by fluid currents. To help maintain the position of the flap during fluid-air exchange, the aspiration cannula is positioned inferior to the ILM flap and close to the retina.

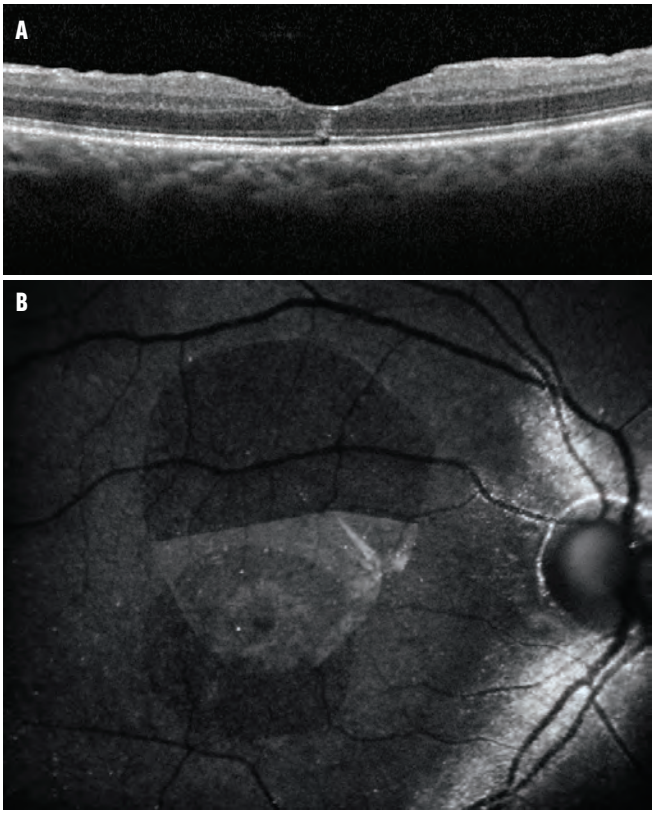

Figure 2. Postoperative OCT imaging and ICG fluorescence imaging in a patient who underwent an ICG-assisted SWIFT procedure. OCT imaging shows a closed MH with a U-pattern (A). ICG fluorescence imaging shows a hypofluorescent area superiorly (flap harvest site) and centrally (removed ILM), with the flap covering the MH (B). Note that the flap has a fold on the nasal aspect.

Adjuncts such as viscoelastics and perfluorocarbon

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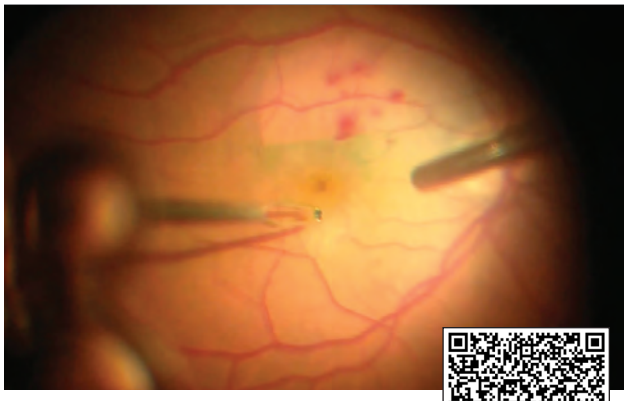

Video. Superior Wide-Base ILM Flap Transposition (SWIFT) Technique for Macular Hole Closure

liquid are usually not required but may be used to stabilize the flap in certain cases. During gas infusion, the infusion cannula is directed away from the ILM flap to avoid flap displacement. The patient is positioned sitting up at the completion of the surgery. Postoperative positioning includes 1 week of downgaze.

STATS

In a series of 17 cases of MH with high-risk characteristics that underwent a SWIFT procedure, the MH closed in 16 (94%) eyes.[18] In this series, 13 eyes had one or more high-risk characteristics, including high myopia, chronic MH, history of prior MH surgery and ILM removal, and MHs > 650 µm. Seven eyes had one high-risk characteristic, four eyes had two high-risk characteristics, and two eyes had three high-risk characteristics.

The position and integrity of the ILM flap was evaluated postoperatively by the detection of ICG fluorescence originating from the residual ILM. This imaging modality provided an en face image of the ILM flap and complements the OCT images. ICG fluorescence imaging showed the ILM flap completely covering the MH in 82% of study eyes. The flap coverage was partial in one eye, and there was no coverage in two eyes. The ILM flap was folded in four (24%) eyes but without visual consequences.[18]

LAST-MINUTE PEARLS

The SWIFT technique combines the advantages of ILM removal with those of an ILM flap. It may be a valuable technique for the management of refractory MHs with previously removed ILM and for cases at high risk of non-closure. Compared with other distal flap techniques, such as free ILM flap or pedicle flaps, the SWIFT flap may be more stable. The technique avoids tucking of the ILM flap into the MH, reducing the risk of surgical trauma to the retinal pigment epithelium and postoperative intraretinal ILM entrapment. Optimal ILM visualization is helpful for all flap techniques, and the SWIFT technique can become challenging in cases with significant media opacity, poor ILM staining, and extensive areas of myopic or geographic atrophy. There is a learning curve associated with the SWIFT technique, and postoperative evaluation of the flap status using ICG fluorescence imaging helps to refine the surgical technique and improve outcomes.[24] ■

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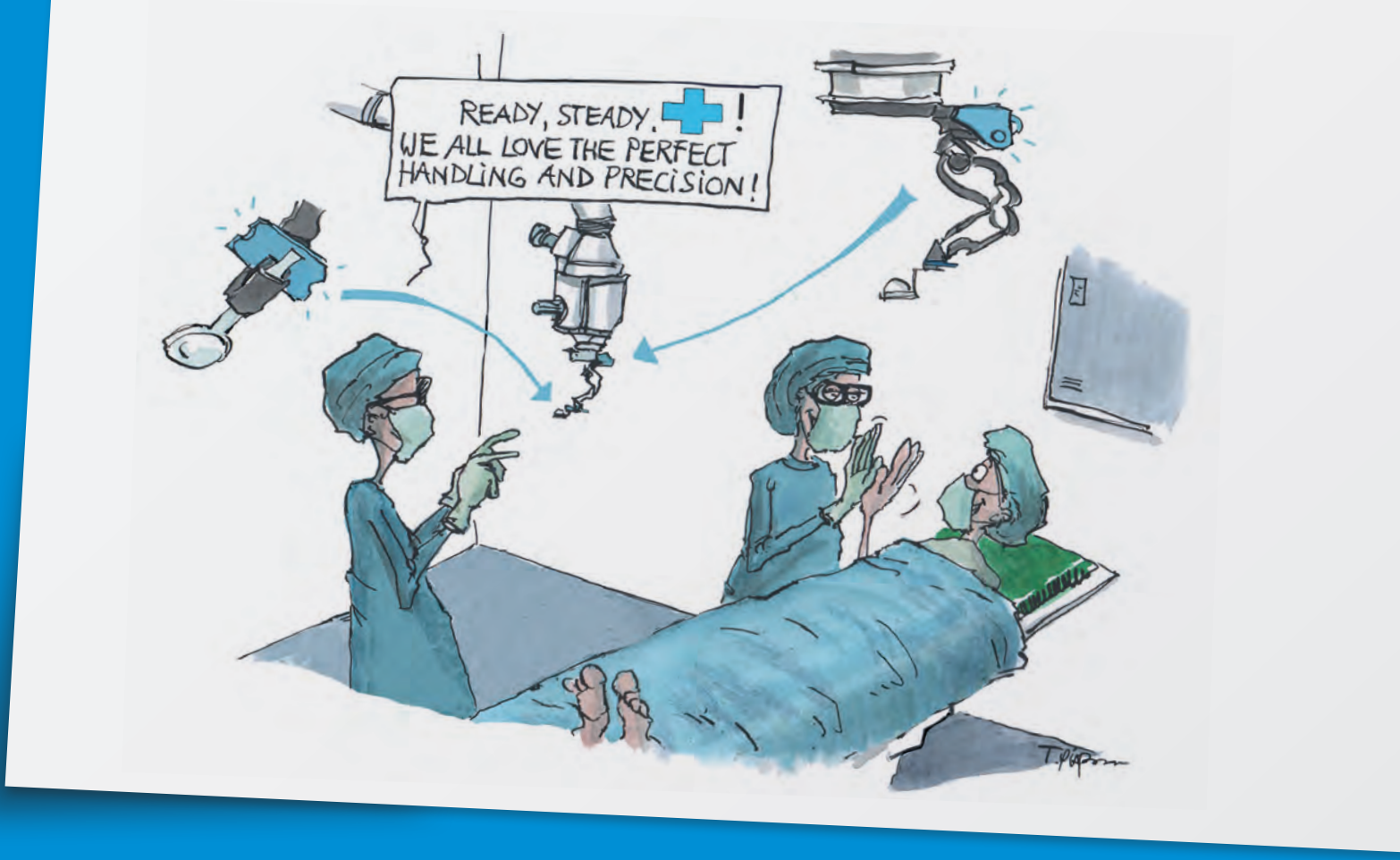

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The associated scleral thinning and large conjunctival defect necessitated some extra surgical steps.

BY JORDAN D. DEANER, MD, AND DILRAJ S. GREWAL, MD


Scleral buckling remains a popular technique to repair retinal detachments (RDs), either as primary treatment or as an adjunct to pars plana vitrectomy (PPV).[1] One of the most frequent indications for silicone scleral buckle removal is extrusion through the conjunctiva with rates of extrusion and infection ranging from 0.5% to 5.6%.[2-9] Despite few implants being removed for suspected clinical infection (8.2%), a majority of the extruded and subsequently removed buckles have been shown to be colonized with bacteria.[9] Observation of the exposed elements coupled with topical antibiotic drops has generally been found inadequate. Similarly, primary closure of a small defect may be attempted but is typically futile with frequent recurrence.[10] Larger defects are difficult to close because of the location typically near the conjunctival fornix, loss of tissue integrity due to necrosis, and limited mobility of the surrounding conjunctival tissue due to scarring and adhesions.

Adjunct techniques such as the use of dehydrated amniotic membrane graft secured with fibrin sealant have been shown to successfully repair large conjunctival defects secondary to an extruded buckle.[11]

Here, we present a case of an extruded silicone scleral buckle with associated scleral thinning and a large conjunctival defect and the surgical steps we took to treat the patient.

THE CASE

A 73-year-old man presented to the emergency department 1 month after a scleral buckle revision with complaints of sudden worsening of ocular pain that woke him up in the middle of the night.

He had no past medical history, but his ocular history was robust. He underwent uncomplicated cataract surgery and IOL placement in the capsular bag in 2015, after which he developed an RD in his right eye that was repaired with PPV and gas tamponade. He experienced a redetachment in late 2015 that required repeat surgery with a scleral buckle, PPV, and gas tamponade. In July of 2021, he developed recurrent episodes of pain and discharge in his right eye. He was seen by his original surgeon who trimmed an "exposed suture," following which his symptoms worsened. He returned to his surgeon and was told that his scleral buckle was exposed. He underwent multiple scleral buckle revisions, most recently in October 2021. Postoperatively, he was treated with 1% prednisolone acetate one drop four times per day and 0.5% ketorolac one drop twice per day in the right eye.

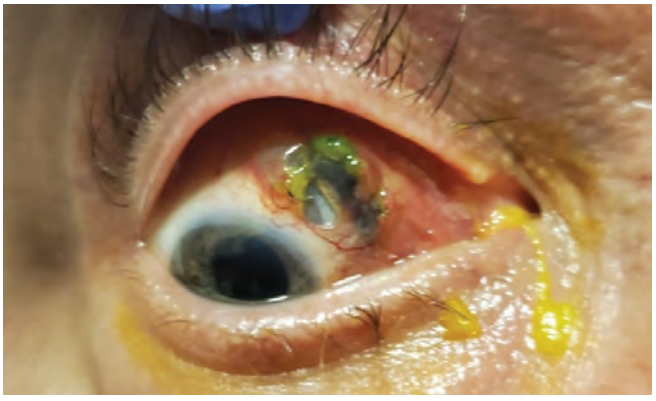


Figure 1. The anterior segment examination revealed an area of focal superonasal injection surrounding a full-thickness conjunctival defect with several loose nylon sutures, an extruded scleral buckle, and an underlying area of significant scleral thinning.

AT A GLANCE

- One of the most frequent indications for silicone scleral buckle removal is extrusion through the conjunctiva.
- Amniotic membrane grafts have been well reported in the reconstruction of the conjunctiva for numerous ocular surface diseases.
- When faced with an extruded scleral buckle, consider using scleral and amniotic patch grafts.

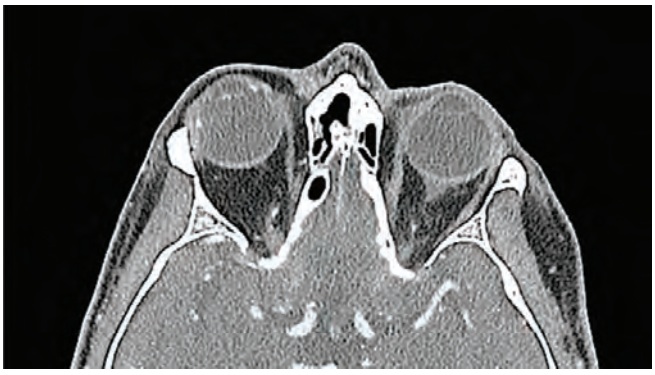


Figure 2. The CT scan revealed the implanted scleral buckle with a somewhat diagonal orientation in the axial plane, but no evidence of associated pre- or post-septal cellulitis.

On examination in the emergency department, his VA was 20/40 OD and 20/20 OS. There were no afferent pupillary defects and IOPs were within normal limits. Extraocular motility was globally diminished in the right eye. The anterior segment examination was notable for an area of focal superonasal injection surrounding a full-thickness conjunctival defect with an extruded scleral buckle and an underlying area of significant scleral thinning (Figure 1).

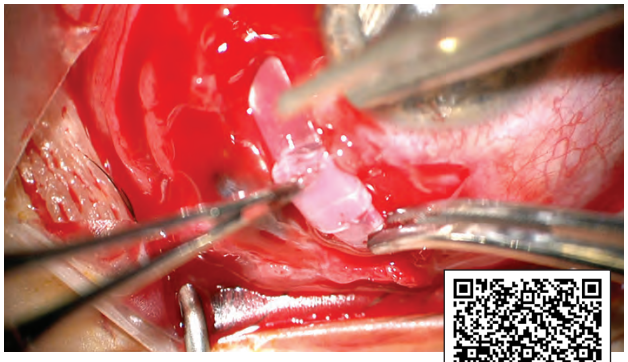
Fundoscopic examination of the right eye showed an attached retina supported on a scleral buckle without evidence of intrusion. The left eye was unremarkable. A CT scan of the orbits revealed the implanted scleral buckle with a somewhat diagonal orientation in the axial plane, but no evidence of pre- or post-septal cellulitis (Figure 2).

The buckle and conjunctival defect were cultured for fungal, bacterial, and mycobacterial infections. Swabs were also sent for varicella zoster and herpes simplex virus detection via polymerase chain reaction. The patient was started on ofloxacin drops four times per day in the right eye and given doses of intravenous vancomycin and moxifloxacin in the emergency department. The patient was asked to discontinue the prednisolone acetate and ketorolac drops.

The patient was taken to the OR for scleral buckle removal, scleral patch graft, and amniotic membrane graft to close the large conjunctival defect (Video). Careful and meticulous dissection of the conjunctiva and Tenon's capsule adjacent to the extruded scleral buckle was performed. The scleral buckle was cut adjacent to the existing conjunctival opening, held by the Watzke sleeve that was in the superonasal quadrant, and removed, limiting exposure of the scleral buckle tunnel to any potential pathogenic microorganisms. The subconjunctival and sub-Tenon's space were gently irrigated with antibiotic rinse. Whole donor sclera was measured and trimmed to 1 mm larger than the area of the original defect. The trimmed donor sclera was tucked under the previously undermined conjunctiva and Tenon's capsule and secured with 8-0 vicryl sutures.

However, there was significant conjunctival scarring and tissue loss that prevented primary closure of the approximately 10 x 10 mm defect despite extensive tissue mobilization. Dehydrated amniotic membrane graft was hydrated, placed stromal side down over the donor sclera, tucked under the conjunctival edges, and secured using 8-0 vicryl sutures to help promote conjunctival growth over the graft and allow closure by secondary intention.

WATCH IT NOW



Video. Management of An Extruded Silicone Scleral Buckle

The donor sclera and amniotic membrane graft were trimmed to the limbus to prevent dellen formation. Subconjunctival antibiotics were given, and a large-diameter bandage contact lens was placed on the eye. Ofloxacin and 1% prednisolone acetate drops four times per day, in additional to oral moxifloxacin, were prescribed postoperatively. Bacterial cultures grew *S. Epidermidis*.

At postoperative week 1, the patient's pain had resolved completely, VA was stable at 20/40 OD, and the conjunctival defect was well closed with the scleral patch graft in good position underneath the amniotic membrane graft. The patient followed up with his local vitreoretinal surgeon.

DISCUSSION

Exposed scleral buckles are at risk for becoming infected, and explantation is almost always required at that point. Primary conjunctival closure is the simplest procedure to correct an extruded buckle.[10] However, this is typically successful only in cases with small conjunctival defects. Larger defects with tissue loss, scarring, and a location in the conjunctival fornix can be difficult to close or result in high wound tension and subsequent dehiscence or forniceal foreshortening.

In the case presented here, we were unsuccessful in undermining the surrounding conjunctiva and performing primary closure. Use of a scleral patch graft is the most frequently reported technique for repair of extruded scleral explants and is useful in the setting of scleral thinning.[12-14] Several other materials have been reported to facilitate closure of the conjunctiva followed extruded scleral buckles, including pericardium, fascial grafts, periosteal patch grafts, and amniotic membrane grafts.[11,15-17]

(Continued on page 55)

CONTROVERSIES IN ILM PEELING

Ongoing research is slowly providing guidance for surgeons who are faced with tough intraoperative decisions.

BY CHARLES DEBOER, MD, AND THEODORE LENG, MD, MS


Internal limiting membrane (ILM) peeling is used in macular hole (MH) surgery for improved surgical outcomes. However, surgeons continue to debate the ideal peel diameter. For other indications such as rhegmatogenous retinal detachment (RRD) and epiretinal membrane (ERM), there is less overall guidance and consensus on the need for ILM peeling. Here, we discuss the controversies surrounding ILM peeling, including when and how much to peel and the risks involved.

DISADVANTAGES

Anatomical damage has been found after ILM removal, as it causes damage to Müller cells. Structural and histological changes occur after manipulation of the ILM.[1] Studies have found that the size of the ILM peel was associated with an increased dissociated optic nerve fiber layer (DONFL) score.[2] Microperimetry has also revealed decreased retinal sensitivities and an increase in the number of absolute and relative microscotomas after ILM peeling.[3] Finally, there are risks associated with the dyes used, such as indocyanine green (ICG) or brilliant blue.[4,5]

HOW MUCH TO PEEL?

ILM peeling can improve closure rates of full-thickness MHs and lower rates of late postoperative recurrence despite no statistically significant improvement in visual acuity.[6,7] Although there is widespread acceptance of ILM peeling in the case of a MH, there is no consensus on how wide to peel. While some will perform a conventional ILM peel (C-ILMP) with a diameter of 2 disc-diameters, others will use extended C-ILMP (EC-ILMP) of up to 4 disc-diameters. Modi et al found similar closure rates in 3-mm and 5-mm peel diameters with better visual acuity in the 3-mm group. Given the lack of improvement in anatomic or visual results and the damage to the retina caused by ILM peeling, the recommendation was made to keep the peel diameter as small as possible to relieve tangential traction without compromising the surgery success rate.[8] However, research has yet to clarify if MHs can be stratified to determine whether some would benefit from a larger peel.

Yao et al evaluated 12-month results of C-ILMP versus EC-ILMP and stratified the results based on the MH closure index (MHCI). When the MHCI was < 0.5, the complete closure rate was 18% with C-ILMP and 76% for EC-ILMP, with better visual acuity at 12 months in the EC-ILMP group. With an MHCI > 0.5, there was no difference in complete closure rate or visual acuity at 12 months.[9] Another study showed that closure rates in MHs with a minimum linear dimension larger than 400 µm were 46% in the C-ILMP group versus 76% in the EC-ILMP group.[10] Two studies showed higher closure rates for EC-ILMP compared with C-ILMP in MHs greater than 400 µm, although there was no statistical difference in visual acuity.[11,12] However, when stratified, there was an improvement for the EC-ILMP group with an MHCI < 0.5.[12]

Bottom line: There are likely methods to stratify risk associated with MHs and determine the optimal conventional ILM peel diameter.

AT A GLANCE

- Anatomical damage has been found after internal limiting membrane (ILM) removal, as it causes damage to Müller cells.
- ILM peeling can improve closure rates of full-thickness macular holes and lower rates of late postoperative recurrence.
- It is generally agreed that epiretinal membrane/ILM peeling does not improve visual acuity but decreases the recurrence rate of epiretinal membranes.

TABLE. SELECTED STUDIES EVALUATING ERM VERSUS ERM/ILM PEELING

Author	BCVA Difference	Statistically Significant Recurrence Difference	Statistically Significant Repeat Surgery Difference	CMT Difference	Other Parameters (ILM vs ERM)	Number of ILMs	Number of ERMs	Follow-up time (months)
Prospective Studies								
Aydin[27]	None	N/A	N/A	N/A	No difference in metamorphopsia scores	17	19	4
De Novelli[28]	None	None	N/A	N/A	No change in metamorphopsia on Amsler grid	28	35	6
El Shafei[30]	None	None	None	ILM thicker in month 1	More ERM with normal foveal contour	20	20	12
Ripandelli[32]	None	None	None	With time and treatment analysis	Decreased retinal sensitivity and increased microscotomas in ILM	30	30	12
Tranos[26]	None	None	No repeat surgery	None	No change in metamorphopsia on Amsler grid, more frequent uninterrupted interdigitation zone with ILM peel	50	52	12
Retrospective Studies								
Ahn[36]	ILM worse	None	None	None	More OCT cone segment tip line defects in ERM at month 1	40	69	12
Bovey[34]	ILM better	9% ILM 56% ERM	ERM: 1 repeat ERM peel (*P* not listed)	N/A	N/A	55	16	21 (mean)
Chang[33]	None	N/A	N/A	ERM with more reduction in CMT in month 1	N/A	40	40	3
Guber[25]	None	N/A	No repeat surgery	None	N/A	62	36	3
Kang[31]	None	Secondary 0% ILM 33% ERM	N/A	N/A	N/A	28	23	25 (mean)
Ozdek[35]	ILM better (due to better preoperative VA)	N/A	N/A	ILM thicker in first year	N/A	634 eyes total		24
Schechet[29]	None	1.8% ILM 22.9% ERM	0% ILM 12% ERM	None	N/A	111	140	32 to 45 (mean)

Definitions: ILM = group with ERM and ILM peeled, ERM = group with only ERM removed
Abbreviations: ILM, internal limiting membrane; ERM, epiretinal membrane; CMT, central macular thickness

WHEN TO PEEL

RRDs. The issue of when to peel the ILM in RRD repair surgery is highly debated in the literature. ERM has been shown to form after standard RRD repair without ILM peeling with rates varying from 6% to 34% and surgical rates of reoperation from 4% to 16%.[13-15] Peeling the ILM at the time of RRD surgery may help reduce the rates of ERM formation (0%–6.5%) and reoperation (0%–2%).[16-22]

However, there is less consensus on postoperative visual acuity, with many authors showing no statistical improvement in visual acuity after ILM peeling in RRD.[15,16,23] Others have stratified data to macula-on and macula-off RDs. With macula-on, some have found improvement in visual acuity with ILM peeling, while others have found no statistical improvement.[16,18] For macula-off RD, some authors showed improvement in visual acuity after ILM peeling,[17] some found no statistical difference,[20,21] and some showed worse visual acuity.[18,19,22]

Likewise, redetachment rates have varied, with some showing higher redetachment rates without ILM peeling and

others finding no statistical difference.[16-18,20,21,23]

There are also concerns regarding the safety of ILM peeling during RRD repair. Abdullah et al found worse visual acuity, more retinal dimples, less density of superficial capillary plexus on OCT angiography, and decreased mean amplitude of multifocal electroretinogram after ILM peeling.[22] Eissa et al found worse visual acuity, decreased retinal sensitivity, and more retinal dimpling in the ILM peeling group compared with the group that did not undergo peeling.[19]

Given the relative consensus on increased postoperative ERM, but conflicting data on postoperative visual acuity and function, others are looking for alternative markers to influence the use of ILM peeling. Akiyama et al used retinal surface wrinkling as a proxy for likelihood of ERM development after RRD repair. At 6 months, they found no ERM formation after ILM peeling with patients who had retinal surface wrinkling, where patients without retinal surface wrinkling and without ILM peeling had a 14% rate of ERM formation. BCVA was similar between the two groups. However, this study had no control group of patients with wrinkling without ILM peeling.[24]

Bottom line: Overall, ERM formation is felt to be reduced in patients who undergo ILM peeling during RRD repair. However, the benefit or detriment to visual function is variable based on the study.

ERMs. The benefits and risks of ERM peeling alone versus combined ERM/ILM peeling remain hotly debated. To complicate things, ILM is often inadvertently removed when the ERM is peeled (Table).

Most research has found no statistical difference in the postoperative BCVA when comparing ERM and ERM/ILM peeling.[25-33] Bovey et al performed histology on ERMs removed from 71 patients and found an association between improved final visual acuity when ILM was removed in addition to ERM.[34] Ozdek et al found better visual acuity after ERM/ILM peeling; however, this was felt to be due to better preoperative visual acuity in the ERM/ILM group.[35] Ahn et al found worse BCVA in the ERM/ILM peeling group at month 1 but no statistical difference at subsequent visits.[36]

Many authors have found a decrease in recurrent ERM formation in the ERM/ILM groups, although only a small fraction of recurrent ERMs required surgery.[29,34] Kang et al did find a significant decrease in recurrence for ERM/ILM peeling in ERMs that were secondary, but no difference in idiopathic ERM.[31] Other authors did not see a statistically significant difference in recurrent ERM formation.[26,28,30,32,36]

Because many of the prospective studies were limited in the numbers of participants and others have been retrospective, some authors have used meta-analyses to further evaluate the differences after ILM peeling in ERM. A meta-analysis of seven randomized control studies found no statistical difference in visual acuity at 12 months, a larger ERM recurrence rate in the ERM group at 12 months, and an increased central macular thickness and reduced foveal sensitivity in the ERM/ILM peeling group.[37] However, the authors cautioned that there was significant heterogeneity in the studies when comparing foveal sensitivity.[37]

There has been interest in ILM peeling's effect on cystoid macular edema, with some authors finding an increase in thickening after ERM/ILM peeling compared with ERM alone.[30,32,33,35] Still, this often resolves over time. Other authors did not observe a statistically significant difference between the two groups.[26,29,36]

Uemura et al used ICG staining and found visual field defects after ERM/ILM peeling, possibly due to ICG toxicity or the mechanical effects of ILM peeling itself.[38] Ripandelli et al performed microperimetry and found decreased mean retinal sensitivity in the ERM/ILM peeling group in the 4-degree central area, as well as an increased number of microscotomas in the 12-degree, but not the 4-degree, central area.[32] Evaluation by Amsler grid did not show a statistical difference in metamorphopsia.[26,28] Aydin et al evaluated metamorphopsia using an M-chart but were unable to find a significant difference.[27]

Bottom line: It is generally agreed that ERM/ILM peeling does not improve the visual acuity but does decrease recurrence rate of ERM. The debate continues about whether ILM peeling causes side effects for patients and whether the risks outweigh the benefits.

TAKEHOME

For MH surgery, ILM peeling has improved closure rates, although the optimal amount of peeling is debatable. Given the risks of ILM removal, including DONFL, decreased retinal sensitivities, microscotomas, and eccentric MHs, surgeons should minimize the ILM peeling to allow closure of the hole without incurring additional risk to the patient. There is evidence that peeling the ILM in RRD and ERM may limit ERM formation or recurrence after surgery, but overall functional outcome improvements are debated.

Future large prospective clinical trials may further refine and develop a consensus on the best use of ILM peeling. ■

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VITREOUS HEMORRHAGE: OBSERVE OR OPERATE?

With recent advances in technology, early vitrectomy for patients with non-diabetic vitreous hemorrhage is an important consideration.

BY MAXWELL WINGELAAR, MD, AND GAURAV K. SHAH, MD


We have all had this patient: phakic with a spontaneous dense vitreous hemorrhage in one eye. Vitreous hemorrhage is a relatively common problem, affecting an estimated seven cases per 100,000 per year—for reference, retinal detachment (RD) has an incidence of 12 cases per 100,000 per year.[1]

The first question is always, "do you have diabetes?" If the answer is "no," your day just got a little longer. The list of possible underlying causes for vitreous hemorrhage is long and includes everything from retinal vascular disease, retinal tears and detachments, retinal vasculitis, retinal macroaneurysm, polypoidal disease, posterior vitreous detachment (PVD), and tumors (Figure 1).

RDs and retinal tears are, arguably, the most concerning cause of spontaneous vitreous hemorrhage because of the increased risk of permanent visual loss if not treated appropriately and in a timely manner. For one, vitreous hemorrhage due to a retinal tear and/or RD comes with an increased risk of developing proliferative vitreoretinopathy (PVR), which decreases a patient's chances of long-term anatomic success.[2]

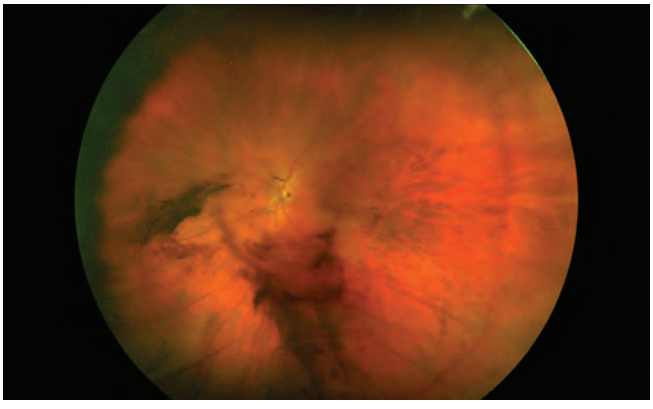

Figure 1. A moderately dense vitreous hemorrhage caused by an acute PVD.

One study of 441,517 eyes found that 2.37% presented with a delayed retinal break after the initial PVD with a median time of 38 (range 1 to 365) days. Most importantly, individuals with vitreous hemorrhage, lattice degeneration, and myopia were at a higher risk of developing delayed breaks than those who did not present with these findings.[3]

To prevent vision loss, clinicians must identify and treat RDs and tears that often accompany a spontaneous vitreous hemorrhage. The problem is that the hemorrhage often obscures the surgeon's view of the retina, potentially hiding the causative pathology.

While B-scan ultrasonography is an important part of your workup for these patients, it's not always the most sensitive tool (Figure 2). For example, shallow RDs and small or very posterior tears can be hard to locate on a B-scan, with a sensitivity in the range of 44% to 56%.[4,5]

AT A GLANCE

- In a healthy patient, a vitreous hemorrhage that was caused by an acute event, not a continuous process, may clear over time without intervention.
- RDs and retinal tears are, arguably, the most concerning cause of spontaneous vitreous hemorrhage because of the increased risk of permanent visual loss if not treated appropriately and in a timely manner.
- If a young, phakic myope with no history of diabetes presents with a fundus-obscuring vitreous hemorrhage, clinicians should have a low threshold to perform early vitrectomy.

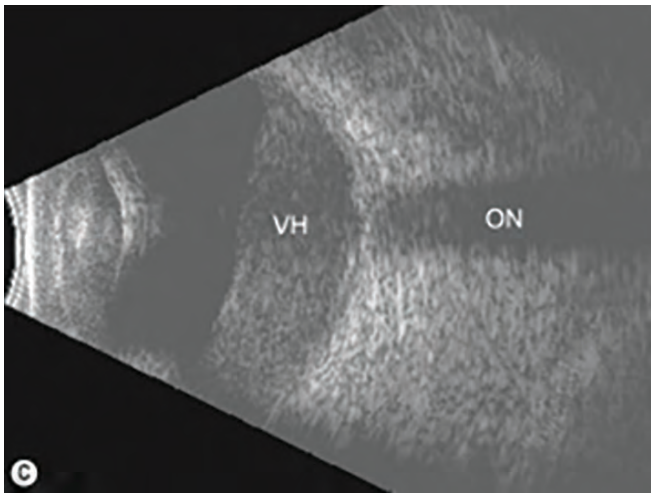

Figure 2. A B-scan demonstrating a dense vitreous hemorrhage overlying the macula (VH = vitreous hemorrhage, ON = optic nerve).

When faced with a non-diabetic vitreous hemorrhage that is obscuring your view (and the patient's), you have two management avenues to consider: observe and follow closely to see if the hemorrhage dissipates or take the patient to the OR. Here, we discuss the pros and cons of each approach.

WAIT IT OUT

In a healthy patient, a hemorrhage that was caused by an acute event, not a continuous process, can clear over time, requiring only close observation. It may take anywhere from a few weeks to several months, but it could resolve on its own. This may be a reasonable approach, particularly if the patient is high-risk for complications from general anesthesia or if the clinician suspects a peripheral exudative hemorrhagic chorioretinopathy type lesion or a retinal artery macroaneurysm.

Nonetheless, waiting for the hemorrhage to clear comes with a concern that the hemorrhage is obscuring a complication that requires surgical intervention, particularly in the retinal periphery (Figure 3).

One study of 36 eyes with fundus-obscuring, unexplained vitreous hemorrhage looked into the outcomes of conservative management (regular follow-up and B-scan ultrasound) and found that, although no RDs were identified on the initial B-scan, 78% of cases required surgery to repair an RD identified on follow-up or to resolve a non-clearing vitreous hemorrhage.[6] In addition, the researchers noted that a retinal tear was the cause of the hemorrhage in 76% of the patients younger than 80 years of age.[6]

Other researchers reported a 9-year series of RDs in patients with vitreous hemorrhage and found that 33% of eyes with fundus-obscuring vitreous hemorrhage developed an RD that was subsequently complicated by PVR.[7]

DON'T FEAR THE OR

The second treatment approach is early vitrectomy, an option that has become more appealing with recent advances in technology. Surgeons are now routinely performing 25- and 27-gauge vitrectomy that offers smaller incisions and minimal recovery time for the patient. Surgical intervention can clear the hemorrhage and provide the surgeon with the necessary visualization to properly rule out retinal tears and detachments—or address them intraoperatively if they are present.

The research is mounting in favor of early vitrectomy, although few randomized clinical trials have directly compared data on early versus delayed vitrectomy for fundus-obscuring vitreous hemorrhage. Tan et al looked at 40 eyes that underwent early vitrectomy for unexplained vitreous hemorrhage and found that 47% of eyes that showed no signs of a retinal tear on preoperative ultrasound had a tear intraoperatively—44% of which had multiple tears.[8] In another series of 12 eyes that had undergone early vitrectomy for fundus-obscuring vitreous hemorrhage, only three eyes had an identifiable RD on preoperative ultrasound. Intraoperatively, nine eyes had a retinal tear (75%).

Our team sought to better understand the surgical and visual outcomes for adult patients with non-diabetic, fundus-obscuring vitreous hemorrhage undergoing either early (within 10 days of symptom onset) or delayed (after 10 days) surgery.[9] We reviewed 275 patients who underwent surgery for vitreous hemorrhage over a 5-year period and included 52 eyes of 52 patients with an average age of 61 years. All patients underwent preoperative ultrasound, and the timing of the surgical intervention was at the clinician's discretion. Eyes with a high suspicion for a retinal tear or RD on ultrasound underwent urgent vitrectomy and were excluded from the study.

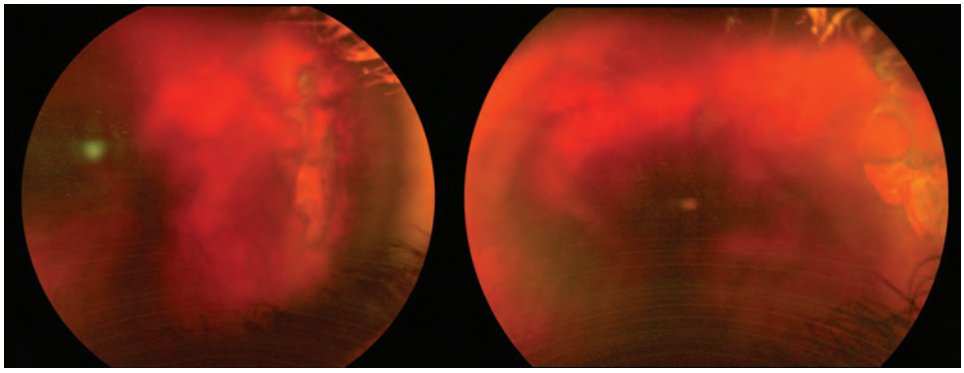

Figure 3. A dense vitreous hemorrhage obscuring the view of the posterior pole.

IMAGING PEARLS

B-scan ultrasonography is the tool of choice when imaging dense vitreous hemorrhages, but it's not perfect. In our study, ultrasound sensitivity was 24.3% for retinal tears and 62.5% for retinal detachments (RDs), which is quite low.[9] Ultrasonography requires a skilled technician or physician, and without skilled ultrasonographers, pathology can easily be missed. Other imaging tools with some clinical utility include the following:

- **OCT** – Depending on the density of the hemorrhage, OCT may help clinicians confirm if the macula is attached or any obvious pathology that might inform the management decision.
- **Fluorescein angiography** – This may be useful, but the view may be just as limited as it is for ultrasound, and its invasiveness makes it less ideal.
- **Infrared imaging** – This may be helpful when attempting to differentiate an RD from retinoschisis. RDs will appear dark and hyporeflective on infrared (Figure 1). Retinal tears with be hyperreflective, and retinoschsis appears isointense (Figure 2).

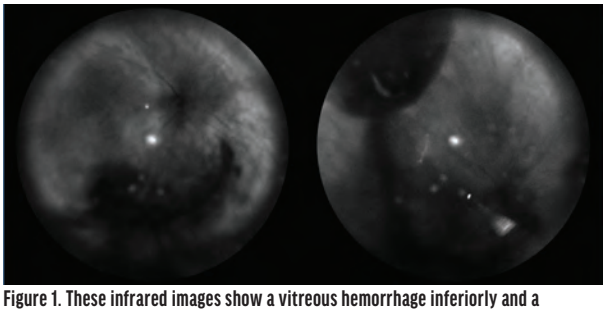

Figure 1. These infrared images show a vitreous hemorrhage inferiorly and a superotemporal RD (hyporeflective) with a horseshoe retinal tear (hyperreflective).

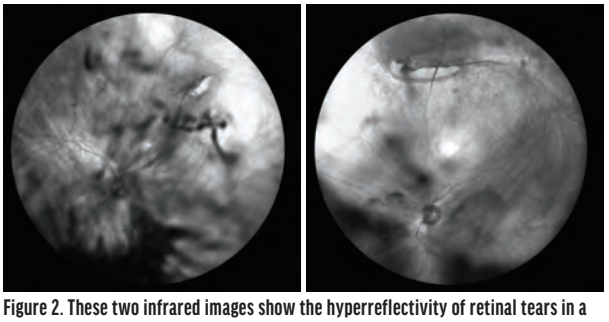

Figure 2. These two infrared images show the hyperreflectivity of retinal tears in a patient with a vitreous hemorrhage.

We found that, intraoperatively, 48% of study eyes had a retinal tear, and 24% had an RD. Preoperative VA was 20/400 and 20/200 in the early and delayed vitrectomy groups, respectively. Postoperatively, VA was 20/66 and 20/89, respectively. The results show no statically significant difference in visual outcomes between the early and later groups, although the mean number of operations was greater in the delayed group (1.1 versus 1.5). All the patients found to have a retinal tear or RD were younger than 80 years of age.[9]

VITRECTOMY TIPS

Surgery for vitreous hemorrhage is always interesting because surgeons aren't certain what is lying beneath the blood. In these patients, surgeons are mostly concerned with damaging the retina and causing iatrogenic breaks. Here are our tips for a successful surgery:

- Stay near the ports.
- If you can, try to start superonasally, unless there's an obvious detachment or other concerns were obvious on the B-scan.
- Start slowly and ease your way in.
- Slowly make your way inward as you improve your view.
- Be sure you can always see the cutter, and keep the port facing up toward you until your view clears.

Most importantly, we found that younger phakic patients presenting with a vitreous hemorrhage were more likely to have a retinal tear or RD compared with pseudophakic patients, with an increased odds ratio of 2.14.[9]

THE BOTTOM LINE

If a young, phakic, high myope with no diabetes presents with a fundus-obscuring vitreous hemorrhage, clinicians should have a low threshold to take them to the OR early. In fact, because of the high rate of tears and RDs identified intraoperatively, clinicians should consider early vitrectomy for most patients with non-diabetic vitreous hemorrhage.

Although conservative treatment may be appropriate for certain patients, poor visual outcomes are possible due to missed retinal tears, RD, and subsequent PVR, which leads to increased patient morbidity. ■

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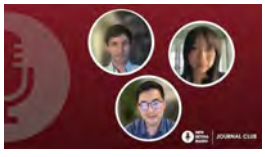

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HEMORRHAGE OVER A CHOROIDAL NEVUS—HARMLESS OR HAZARDOUS?

Choroidal neovascularization may lead to worrisome findings on fundus autofluorescence, but these do not necessarily indicate malignancy.

BY SAMANTHA PASTORE, BS; JENNIFER S. ZEIGER, BA; GUY S. NEGRETTI, FRCOPHTH; AND CAROL L. SHIELDS, MD

Choroidal nevi are common intraocular melanocytic tumors found in approximately 6% of the White population.[1] Despite their benign nature, these lesions can assume suspicious features that may be misdiagnosed as choroidal melanoma. Choroidal neovascularization (CNV), a rare complication of choroidal nevi, can cause visual impairment and pseudo-enlargement of the mass in both base and thickness, raising suspicion for malignancy.[2] Herein, we describe a case of a choroidal nevus that raised concern for malignancy following abrupt evolution with subretinal and subhyaloid hemorrhages.

CASE

A 66-year-old White man presented to the Ocular Oncology Service with decreased vision in his left eye for 2 weeks. He was known to have a choroidal nevus in his left eye identified 9 years earlier. At that time, the nevus was 2.9 mm in thickness and 8 mm in largest basal diameter with overlying drusen and focal retinal pigment epithelial (RPE) hyperplasia (Figure 1A). Fundus autofluorescence (FAF) demonstrated focal patches of hypoautofluorescence overlying the nevus, corresponding to the areas of RPE hyperplasia and atrophy (Figure 1B). Ultrasonography revealed a somewhat acoustically hollow, dome-shaped mass of 2.9 mm thickness (Figure 1C). Routine monitoring was advised.

At presentation, the patient's VA was 20/30 OD and 20/60 OS, and the nevus in his left eye had changed. There was a pigmented choroidal mass measuring 8 mm in largest basal diameter, with overlying RPE atrophy. The most striking change was the presence of overlying fresh subretinal hemorrhage and curvilinear dependent yellow, partially dehemoglobinized chronic subretinal hemorrhage, and "breakthrough"

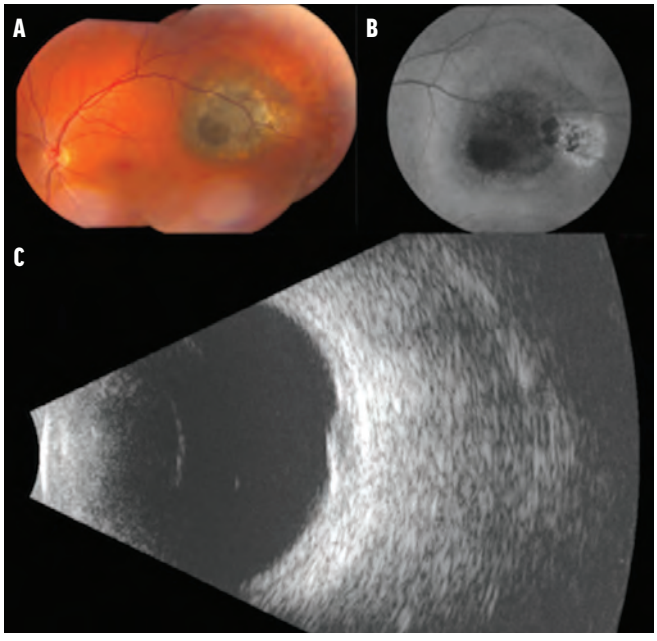

Figure 1. Wide-angle color fundus photography shows a choroidal nevus measuring 8 mm in basal diameter with overlying drusen and RPE hyperplasia in the left eye (A). FAF shows focal patches of hypoautofluorescence overlying the nevus corresponding to areas of RPE hyperplasia and atrophy (B). Ultrasonography shows an echolucent, dome-shaped mass 2.9 mm in thickness (C).

subhyaloid hemorrhage in the inferior macular region (Figure 2A). The fresh hemorrhage was hypoautofluorescent, whereas the more chronic, dehemoglobinized hemorrhage was hyperautofluorescent (Figure 2B).

Ultrasonography confirmed a shallow, dome-shaped, echodense choroidal mass measuring 2.6 mm in thickness (Figure 2C). OCT imaging showed vitreomacular traction

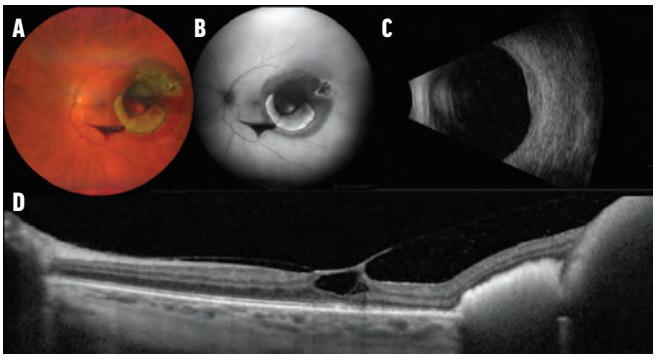

Figure 2. Wide-angle color fundus photography shows the choroidal nevus with fresh overlying subretinal hemorrhage, yellow, partially dehemoglobinized curvilinear subretinal hemorrhage inferiorly, and "breakthrough" subhyaloid hemorrhage in the inferior macular region (A). FAF reveals hypoautofluorescence of the fresh blood and hyperautofluorescence of the chronic blood (B). Ultrasonography confirms a shallow, dome-shaped, echodense choroidal mass of 2.6 mm in thickness (C). OCT shows vitreomacular traction with cystoid macular edema, as well as subretinal and subhyaloid hemorrhage (D).

with cystoid macular edema, as well as subretinal and subhyaloid hemorrhage (Figure 2D). Although the associated hemorrhages were new and suspicious on clinical examination, these features, along with ancillary testing, were more consistent with a chronic choroidal nevus with CNV and hemorrhage rather than evolution to melanoma. Anti-VEGF injections were administered, and observation was advised.

DISCUSSION

Distinguishing between choroidal nevus and melanoma can be facilitated by the use of the mnemonic: To Find Small Ocular Melanomas Doing IMaging (TFSOM-DIM), look for Thickness > 2 mm on ultrasound, subretinal Fluid on OCT, Symptoms of vision loss, Orange pigment on FAF, hollow Melanoma on ultrasound, and DIaMeter > 5 mm). As the number of TFSOM-DIM factors increases for a given lesion, the risk of growth into melanoma increases. The mean 5-year estimates of nevus growth into melanoma are 1% for no risk factors, 11% with one factor, 22% with two, 34% with three, 51% with four, and 55% with five or more risk factors.[3]

CNV is a rarely reported complication of choroidal nevus. The presence of CNV is not a recognized risk factor for malignant transformation and likely represents a sign of nevus chronicity.[3-5] Shields et al found that, of 3,806 choroidal nevi followed over time, 1% were associated with CNV.[3] A retrospective analysis of 23 patients with choroidal nevus–related CNV demonstrated that only one nevus (4%) exhibited slight growth, and no nevi demonstrated transformation into melanoma.[4] A more recent retrospective study of 17 patients with choroidal nevus–related CNV found that none of the lesions developed signs of malignancy after a mean follow-up period of 12 months.[5]

The autofluoresence findings are interesting relative to the chronicity of the overlying hemorrhage. The fresh subhyaloid and subretinal blood demonstrated hypoautofluorescence, and the chronic subretinal blood showed hyperautofluorescence, as has been shown by others.[6] The intense hyperautofluorescence of devitalized blood is related to the degree of fluorescence in free-base porphyrins, which are breakdown products of heme that exhibit intense fluorescence in the range of wavelengths recorded by FAF imaging systems.[6] With time, as the free-base porphyrins are further broken down, the hyperautofluorescence gradually fades. This phenomenon has been demonstrated in diabetic retinopathy,[6] and it was described in a previous *Retina Today* article by our group on neovascularization secondary to radiation retinopathy.[7]

Despite the dramatic appearance of bleeding present in both the subretinal and subhyaloid spaces, our patient presented with only two risk factors for growth to melanoma (thickness > 2 mm and diameter > 5 mm), so an anti-VEGF injection was given and observation was advised.

CONCLUSION

The features described here might superficially appear worrisome for tumor growth, but they ultimately represent tumor chronicity with development of CNV. ■

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CODING ADVISOR
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THREE QUESTIONS WHEN CODING LASER THERAPY

Lasers are a great tool in the retina clinic–just make sure you know how to properly code for them.

BY JOY WOODKE, COE, OCS, OCSR

Laser treatment is a valuable approach for many retinal conditions, including diabetic macular edema, retinal tears and detachments, proliferative retinopathy, and choroidal neovascularization. Correct coding for retinal laser treatments starts with answering these three key questions.

WHAT IS THE DIAGNOSIS?

A single laser treatment can be used in many different procedures and is represented by a variety of CPT codes. The appropriate CPT code to use is based on the patient's diagnosis, not the treatment itself (Table 1).[1] For example, if laser treatment is indicated for a retinal detachment, the correct CPT code is 67105. If the same laser procedure is indicated for a retinal tear and prophylaxis of retinal detachment, CPT code 67145 is correct.

IS THIS A MAJOR OR MINOR PROCEDURE?

The next question to answer is whether the laser treatment is considered a major or minor procedure. This is determined by the global period. A major surgery is defined as a procedure with a 90-day global period; a minor surgery has either no global period or a 10-day global period.

Retinal laser therapy can be considered either a major or minor surgery. A crucial step to confirm the correct coding is to note if an examination was performed on the same day. For examinations performed on the same day as a major surgery, append modifier -57, decision for major surgery.

TABLE 1. LASER TREATMENT CPT CODE BY DIAGNOSIS[1]

What is the Diagnosis?				
DME, CME, Retinal Edema	Retinal Detachment	Prophylaxis of RD, Retinal Break or Tear, Lattice Degeneration	Proliferative Retinopathy	Choroidal Neovascularization
67210: Focal Macular Laser, Grid	67105: Repair RD, Photocoagulation	67145: Repair Retinal Tear, Prophylaxis of RD, Photocoagulation	67228: PRP, Photocoagulation	67220: Destruction of Localized Lesion of Choroid

Abbreviations: CME, cystoid macular edema; DME, diabetic macular edema; PRP, panretinal photocoagulation; RD, retinal detachment.

TABLE 2. MEDICARE GLOBAL PERIODS FOR RETINAL LASER THERAPY

CPT Code	Medicare Global Period	Same-Day Examination Modifier
67105	10 days	-25
67145	10 days	-25
67210	90 days	-57
67220	90 days	-57
67228	10 days	-25

When the laser treatment is a minor surgery, review the documentation for the examination and confirm it meets the definition for modifier -25, or significant, separately identifiable examination the same day as a minor surgery. Consider that, while medically necessary, if the examination was performed to confirm the need for the laser therapy, it is not separately billable. Table 2 is a quick reference guide that provides the Medicare global period for each retinal laser therapy approach and the appropriate modifier to consider for the same-day examination.

WHO IS THE PAYER?

Although Medicare Part B has designated global periods for retinal laser therapy codes, other payers may not recognize the same postoperative days. For example, since January 2016, Medicare has assigned a 10-day global period to CPT code 67228 (treatment of extensive or progressive retinopathy [eg, diabetic retinopathy], photocoagulation), while some Medicaid plans still recognize CPT code 67228 as a major surgery with a 90-day postoperative period.

Another good example is CPT code 67145—the global period changed in January 2022 to 10 days, but many commercial and other payers have a delayed implementation.

Determining the global period based on the laser code and payer is essential to correct coding. This will help you properly track the postoperative days and know when to bill for office visits. Additionally, for the same-day examination, the correct modifier, -25 or -57, is dependent on the payers' global period assignment and the designation of a major or minor surgery.

Developing an internal quick reference guide that outlines the unique payer nuances related to retinal laser therapy codes will assist in appropriate coding of these procedures. For more resources related to retina coding, visit aao.org/retinapm. ■

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(Continued from page 43)

Amniotic membrane grafts have been well reported in the reconstruction of the conjunctiva for numerous ocular surface diseases, in part due to their ability to stimulate epithelialization and exhibit antifibrotic, antiinflammatory, antiangiogenic, and antimicrobial properties.[18] Importantly, they have an inherent lack of immunogenicity, which is important for their utility as a graft, and makes them a more appealing option compared with other allografts.[18]

THE PEARLS

This case of an extruded and infected silicone scleral buckle with associated scleral thinning and a large conjunctival defect required buckle removal, sutured donor scleral graft, and dehydrated amniotic membrane graft.

Extruded scleral buckles are intimidating cases, and although conservative treatment seems reasonable at first, eventual removal of the scleral buckle is often required. Primary closure of the defect can be attempted, but if that proves unsuccessful, consider using scleral and amniotic patch grafts in these complex cases. ■

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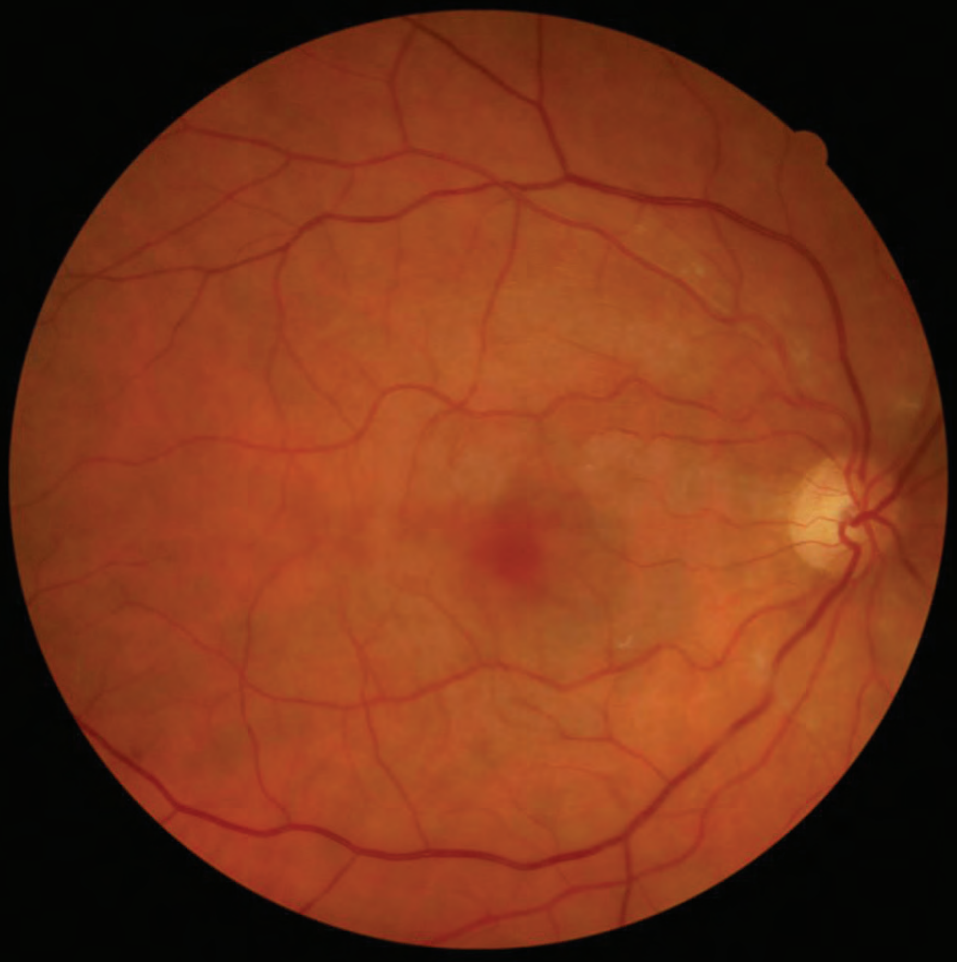
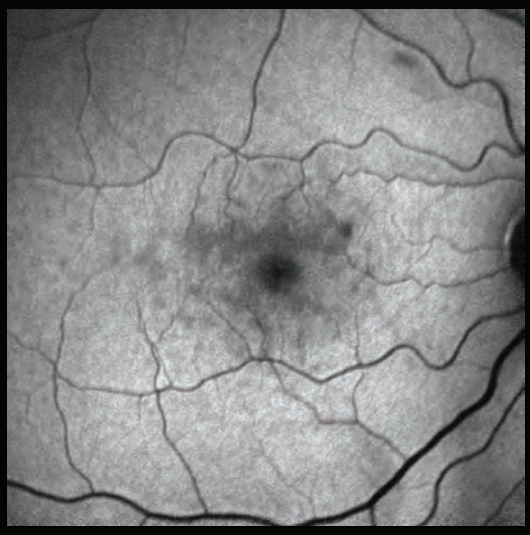
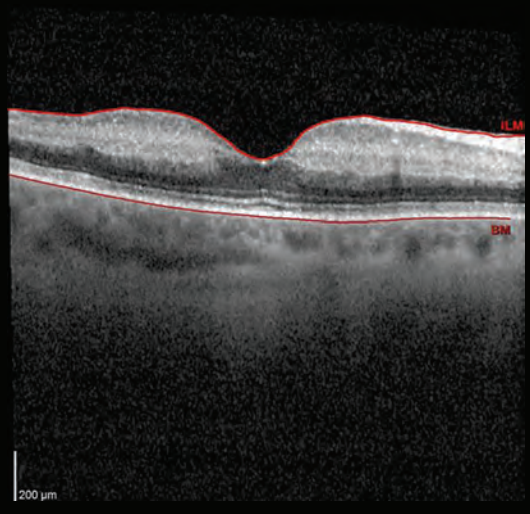






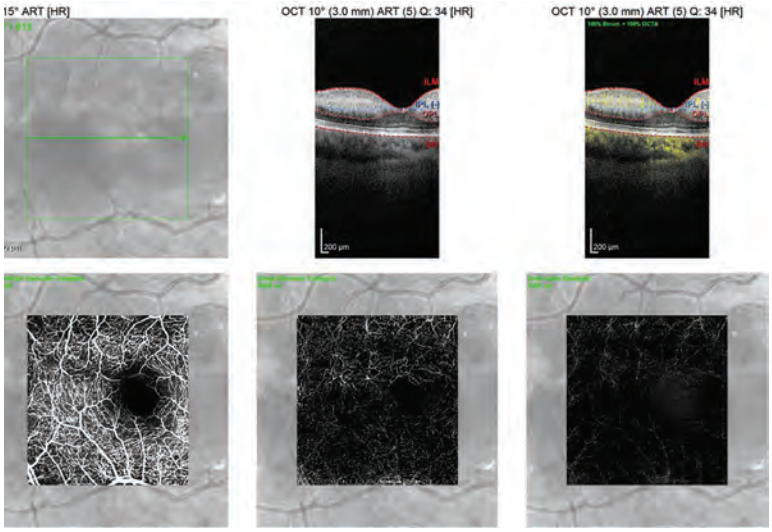
IDIOPATHIC PARACENTRAL ACUTE MIDDLE MACULOPATHY (PAMM)

It is important to send patients for urgent stroke testing when you note signs of paracentral acute middle maculopathy.

BY REHAN M. HUSSAIN, MD

This patient presented with a VA of counting fingers OD, stating her vision had progressively worsened over the last 4 weeks and she now saw a "cloud" over her right eye. The fundus photograph showed confluent white patches throughout the macula, which are more apparent on infrared imaging (Main Figure). The OCT shows hyperreflective bands that involve the middle layers of the retina but spare the fovea, a finding known as paracentral acute middle maculopathy (PAMM).

OCT angiography showed loss of capillary blood flow in the deep capillary plexus of the right eye, which is more noticeable when compared with the left eye (Figure, next page). The



patient was sent to her primary care provider for an urgent stroke workup, including erythrocyte sedimentation rate and C-reactive protein labs, neuroimaging, and carotid artery Doppler ultrasound, all of which were normal.

DISCUSSION

PAMM is caused by retinal ischemia specific to the deep capillary plexus. Because PAMM may be a sign of a secondary underlying condition, it is important that clinicians order an immediate systemic workup to rule out cardiovascular conditions or stroke, much like the management of a central or branch retinal artery occlusion. This may include brain MRI, carotid Dopplers, and echocardiogram. Nonetheless, PAMM may be idiopathic and can affect young healthy individuals, although the patient described here was in her 60s. Unfortunately, as with retinal arterial occlusions, there is no effective treatment for PAMM and treatment of underlying systemic disorders does not result in reversal of vision loss. ■

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JORDANA G. FEIN, MD, MS

What led you to a career as a medical retina specialist?

From the moment I started residency at Tufts New England Eye Center, I was drawn to the retina service. I loved the mix of medicine and surgery, which is at the core of the practice of retina. In addition, the imaging technology got me excited about and invested in clinical research. My mentors, including Caroline R. Baumal, MD; Elias Reichel, MD; and Jay Duker, MD, were inspirational to me in terms of their knowledge, dedication to teaching, and ability to incorporate research into a busy clinical practice.

Photo courtesy of The Penny Gray Photography Co.

Figure. Dr. Fein with her husband, Adam, and children. Harper and Thatcher.

Although I love surgery, my interest has always been in complex medical retina, uveitis, and clinical research, which ultimately led me to pursue a medical retina fellowship. The complex medical cases, such as diagnosing syphilitic retinitis and saving a patient's life, excited me the most. The most interesting, complicated, and mysterious presentations always made their way to the retina clinic and were my favorite cases to unravel.

What has been one of the most memorable moments of your career?

The most memorable moment in my career was when I got the offer to work at the Retina Group of Washington (RGW). My husband is an electrophysiologist and had taken a job in northern Virginia with a large cardiology practice. I had been on faculty at Tufts New England Eye Center after training, and I wanted to continue to work in a similar environment with a high-volume private practice coupled with teaching and clinical research. The only practice in the DC area that fit the bill was the RGW, and I knew that was where I wanted to practice. However, when we first relocated, there were no open positions, so I took a job with a different multispecialty practice in the area. About 2 years later, one of the doctors at RGW retired, and I was offered the position. I remember getting the phone call and feeling incredible excitement and gratitude to have found the right job for myself. I have been at RGW since 2016 and have been fortunate to work alongside outstanding physicians, help train the next generation, conduct clinical research, and build a thriving practice.

Can you tell us about your experience co-founding the International Society for the Advancement of Medical Retina?

Heeral R. Shah, MD, FASRS, and I founded the International Society for the Advancement of Medical Retina in 2014 to create a forum for retina specialists interested in discussing medical retina, both clinical cases and the nitty gritty of clinical practice. For the first few years we held in-person meetings during AAO or ASRS, and our members presented cases, interacted socially, and shared their experiences as physicians. Since the COVID-19 pandemic, we have transitioned to a virtual case format, but we hope to be in person soon.

You have traveled to Honduras to provide much-needed ophthalmic care. What was that experience like?

I went to Honduras twice with the Virginia Hospital Center Medical Brigade (www.vhcmedicalbrigade.org) and plan to go again this fall. The brigade was started in 1999 to bring transformational health care and development to the most vulnerable people in Honduras. I participated in the Health Services component by providing cataract surgery in Comayagua, Honduras.

In the United States, cataract surgery is very common, and most patients get cataract surgery while they still retain good vision. In remote areas of Honduras, there is less access to care, and some patients do not get care before they become legally blind. By removing a hand motion cataract and restoring functional vision in one eye, we give these patients a renewed opportunity at life. It was incredibly emotional for me to understand how big a difference this surgery can make for an individual. Participating in this trip makes me a better physician and more appreciative of all that we take for granted every day here in the United States.

What is your favorite hobby outside of work?

I love to exercise and be outdoors whenever possible. I can often be found at Pure Barre, doing a Peloton class in my basement, or playing tennis. I have recently taken up golf, mostly for the wardrobe. I play Mah Jong with a group one or two times a month. Most importantly, I enjoy spending time with my two children, Harper and Thatcher, my husband, Adam, and our dog, Brooklyn (Figure). ■

JORDANA G. FEIN, MD, MS

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- Assistant Clinical Professor of Ophthalmology, Georgetown University School of Medicine, Washington, DC
- Co-Founder, International Society for the Advancement of Medical Retina
- jfein@rgw.com
- Financial disclosure: Consultant (Bausch + Lomb, Regeneron); Speaker's Bureau (Apellis, Genentech/Roche, Regeneron)

VABYSMO™
faricimab-svoa injection 6 mg

VABYSMO™ (faricimab-svoa) injection, for intravitreal use

This is a brief summary. Before prescribing, please refer to the full Prescribing Information

1 INDICATIONS AND USAGE

VABYSMO is a vascular endothelial growth factor (VEGF) and angiopoietin 2 (Ang-2) inhibitor indicated for the treatment of patients with:

1.1 Neovascular (wet) Age-Related Macular Degeneration (nAMD)

1.2 Diabetic Macular Edema (DME)

4 CONTRAINDICATIONS

4.1 Ocular or Periocular Infections

VABYSMO is contraindicated in patients with ocular or periocular infections.

4.2 Active Intraocular Inflammation

VABYSMO is contraindicated in patients with active intraocular inflammation.

4.3 Hypersensitivity

VABYSMO is contraindicated in patients with known hypersensitivity to faricimab or any of the excipients in VABYSMO. Hypersensitivity reactions may manifest as rash, pruritus, urticaria, erythema, or severe intraocular inflammation.

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis and Retinal Detachments

Intravitreal injections have been associated with endophthalmitis and retinal detachments *[see Adverse Reactions (6.1)]*. Proper aseptic injection techniques must always be used when administering VABYSMO. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay, to permit prompt and appropriate management *[see Dosage and Administration (2.6) and Patient Counseling Information (17)]*.

5.2 Increase in Intraocular Pressure

Transient increases in intraocular pressure (IOP) have been seen within 60 minutes of intravitreal injection, including with VABYSMO *[see Adverse Reactions (6.1)]*. IOP and the perfusion of the optic nerve head should be monitored and managed appropriately *[see Dosage and Administration (2.6)]*.

5.3 Thromboembolic Events

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

The incidence of reported ATEs in the nAMD studies during the first year was 1% (7 out of 664) in patients treated with VABYSMO compared with 1% (6 out of 662) in patients treated with aflibercept *[see Clinical Studies (14.1)]*.

The incidence of reported ATEs in the DME studies during the first year was 2% (25 out of 1,262) in patients treated with VABYSMO compared with 2% (14 out of 625) in patients treated with aflibercept *[see Clinical Studies (14.2)]*.

6 ADVERSE REACTIONS

The following potentially serious adverse reactions are described elsewhere in the labeling:

- Hypersensitivity *[see Contraindications (4)]*
- Endophthalmitis and retinal detachments *[see Warnings and Precautions (5.1)]*
- Increase in intraocular pressure *[see Warnings and Precautions (5.2)]*
- Thromboembolic events *[see Warnings and Precautions (5.3)]*

6.1 Clinical Trial 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 other clinical trials of the same or another drug and may not reflect the rates observed in practice.

The data described below reflect exposure to VABYSMO in 1,926 patients, which constituted the safety population in four Phase 3 studies *[see Clinical Studies (14.1, 14.2)]*.

Table 1: Common Adverse Reactions (≥ 1%)

Adverse Reactions	VABYSMO		Active Control (aflibercept)	
	AMD N=664	DME N=1262	AMD N=622	DME N=625
Conjunctival hemorrhage	7%	7%	8%	6%
Vitreous floaters	3%	3%	2%	2%
Retinal pigment epithelial tear[a]	3%		1%	
Intraocular pressure increased	3%	3%	2%	2%
Eye pain	3%	2%	3%	3%
Intraocular inflammation[b]	2%	1%	1%	1%
Eye irritation	1%	1%	< 1%	1%
Ocular discomfort	1%	1%	< 1%	< 1%
Vitreous hemorrhage	< 1%	1%	1%	< 1%

[a]AMD only
[b]Including iridocyclitis, iritis, uveitis, vitritis

Less common adverse reactions reported in < 1% of the patients treated with VABYSMO were corneal abrasion, eye pruritus, lacrimation increased, ocular hyperemia, blurred vision, eye irritation, sensation of foreign body, endophthalmitis, visual acuity reduced transiently, retinal tear and rhegmatogenous retinal detachment.

6.2 Immunogenicity

The immunogenicity of VABYSMO was evaluated in plasma samples. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to VABYSMO in immunoassays. The detection of an immune response is highly dependent on the sensitivity and specificity of the assays used, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to VABYSMO with the incidence of antibodies to other products may be misleading.

There is a potential for an immune response in patients treated with VABYSMO. In the nAMD and DME studies, the pre-treatment incidence of anti-faricimab antibodies was approximately 1.8% and 0.8%, respectively. After initiation of dosing, anti-faricimab antibodies were detected in approximately 10.4% and 8.4% of patients with nAMD and DME respectively, treated with VABYSMO across studies and across treatment groups. As with all therapeutic proteins, there is a potential for immunogenicity with VABYSMO.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate and well-controlled studies of VABYSMO administration in pregnant women.

Administration of VABYSMO to pregnant monkeys throughout the period of organogenesis resulted in an increased incidence of abortions at intravenous (IV) doses 158 times the human exposure (based on C_{max}) of the maximum recommended human dose *[see Animal Data]*. Based on the mechanism of action of VEGF and Ang-2 inhibitors, there is a potential risk to female reproductive capacity, and to embryo-fetal development. VABYSMO should not be used during pregnancy unless the potential benefit to the patient outweighs the potential risk to the fetus.

All pregnancies have a background risk of birth defect, loss, and other adverse outcomes. The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects is 2%-4% and of miscarriage is 15%-20% of clinically recognized pregnancies.

Data

Animal Data

An embryo fetal developmental toxicity study was performed on pregnant cynomolgus monkeys. Pregnant animals received 5 weekly IV injections of VABYSMO starting on day 20 of gestation at 1 or 3 mg/kg. A non-dose dependent increase in pregnancy loss (abortions) was observed at both doses evaluated. Serum exposure (C_{max}) in pregnant monkeys at the low dose of 1 mg/kg was 158 times the human exposure at the maximum recommended intravitreal dose of 6 mg once every 4 weeks. A no observed adverse effect level (NOAEL) was not identified in this study.

8.2 Lactation

Risk Summary

There is no information regarding the presence of faricimab in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. Many drugs are transferred in human milk with the potential for absorption and adverse reactions in the breastfed child.

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

8.3 Females and Males of Reproductive Potential

Contraception

Females of reproductive potential are advised to use effective contraception prior to the initial dose, during treatment and for at least 3 months following the last dose of VABYSMO.

Infertility

No studies on the effects of faricimab on human fertility have been conducted and it is not known whether faricimab can affect reproduction capacity. Based on the mechanism of action, treatment with VABYSMO may pose a risk to reproductive capacity.

8.4 Pediatric Use

The safety and efficacy of VABYSMO in pediatric patients have not been established.

8.5 Geriatric Use

In the four clinical studies, approximately 60% (1,149/1,929) of patients randomized to treatment with VABYSMO were ≥ 65 years of age. No significant differences in efficacy or safety of faricimab were seen with increasing age in these studies. No dose adjustment is required in patients 65 years and above.

17 PATIENT COUNSELING INFORMATION

Advise patients that in the days following VABYSMO administration, patients are at risk of developing endophthalmitis. If the eye becomes red, sensitive to light, painful, or develops a change in vision, advise the patient to seek immediate care from an ophthalmologist *[see Warnings and Precautions (5)]*.

Patients may experience temporary visual disturbances after an intravitreal injection with VABYSMO and the associated eye examinations *[see Adverse Reactions (6)]*. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

VABYSMO™ [faricimab-svoa]
Manufactured by:
Genentech, Inc.
A Member of the Roche Group
1 DNA Way
South San Francisco, CA 94080-4990
U.S. License No.: 1048

M-US-00013249(v1.0) 2/22

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faricimab-svoa injection 6 mg

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VABYSMO Is the First IVT Injection Approved for Q4W-Q16W Dosing Intervals in nAMD and DME[1-4]*

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INDICATIONS

VABYSMO (faricimab-svoa) is a vascular endothelial growth factor (VEGF) inhibitor and angiopoietin-2 (Ang-2) inhibitor indicated for the treatment of patients with Neovascular (Wet) Age-Related Macular Degeneration (nAMD) and Diabetic Macular Edema (DME).

IMPORTANT SAFETY INFORMATION

Contraindications

VABYSMO is contraindicated in patients with ocular or periocular inflammation, in patients with active intraocular inflammation, and in patients with known hypersensitivity to faricimab or any of the excipients in VABYSMO.

Warnings and Precautions

- Endophthalmitis and retinal detachments may occur following intravitreal injections. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay, to permit prompt and appropriate management.
- Increases in intraocular pressure have been seen within 60 minutes of an intravitreal injection.
- There is a potential risk of arterial thromboembolic events (ATEs) associated with VEGF inhibition.

Adverse Reactions

The most common adverse reaction (≥5%) reported in patients receiving VABYSMO was conjunctival hemorrhage (7%).

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

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

*Dosing Information:

In nAMD, the recommended dose for VABYSMO is 6 mg (0.05 mL of 120 mg/mL solution) IVT Q4W for the first 4 doses, followed by OCT and visual acuity evaluations 8 and 12 weeks later to inform whether to extend to: 1) Q16W (weeks 28 and 44); 2) Q12W (weeks 24, 36, and 48); or 3) Q8W (weeks 20, 28, 36, and 44).

In DME, the recommended dose for VABYSMO is 6 mg (0.05 mL of 120 mg/mL solution) IVT Q4W for ≥4 doses until CST is ≤325 µm (by OCT), followed by treat-and-extend dosing with 4-week interval extensions or 4- to 8-week interval reductions based on CST and visual acuity evaluations through week 52. Alternatively, VABYSMO can be administered IVT Q4W for the first 6 doses, followed by Q8W dosing over the next 28 weeks.

Although VABYSMO may be dosed as frequently as Q4W, additional efficacy was not demonstrated in most patients when VABYSMO was dosed Q4W vs Q8W. Some patients may need Q4W dosing after the first 4 doses. Patients should be assessed regularly and the dosing regimen reevaluated after the first year.

CST=central subfield thickness; IVT=intravitreal; OCT=optical coherence tomography; Q4W=every 4 weeks; Q8W=every 8 weeks; Q12W=every 12 weeks; Q16W=every 16 weeks.

References: 1. VABYSMO [package insert]. South San Francisco, CA: Genentech, Inc; 2022. **2.** Beovu® (brolucizumab) [package insert]. East Hanover, NJ: Novartis; 2020. **3.** Eylea® (aflibercept) [package insert]. Tarrytown, NY: Regeneron Pharmaceuticals, Inc; 2021. **4.** LUCENTIS® (ranibizumab) [package insert]. South San Francisco, CA: Genentech, Inc; 2018. **5.** SUSVIMO™ (ranibizumab injection) [package insert]. South San Francisco, CA: Genentech, Inc; 2021.

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