POWERED BY bmc

RT
Retina Today

SEPTEMBER 2023 VOL. 18, NO. 6
RETINATODAY.COM

DIABETIC EYE DISEASE

Expert advice on diagnostics, therapeutics, and surgical techniques.

eyetube

ASSESSING DR WITH ULTRA-WIDEFIELD IMAGING

YOUR COMPLEX TRD QUESTIONS ANSWERED

A LOOK AT ANTI-VEGF RESPONSES IN DME

SUBSCRIBE FOR FREE

THIS IS DEXTERITY

This is

FINESSE Reflex™ Handle

FREEDOM YOU CAN FEEL

Introducing the **FINESSE REFLEX™ Handle** from GRIESHABER®, which has been designed to help you work more freely, securely, and precisely.

Increased freedom resulting from expanded extraocular working space[1-7,*]

Improved command made possible by optimized contact[7-10,*,†]

Precision performance due to broad maneuverability[7-10,*]

*Compared to the GRIESHABER REVOLUTION® Handle.

†Based on a surgeon survey where n=54.

Visit surgicalretina.com to learn more about FINESSE REFLEX™ today.

GRIESHABER® DSP IMPORTANT PRODUCT INFORMATION

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

References: 1. Alcon data on file, 2020. **2.** Alcon data on file, 2020. **3.** Alcon data on file, 2020. **4.** Alcon data on file, 2020. **5.** Alcon data on file, 2020. **6.** Alcon data on file, 2020. **7.** Alcon data on file, 2020. **8.** Alcon data on file, 2020. **9.** Alcon data on file, 2020. **10.** Alcon data on file, 2020.

Alcon

THIS IS STABILITY

This is

HYPERVIT™

DUAL BLADE VITRECTOMY PROBE

Designed to:

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

*At similar single-blade flow rates

MIVS IMPORTANT PRODUCT INFORMATION

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

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

Alcon

Retina Today (ISSN 1942-1257) © 2023 Bryn Mawr Communications LLC is published January/February, March, April, May/June, July/August, September, October, and November/December by Bryn Mawr Communications LLC, 125 East Elm Street, Suite 400, Conshohocken, PA 19428. Subscription is free to all applicable US retina physicians. All others, applicable subscription charges apply. For subscription information call +1 800 492 1267 (US only) or e-mail retinatoday@bmctoday.com. Pending periodical postage paid at Wayne PA and additional entry offices. POSTMASTER Please send address changes to Bryn Mawr Communications LLC, 125 East Elm Street, Suite 400, Conshohocken, PA 19428. Bryn Mawr Communications LLC provides certain customer contact data, which may include customer names, addresses, phone numbers and e-mail addresses, to third parties for promotional and/or marketing purposes. If you do not wish Bryn Mawr Communications LLC to make your contact information available to third parties for any marketing purposes, please contact us at 800-492-1267 or e-mail us at retinatoday@bmctoday.com. This publication is intended for health care professionals and providers only. The information contained in this publication, including text, graphics and images, is for informational purposes only and is not intended to be a substitute for professional medical advice. Bryn Mawr Communications LLC, via its Editors and the Publisher, accepts no responsibility for any injury or damage to persons or property occasioned through the implementation of any ideas or use of any product described herein. While great care is taken by the Publisher and Editors to ensure that all information is accurate, it is recommended that readers seek independent verification of advice on drug or other product usage, surgical techniques and clinical processes prior to their use. The opinions expressed in this publication are those of the authors and are not attributable to the sponsors, the publication or the Editorial Board. References made in articles may indicate uses of medical equipment or drugs at dosages, for periods of time and in combinations not included in the current prescribing information. Inclusion of advertising material in this publication, or in supplements thereof, does not constitute any representation or guarantee by Bryn Mawr Communications LLC of the quality of such products or of the claims made by the manufacturers.

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

For vision and anatomic outcomes

EYLEA Is the #1 Prescribed Anti-VEGF FDA Approved for DME[1,*]

*IQVIA U.S. Medical Claims Data: number of injections administered from Q4 2020 through Q3 2021; Data on file.

Established efficacy data

Proven **vision and anatomic outcomes** in DME[1,2]

Demonstrated safety profile

Evaluated in **over 850 patients** across DME pivotal studies[1]

Real-world experience

More than 57 million doses administered worldwide since launch across all indications[1,3]

Broad market access

82% of lives with DME have access to EYLEA first line with **no step edit** required[1,†]

†Data represent payers across the following channels as of November 2022: Medicare Part B, Commercial, Medicare Advantage, and VA. Individual patient coverage is subject to patient's specific plan.

FIND OUT MORE
at hcp.eylea.us

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

- 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. February 2023. **2.** Brown DM, Schmidt-Erfurth U, Do DV, et al. Intravitreal aflibercept for diabetic macular edema: 100-week results from the VISTA and VIVID studies. *Ophthalmology.* 2015;122(10):2044-2052. doi:10.1016/j.ophtha.2015.06.017 **3.** Data on file. Regeneron Pharmaceuticals, Inc.

REGENERON®

777 Old Saw Mill River Road, Tarrytown, NY 10591 02/2023 EYL.23.02.0167

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.

5.4 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 (5.4)*]

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 adult 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).

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 adult patients 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 in adult patients 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 have been demonstrated in two clinical studies of pre-term infants with ROP. These two studies randomized pre-term infants between initial treatment with EYLEA or laser. Efficacy of each treatment is supported by the demonstration of a clinical course which was better than would have been expected without treatment.

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.

10 OVERDOSAGE
Overdosing with increased injection volume may increase intraocular pressure. Therefore, in case of overdosage, intraocular pressure should be monitored and if deemed necessary by the treating physician, adequate treatment should be initiated.

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

Issue Date: 02/2023
Initial U.S. Approval: 2011

Based on the February 2023 EYLEA® (aflibercept) Injection full Prescribing Information.

EYL.23.02.0006

DON'T FORGET ABOUT DIABETES


This summer has been a hotbed of activity in the retina space, and geographic atrophy (GA) has taken center stage. We know that this is the diabetes issue, and we will get to that, but we would be remiss if we didn't spend a few minutes discussing the new kids on the block. We now have two therapies, pegcetacoplan (Syfovre, Apellis) and avacincaptad pegol (Izervay, Iveric Bio/Astellas), for the treatment of GA, a condition that previously had no therapeutic options. These approvals mean that we have important—and careful—conversations ahead of us with our patients with GA.

A show of hands at the annual American Society of Retina Specialists (ASRS) meeting revealed that nearly a third of a packed conference room had already started treating patients with GA. However, it's been a rocky start to the era of GA therapy, considering that, at the time of the meeting, there were seven cases of occlusive retinal vasculitis after the injection of pegcetacoplan presented by the Research and Safety in Therapeutics committee of the ASRS. Of those ASRS attendees who said they had already treated patients, at least half, if not more, also indicated that they planned to ease off treatment until more safety information becomes available. With avacincaptad pegol entering the market in August, the clinical decisions have only gotten more challenging.

It's exciting, for sure. Our field is abuzz with excitement, speculation, conversations, and concerns.

Amid the hubbub, some of our other bread-and-butter clinical scenarios, like diabetic eye disease, seem to have taken a back seat in our conversations. Treating diabetic retinopathy (DR) isn't as novel or controversial as GA therapy, but it's a critical topic that deserves our attention. We also have a few advances to spice up our DR treatment paradigm, including the newly FDA-approved 8 mg aflibercept (Eylea HD, Regeneron), which may extend therapy for some patients out to 16 weeks.[1]

Just a few months ago, authors published updated DR prevalence numbers in *JAMA Ophthalmology*, and the statistics are daunting.[2] As of 2021, an estimated 9.6 million people in the United States have DR—a whopping 26.43% of patients with diabetes. Of those patients with DR, nearly 2 million (5.06%) already have vision-threatening disease.[2] The study authors note that these numbers have skyrocketed since we last checked the prevalence in 2004. Back then, researchers estimated that 10.2 million US adults at least 40 years of age had diabetes—now, we have almost as many with DR alone.[3] In addition, just shy of 900,000 patients had vision-threatening DR in 2004, and that number is now approaching 2 million.[3] Scary stuff.

What can we—the clinicians who see these patients after the damage has already been done—do to help? The first is awareness. The author of the *JAMA Ophthalmology* invited commentary, Xiangrong Kong, MD, at Wilmer Eye Insitute, uses the appropriate term *pandemic* to describe what we are dealing with.[4] However, after the COVID-19 pandemic, the term has lost much of its oomph, even though COVID-19 affected more than 700 million people globally and led to nearly 7 million deaths.[5] We do wonder what would happen if we started telling our patients with diabetes that they are part of a long-standing pandemic. Maybe that type of language would help them better understand the seriousness of their diagnosis and the importance of adhering to treatment.

We probably aren't going to start tossing around the term *pandemic* every time we see a patient with DR, but there are many simple way to affect change in our clinics. In one of this issue's featured articles, Brittany Long, BS, and Allison Menezes, MD, suggest that retina specialists can spend 2 minutes discussing healthy eating habits and help more than 20% of patients improve their diets and glycemic control. Other authors share pearls for improved diagnostics with ultra-widefield imaging, approaches for medical and surgical treatment, and tips for identifying rare cases of maturity-onset diabetes of the young.

Taken together, these articles are designed to help refocus our attention on the pandemic that has plagued our offices for decades. An estimated 1.49 million people have late-stage AMD (wet AMD or GA).[6] We know that this is a gross underrepresentation of the population at large, and it is an essential population to serve and treat, but it's still a far cry from the 9.6 million patients with DR.[2] We must remain diligent and work hard to screen, educate, and treat patients with diabetes—to get the pandemic under control, once and for all. ■

1. FDA Approves Regeneron's High-Dose Aflibercept, Eylea HD [press release]. Eyewire+. August 19, 2023. Accessed August 21, 2023. eyewire.news/news/fda-approves-regenerons-high-dose-aflibercept-eylea-hd
2. Lundeen EA, Burke-Conte Z, Rein DB, et al. Prevalence of diabetic retinopathy in the US in 2021 [published online ahead of print June 15, 2023]. *JAMA Ophthalmol*.
3. The Eye Diseases Prevalence Research Group. The prevalence of diabetic retinopathy among adults in the United States. *Arch Ophthalmol*. 2004;122(4):552-563.
4. Kong X. Diabetic retinopathy in the US–Where we are now and what is next [published online ahead of print June 15, 2023]. *JAMA Ophthalmol*.
5. WHO Coronavirus (COVID-19) Dashboard. Updated August 13,2023. Accessed August 21, 2023. covid19.who.int
6. Rein DB, Wittenborn JS, Burke-Conte Z, et al. Prevalence of age-related macular degeneration in the US in 2019. *JAMA Ophthalmol*. 2022;140(12):1202-1208.

ALLEN C. HO, MD
CHIEF MEDICAL EDITOR

ROBERT L. AVERY, MD
ASSOCIATE MEDICAL EDITOR

SYFOVRE®
(pegcetacoplan injection)
15 mg / 0.1 mL

GA unravels so much

Save retinal tissue by slowing progression[1-3]

INDICATION

SYFOVRE® (pegcetacoplan injection) is indicated for the treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD).

IMPORTANT SAFETY INFORMATION

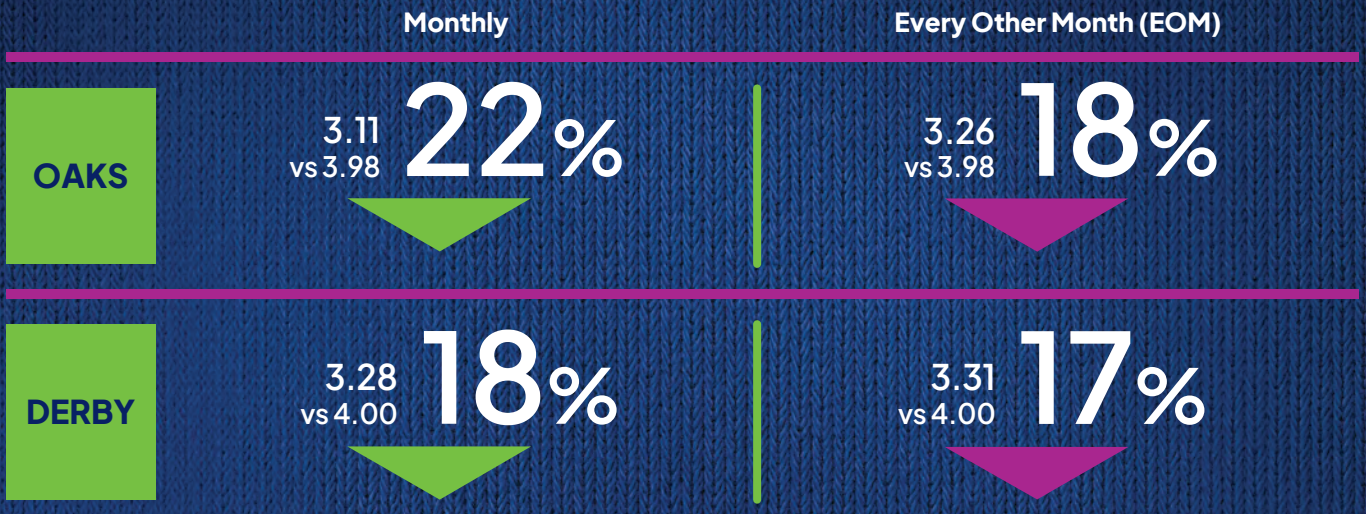
CONTRAINDICATIONS

- SYFOVRE is contraindicated in patients with ocular or periocular infections, and in patients with active intraocular inflammation

WARNINGS AND PRECAUTIONS

- **Endophthalmitis and Retinal Detachments**
  - Intravitreal injections, including those with SYFOVRE, may be associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering SYFOVRE to minimize the risk of endophthalmitis. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately.
- **Neovascular AMD**
  - In clinical trials, use of SYFOVRE was associated with increased rates of neovascular (wet) AMD or choroidal neovascularization (12% when administered monthly, 7% when administered every other month and 3% in the control group) by Month 24. Patients receiving SYFOVRE should be monitored for signs of neovascular AMD. In case anti-Vascular Endothelial Growth Factor (anti-VEGF) is required, it should be given separately from SYFOVRE administration.
- **Intraocular Inflammation**
  - In clinical trials, use of SYFOVRE was associated with episodes of intraocular inflammation including: vitritis, vitreal cells, iridocyclitis, uveitis, anterior chamber cells, iritis, and anterior chamber flare. After inflammation resolves, patients may resume treatment with SYFOVRE.

SYFOVRE achieved continuous reductions in mean lesion growth rate* (mm^2) vs sham pooled from baseline to Month 24[1]



SE in trials (monthly, EOM, sham pooled): OAKS: 0.15, 0.13, 0.14; DERBY: 0.13, 0.13, 0.17.

*Slope for baseline to Month 24 is an average of slope of baseline to Month 6, Month 6 to Month 12, Month 12 to Month 18, and Month 18 to Month 24.[1]
Based on a mixed effects model for repeated measures assuming a piecewise linear trend in time with knots at Month 6, Month 12, and Month 18.[1]
GA=geographic atrophy; SE=standard error.

Explore the long-term data

IMPORTANT SAFETY INFORMATION (CONT'D)

WARNINGS AND PRECAUTIONS (CONT'D)

- **Increased Intraocular Pressure**
  - Acute increase in IOP may occur within minutes of any intravitreal injection, including with SYFOVRE. Perfusion of the optic nerve head should be monitored following the injection and managed as needed.

ADVERSE REACTIONS

- Most common adverse reactions (incidence ≥5%) are ocular discomfort, neovascular age-related macular degeneration, vitreous floaters, conjunctival hemorrhage.

Trial Design: SYFOVRE safety and efficacy were assessed in OAKS (N=637) and DERBY (N=621), multi-center, 24-month, Phase 3, randomized, double-masked trials. Patients with GA (atrophic nonexudative age-related macular degeneration), with or without subfoveal involvement, secondary to AMD were randomly assigned (2:2:1:1) to receive 15 mg/0.1 mL intravitreal SYFOVRE monthly, SYFOVRE EOM, sham monthly, or sham EOM for 24 months. Change from baseline in the total area of GA lesions in the study eye (mm^2) was measured by fundus autofluorescence (FAF).[1,4]

References: 1. SYFOVRE (pegcetacoplan injection) [package insert]. Waltham, MA: Apellis Pharmaceuticals, Inc.; 2023. **2.** Pfau M, von der Emde L, de Sisternes L, et al. Progression of photoreceptor degeneration in geographic atrophy secondary to age-related macular degeneration. *JAMA Ophthalmol*. 2020;138(10):1026–1034. **3.** Bird AC, Phillips RL, Hageman GS. Geographic atrophy: a histopathological assessment. *JAMA Ophthalmol*. 2014;132(3):338–345. **4.** Data on file. Apellis Pharmaceuticals, Inc.

Please see Brief Summary of Prescribing Information for SYFOVRE on the adjacent page.

Apellis

SYFOVRE® (pegcetacoplan injection), for intravitreal use
BRIEF SUMMARY OF PRESCRIBING INFORMATION
Please see SYFOVRE full Prescribing Information for details.

INDICATIONS AND USAGE

SYFOVRE is indicated for the treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD).

CONTRAINDICATIONS

Ocular or Periocular Infections

SYFOVRE is contraindicated in patients with ocular or periocular infections.

Active Intraocular Inflammation

SYFOVRE is contraindicated in patients with active intraocular inflammation.

WARNINGS AND PRECAUTIONS

Endophthalmitis and Retinal Detachments

Intravitreal injections, including those with SYFOVRE, may be associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering SYFOVRE in order to minimize the risk of endophthalmitis. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately.

Neovascular AMD

In clinical trials, use of SYFOVRE was associated with increased rates of neovascular (wet) AMD or choroidal neovascularization (12% when administered monthly, 7% when administered every other month and 3% in the control group) by Month 24. Patients receiving SYFOVRE should be monitored for signs of neovascular AMD. In case anti-Vascular Endothelial Growth Factor (anti-VEGF) is required, it should be given separately from SYFOVRE administration.

Intraocular Inflammation

In clinical trials, use of SYFOVRE was associated with episodes of intraocular inflammation including: vitritis, vitreal cells, iridocyclitis, uveitis, anterior chamber cells, iritis, and anterior chamber flare. After inflammation resolves patients may resume treatment with SYFOVRE.

Increased Intraocular Pressure

Acute increase in IOP may occur within minutes of any intravitreal injection, including with SYFOVRE. Perfusion of the optic nerve head should be monitored following the injection and managed as needed.

ADVERSE REACTIONS

Clinical Trials Experience

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

A total of 839 patients with GA in two Phase 3 studies (OAKS and DERBY) were treated with intravitreal SYFOVRE, 15 mg (0.1 mL of 150 mg/mL solution). Four hundred nineteen (419) of these patients were treated in the affected eye monthly and 420 were treated in the affected eye every other month. Four hundred seventeen (417) patients were assigned to sham.

The most common adverse reactions (≥5%) reported in patients receiving SYFOVRE were ocular discomfort, neovascular age-related macular degeneration, vitreous floaters, and conjunctival hemorrhage.

Table 1: Adverse Reactions in Study Eye Reported in ≥2% of Patients Treated with SYFOVRE Through Month 24 in Studies OAKS and DERBY

Adverse Reactions	PM (N = 419) %	PEOM (N = 420) %	Sham Pooled (N = 417) %
Ocular discomfort*	13	10	11
Neovascular age-related macular degeneration*	12	7	3
Vitreous floaters	10	7	1
Conjunctival hemorrhage	8	8	4
Vitreous detachment	4	6	3
Retinal hemorrhage	4	5	3
Punctate keratitis*	5	3	<1
Posterior capsule opacification	4	4	3
Intraocular inflammation*	4	2	<1
Intraocular pressure increased	2	3	<1

PM: SYFOVRE monthly; PEOM: SYFOVRE every other month

*The following reported terms were combined:

Ocular discomfort included: eye pain, eye irritation, foreign body sensation in eyes, ocular discomfort, abnormal sensation in eye

Neovascular age-related macular degeneration included: exudative age-related macular degeneration, choroidal neovascularization

Punctate keratitis included: punctate keratitis, keratitis

Intraocular inflammation included: vitritis, vitreal cells, iridocyclitis, uveitis, anterior chamber cells, iritis, anterior chamber flare

Endophthalmitis, retinal detachment, hyphema and retinal tears were reported in less than 1% of patients. Optic ischemic neuropathy was reported in 1.7% of patients treated monthly, 0.2% of patients treated every other month and 0.0% of patients assigned to sham. Deaths were reported in 6.7% of patients treated monthly, 3.6% of patients treated every other month and 3.8% of patients assigned to sham. The rates and causes of death were consistent with the elderly study population.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

There are no adequate and well-controlled studies of SYFOVRE administration in pregnant women to inform a drug-associated risk. The use of SYFOVRE may be considered following an assessment of the risks and benefits.

Systemic exposure of SYFOVRE following ocular administration is low. Subcutaneous administration of pegcetacoplan to pregnant monkeys from the mid gestation period through birth resulted in increased incidences of abortions and stillbirths at systemic exposures 1040-fold higher than that observed in humans at the maximum recommended human ophthalmic dose (MRHOD) of SYFOVRE (based on the area under the curve (AUC) systemically measured levels). No adverse maternal or fetal effects were observed in monkeys at systemic exposures approximately 470-fold higher than that observed in humans at the MRHOD.

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.

Lactation

Risk Summary

It is not known whether intravitreal administered pegcetacoplan is secreted in human milk or whether there is potential for absorption and harm to the infant. Animal data suggest that the risk of clinically relevant exposure to the infant following maternal intravitreal treatment is minimal. 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 SYFOVRE is administered to a nursing woman.

Females and Males of Reproductive Potential

Contraception

Females: It is recommended that women of childbearing potential use effective contraception methods to prevent pregnancy during treatment with intravitreal pegcetacoplan. Advise female patients of reproductive potential to use effective contraception during treatment with SYFOVRE and for 40 days after the last dose. For women planning to become pregnant, the use of SYFOVRE may be considered following an assessment of the risks and benefits.

Pediatric Use

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

Geriatric Use

In clinical studies, approximately 97% (813/839) of patients randomized to treatment with SYFOVRE were ≥ 65 years of age and approximately 72% (607/839) were ≥ 75 years of age. No significant differences in efficacy or safety were seen with increasing age in these studies. No dosage regimen adjustment is recommended based on age.

PATIENT COUNSELING INFORMATION

Advise patients that following SYFOVRE administration, patients are at risk of developing neovascular AMD, endophthalmitis, and retinal detachments. If the eye becomes red, sensitive to light, painful, or if a patient develops any change in vision such as flashing lights, blurred vision or metamorphopsia, instruct the patient to seek immediate care from an ophthalmologist.

Patients may experience temporary visual disturbances associated either with the intravitreal injection with SYFOVRE or the eye examination. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

Manufactured for:
Apellis Pharmaceuticals, Inc.
100 Fifth Avenue
Waltham, MA 02451

SYF-PI-17Feb2023-1.0

7/23 US-PEGGA-2200163 v3.0

TABLE OF CONTENTS

RT NEWS

SEPTEMBER 2023

VOL. 18, NO. 6 | RETINATODAY.COM

STUDY HIGHLIGHTS EFFICACY OF SCLERAL BUCKLE REMOVAL

Researchers recently looked at the outcomes of scleral buckle (SB) removal and found that the procedure can provide symptomatic relief with a low risk of redetachment.[1] The retrospective observational study included a review of 86 cases with a history of SB removal seen in a large academic center and a private retina-only practice over a span of 20 years. The primary outcomes included patient symptoms before SB removal, indications for removal, resolution of symptoms following removal, the rate of redetachment, and the rate of subsequent ocular surgery. There were several key findings, including the following:

- **Causes for removal:** The most significant reasons for SB removal were exposure (61.63%), infection (20.93%), and diplopia/strabismus (19.77%).
- **Symptoms and relief:** Most patients (65.12%) reported experiencing pain and discomfort before the procedure, 22.09% presented with diplopia, and 18.06% had drainage/discharge. Post removal, 86.59% of these patients experienced relief of their symptoms.
- **Redetachment:** Of all eyes with at least 1 year of follow-up post-SB removal, four presented with a redetachment, requiring surgical intervention.
- **Additional surgeries:** Nine percent of the patients needed strabismus or oculoplastic procedures after the SB removal.

The study showed that SB removal offers a considerable rate of symptom relief and carries a low risk of redetachment. However, the researchers noted that patients undergoing SB removal should be closely monitored to check for any signs of recurrent retinal detachments.

1. Patel P, Heo JY, Shepherd EA, Chaturvedi V. Scleral buckle removal: long-term patient outcomes [published online ahead of print July 31, 2023]. *Ophthalmol Retina*.

FDA APPROVES IVERIC BIO'S TREATMENT FOR GEOGRAPHIC ATROPHY

Iveric Bio, an Astellas company, received FDA approval for its avacincaptad pegol intravitreal solution (Izervay), for the treatment of geographic atrophy (GA) secondary to AMD.[1] The approval is based on the results of the phase 3 GATHER1 and GATHER2 clinical trials, which showed positive safety and efficacy outcomes. In these trials, patients saw a significant decline in GA growth rates compared with sham, with up to a 35% reduction in the first year of treatment.

Avacincaptad pegol is approved for monthly treatment (28 ± 7 days) for up to 12 months. In addition, the pending 24-month data will include every-other-month dosing.[1] The most common adverse reactions include conjunctival hemorrhage (13%), increased IOP (9%), and blurred vision (8%). Notably, the GATHER program showed no cases of retinal vasculitis at the 12-month trial endpoints. The drug comes with a warning to monitor patients for endophthalmitis, retinal detachments, and conversion to wet AMD.[2]

In an interview with EyewireTV, Iveric Bio President Pravin Dugel, MD, said that each vial will be priced at $2,100, and the company is planning programs to assist patients who might find it out of reach financially.[1]

1. Iveric Bio receives FDA approval for Izervay for geographic atrophy [press release]. EyeWire+. August 5, 2023. Accessed August 14, 2023. eyewire.news/news/iveric-bio-receives-fda-approval-for-izervay-for-geographic-atrophy
2. Izervay prescribing information. Iveric Bio. August 2023. ivericbio.com/wp-content/uploads/IZERVAY-avacincaptad-pegol-intravitreal-solution-PI_Final_8.4.23.pdf

FDA APPROVES HIGH-DOSE AFLIBERCEPT

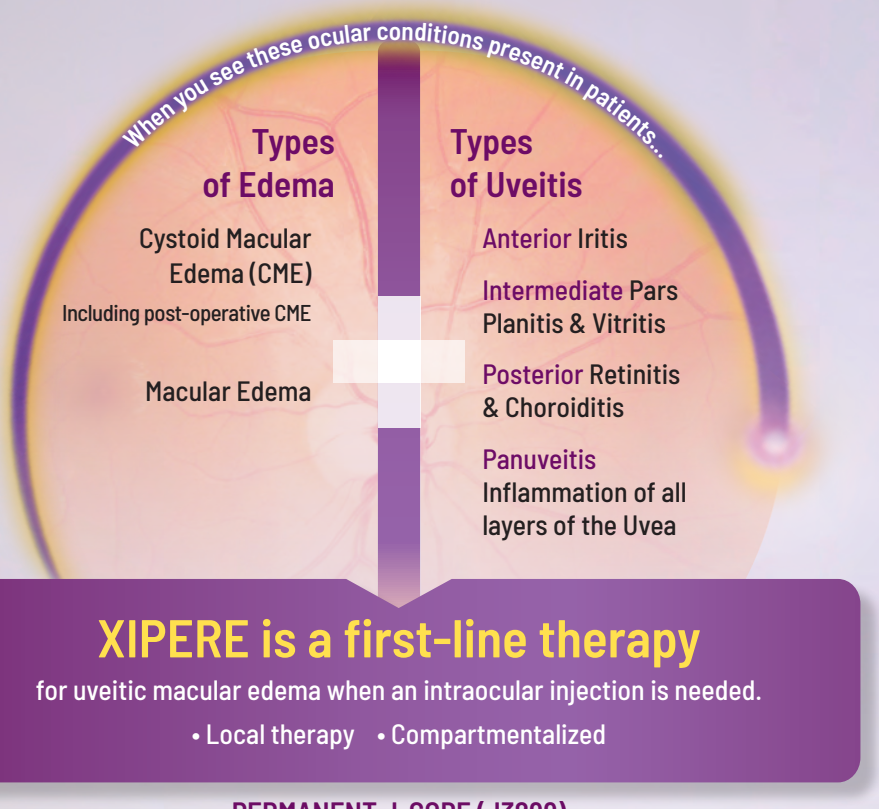
Approximately 1 month after declining to approve 8 mg aflibercept (Eylea HD, Regeneron) due to inspection issues at a third-party filler, the FDA approved high-dose aflibercept for wet AMD, diabetic macular edema (DME), and diabetic retinopathy (DR). The recommended treatment is every 4 weeks for the first 3 months followed by extension to every 8 to 16 weeks for patients with wet AMD or DME and every 8 to 12 weeks for those with DR.[1]

Per single-use vial, the drug will have a wholesale acquisition cost of $2,625, which, when used as indicated, is close to (if not lower than) the cost of 2 mg aflibercept (Eylea, Regeneron), according to the company.[1]

The approval is based on the 48-week data from the PULSAR and PHOTON trials that compared 8 mg aflibercept

FOR TREATMENT OF UVEITIC MACULAR EDEMA

Recognizing the XIPERE® Patient in Your Practice



XIPERE is a first-line therapy

for uveitic macular edema when an intraocular injection is needed.

• Local therapy • Compartmentalized

PERMANENT J-CODE (J3299)

INDICATION

XIPERE® (triamcinolone acetonide injectable suspension) for suprachoroidal use is a corticosteroid indicated for the treatment of macular edema associated with uveitis.

IMPORTANT SAFETY INFORMATION

Patients should be monitored following injection for elevated intraocular pressure. See Dosage and Administration instructions in full Prescribing Information.

- XIPERE® is contraindicated in patients with **active or suspected ocular or periocular infections** including most viral diseases of the cornea and conjunctiva, including active epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections, and fungal diseases.
- XIPERE® is contraindicated in patients with known **hypersensitivity to triamcinolone acetonide** or any other components of this product.
- Use of corticosteroids may produce cataracts, increased intraocular pressure, and glaucoma. Use of corticosteroids may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses, and should be used cautiously in patients with a history of ocular herpes simplex.
- Hypothalamic-pituitary-adrenal (HPA) axis suppression, Cushing's syndrome, and hyperglycemia can occur following administration of a corticosteroid. Monitor patients for these conditions with chronic use.
- In controlled studies, the most common ocular adverse reactions were increased ocular pressure, non-acute (14%), eye pain, non-acute (12%), cataract (7%), increased intraocular pressure, acute (6%), vitreous detachment (5%), injection site pain (4%), conjunctival hemorrhage (4%), visual acuity reduced (4%), dry eye (3%), eye pain, acute (3%), photophobia (3%), and vitreous floaters (3%), and in 2% of patients: uveitis, conjunctival hyperaemia, punctate keratitis, conjunctival oedema, meibomianitis, anterior capsule contraction, chalazion, eye irritation, eye pruritus, eyelid ptosis, photopsia, and vision blurred.
  The most common non-ocular adverse event was headache (5%).
- Corticosteroids should be used during pregnancy or nursing only if the potential benefit justifies the potential risk to the fetus or nursing infant.

To report SUSPECTED ADVERSE REACTIONS, contact Bausch + Lomb at 1-800-321-4576 or FDA at 1-800-FDA-1088 or visit www.fda.gov/medwatch.

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

BAUSCH + LOMB

XIPERE® (triamcinolone acetonide injectable suspension) 40 mg/mL

BRIEF SUMMARY OF PRESCRIBING INFORMATION
This Brief Summary does not include all the information needed to use XIPERE™ safely and effectively. See full Prescribing Information for XIPERE™.

XIPERE™ (triamcinolone acetonide injectable suspension), for suprachoroidal use

Initial U.S. Approval: 1957

INDICATIONS AND USAGE

XIPERE™ (triamcinolone acetonide injectable suspension) 40 mg/mL is indicated for the treatment of macular edema associated with uveitis.

CONTRAINDICATIONS

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

4.2 Hypersensitivity XIPERE™ is contraindicated in patients with known hypersensitivity to triamcinolone acetonide or any other components of this product.

WARNINGS AND PRECAUTIONS

5.1 Potential Corticosteroid-Related Effects Use of corticosteroids may produce cataracts, increased intraocular pressure, and glaucoma. Use of corticosteroids may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses. Corticosteroids should be used cautiously in patients with a history of ocular herpes simplex. Corticosteroids should not be used in patients with active ocular herpes simplex.

5.2 Alterations in Endocrine Function Hypothalamic-pituitary-adrenal (HPA) axis suppression, Cushing's syndrome, and hyperglycemia can occur following administration of a corticosteroid. Monitor patients for these conditions with chronic use. Corticosteroids can produce reversible HPA axis suppression with the potential for glucocorticosteroid insufficiency after withdrawal of treatment. Drug induced secondary adrenocortical insufficiency may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted. Metabolic clearance of corticosteroids is decreased in hypothyroid patients and increased in hyperthyroid patients. Changes in thyroid status of the patient may necessitate adjustment in dosage.

ADVERSE REACTIONS

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 the clinical trials of another drug and may not reflect the rates observed in practice. XIPERE™ was studied in a multicenter, randomized, sham-controlled, double-masked study in patients with macular edema associated with uveitis. Table 1 summarizes data available from the clinical trial for XIPERE™ treated patients and control patients. The most common ocular (study eye) adverse reactions occurring in ≥ 2% of patients and nonocular adverse reactions occurring in ≥ 5% of patients are shown in Table 1.

Adverse Reaction	XIPERE™ (N = 96) n (%)	Control (N = 64) n (%)
Ocular		
Increased intraocular pressure, non-acute [a, b]	13 (14%)	9 (14%)
Eye pain, non-acute [b]	11 (12%)	0
Cataract [c]	7 (7%)	4 (6%)
Increased intraocular pressure, acute [a, d]	6 (6%)	0
Vitreous detachment	5 (5%)	1 (2%)
Injection site pain	4 (4%)	2 (3%)
Conjunctival haemorrhage	4 (4%)	2 (3%)
Visual acuity reduced	4 (4%)	1 (2%)
Dry eye	3 (3%)	1 (2%)
Eye pain, acute [d]	3 (3%)	0
Photophobia	3 (3%)	0
Vitreous floaters	3 (3%)	0
Uveitis	2 (2%)	7 (11%)
Conjunctival hyperaemia	2 (2%)	2 (3%)
Punctate keratitis	2 (2%)	1 (2%)
Conjunctival oedema	2 (2%)	0
Meibomianitis	2 (2%)	0
Anterior capsule contraction	2 (2%)	0
Chalazion	2 (2%)	0
Eye irritation	2 (2%)	0
Eye pruritus	2 (2%)	0
Eyelid ptosis	2 (2%)	0
Photopsia	2 (2%)	0
Vision blurred	2 (2%)	0
Non-ocular		
Headache	5 (5%)	2 (3%)

[a] Includes intraocular pressure increased and ocular hypertension [b] Defined as not occurring on the day of the injection procedure, or occurring on the day of the injection procedure and not resolving the same day [c] Includes cataract, cataract cortical, and cataract subcapsular [d] Defined as occurring on the day of the injection procedure and resolving the same day

USE IN SPECIAL POPULATIONS

8.1 Pregnancy Risk Summary There are no adequate and well-controlled studies with XIPERE™ in pregnant women to inform drug-associated risks. In animal reproductive studies from the published literature, topical ocular administration of corticosteroids has been shown to produce teratogenicity at clinically relevant doses. There is negligible systemic XIPERE™ exposure following suprachoroidal injection [see Clinical Pharmacology (12.3)]. Corticosteroids 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. In the U.S. general population, the estimated risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. Animal Data Animal reproduction studies using XIPERE™ have not been conducted. In animal reproductive studies from the published literature, topical ocular administration of corticosteroids to pregnant mice and rabbits during organogenesis has been shown to produce cleft palate, embryofetal death, herniated abdominal viscera, hypoplastic kidneys and craniofacial malformations.

8.2 Lactation Risk Summary It is not known whether ocular administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for XIPERE™ and any potential adverse effects on the breastfed infant from XIPERE™. There are no data on the effects of XIPERE™ on milk production.

8.4 Pediatric Use Safety and effectiveness of XIPERE™ 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 following XIPERE™ administration.

NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis No information is available on the carcinogenic potential of triamcinolone acetonide.

Mutagenesis No information is available on the mutagenic potential of triamcinolone acetonide.

Fertility No information is available on the effect of triamcinolone acetonide on fertility.

Manufactured for: Clearside Biomedical, Inc.
900 North Point Parkway, Suite 200
Alpharetta, GA 30005 www.clearsidebio.com/patents

Revised 10/2021 XIP.0015.USA.22 Issued: 02/2022

with 2 mg aflibercept in patients with wet AMD and DME, respectively. Both trials met their primary endpoints, with high-dose aflibercept demonstrating noninferior vision gains with 12- and 16-week dosing after the initial loading doses compared with 8-week dosing with 2 mg aflibercept after the initial monthly doses (3 months in PULSAR and 5 months in PHOTON). Most patients randomized to 12- or 16-week dosing with 8 mg aflibercept were able to maintain those dosing intervals. Safety was similar to that found with 2 mg aflibercept.[1]

1. FDA approves Regeneron's high-dose aflibercept, Eylea HD [press release]. Eyewire+. August 19, 2023. Accessed August 21, 2023. eyewire.news/news/fda-approves-regenerons-high-dose-aflibercept-eylea-hd

RESEARCHERS IDENTIFY BIOMARKERS FOR AMD LESION CHANGES

A recent study analyzing the changes in lesions related to incomplete retinal pigment epithelium (RPE) and outer retinal atrophy and complete RPE and outer retinal atrophy identified several biomarkers of change in patients with intermediate AMD.[1]

The study found that choroidal hypertransmission, external limiting membrane disruption, outer plexiform layer/inner nuclear layer subsidence, and a wedge-shaped band could serve as reliable biomarkers. However, not all OCT features correlated with disease progression. Notably, choroidal hypertransmission showed the highest agreement, while RPE attenuation/disruption had the least agreement.

The study included OCT images from patients in the Proxima B clinical trial, specifically those with GA in one eye and intermediate AMD in the other. Junior and senior readers examined nine early atrophic features, quantifying seven of them with a defined tolerance of 50 µm. The main outcomes included inter-reader agreement for qualitative and quantitative measurements and the progression of the lesion features over time.

1. Schmitz-Valckenberg S, Saßmannshausen M, Braun M, et al. Inter-reader agreement and longitudinal progression of incomplete/complete retinal pigment epithelium and outer retinal atrophy in AMD [published online ahead of print July 28, 2023]. *Ophthalmol Retina*.

UPDATE ON RETINAL VASCULITIS EVENTS AFTER GA THERAPY

Apellis Pharmaceuticals provided an update on the rare events of retinal vasculitis that have been reported with treatment of GA with pegcetacoplan injection (Syfovre). Apellis' internal safety committee identified eight events of retinal vasculitis after injection, five of which are occlusive.[1]

The ongoing review of these safety issues has identified "internal structural variations" in the 19-gauge filter needle that was included in certain injection kits.[1]

The company has not established a causal relationship between these variations and the rare adverse events. Still, the company recommends clinicians discontinue use of injection kits that include the 19-gauge filter needle and instead use the kits that include the 18-gauge filter needle. Moving forward, Apellis is only supplying 18-gauge filter needles with its injection kits.[1]

During the American Society of Retina Specialists (ASRS) annual meeting, Andre J. Witkin, MD, FASRS, chair-elect of the ASRS Research and Safety in Therapeutics (ReST) Committee, reviewed cases of intraocular inflammation after intravitreal drug injections. His presentation included a brief review of the seven cases of retinal vasculitis following intravitreal injection of pegcetacoplan. Members were encouraged to continue to report adverse events to the ReST committee for evaluation.[2] ■

1. Apellis provides updates on injection kits and rare safety events with GA drug Syfovre [press release]. Eyewire+. August 23, 2023. Accessed August 23, 2023. eyewire.news/news/apellis-provides-updates-on-injection-kits-and-rare-safety-events-with-ga-drug-syfovre
2. American Society of Retina Specialists. Adverse events reporting. Accessed August 15, 2023. www.asrs.org/clinical/adverse-events-reporting

Eyewire+ Pharma Update

- The LEOPARD clinical trial of OCS-01 (Oculis), a topical formulation of dexamethasone for the treatment of cystoid macular edema, enrolled its first patient. The trial plans to enroll 24 patients for a treatment period of 24 weeks. The 12-week primary endpoints are improvement in central subfield thickness and visual acuity.
- Kodiak Sciences discontinued development of tarcocimab tedromer, an antibody biopolymer conjugate for the treatment of AMD and diabetic macular edema. This decision is based on the drug candidate's failure to reach its primary endpoints in the GLEAM and GLIMMER trials.
- The American Medical Association United States Adopted Names Council approved the nonproprietary drug name *sozinibercept* for Opthea's biologic drug candidate, OPT-302, a recombinant "trap" fusion protein targeting inhibition of VEGF-C and VEGF-D. This drug is currently being investigated in phase 3 clinical trials of wet AMD in combination with standard anti-VEGF-A therapy.
- The FDA granted investigational new drug clearance for a phase 1/2a clinical trial of SKG0106 (Skyline Therapeutics), a recombinant adeno-associated virus-mediated gene therapy for the treatment of wet AMD.
- OcuTerra Therapeutics has now fully enrolled the DR:EAM phase 2 clinical trial of its topically delivered OTT166 eye drop, a small molecule arginylglycylaspartic acid integrin inhibitor for the treatment of moderately severe to severe nonproliferative diabetic retinopathy or mild proliferative diabetic retinopathy with minimal vision loss. The trial is evaluating the safety and efficacy of a high and low dose of OTT166 compared with vehicle.

Want more retina news from *Eyewire+*?

WHERE IT ALL BEGAN

As a child, Dr. Mackin was captivated by her parents' clinical and research work—her father is an orthopedic surgeon, and her mother is a clinical pathologist. She was determined to one day be a physician, too. She received a bachelor's degree with distinction in biochemistry and integrative physiology and attended medical school at the University of Colorado. Several of Dr. Mackin's core clinical rotations took place in underserved rural counties in south-central Colorado, which gave her a great appreciation for the desperate need for care among rural communities.

Dr. Mackin's Advice:
Look for a practice where the clinical and administrative teams share your goals and strive to facilitate your efforts to practice ethically, effectively, and efficiently.

HER PATH TO RETINA

Dr. Mackin quickly realized that ophthalmology was her career aspiration during medical school clinical rotations. She remembers the feeling of curiosity and awe when examining the eye in search of the answer to the patient's symptoms; she still feels this way when examining a patient. She helped to research novel therapeutic approaches to AMD with her mentor, Jeffrey Olson, MD. This was only the beginning of her discovery that exciting therapies and diagnostic techniques play an integral role in the everyday practice of vitreoretinal surgery. Once in residency at the University of Colorado, Dr. Mackin was drawn to the complex and diverse pathology of retinal diseases. Residency at UCHealth Sue Anschutz-Rodgers Eye Center exposed her to the full gamut of vitreoretinal pathologies, including inherited retinal disease, pediatrics, ocular oncology, and uveitis, confirming her decision to dedicate her career to the field of retina. Dr. Mackin matched at her number one program, the Snyder Family Endowed Fellowship in vitreoretinal surgery at the University of Chicago.

SUPPORT ALONG THE WAY

Dr. Mackin is forever grateful to her residency and fellowship mentors for teaching her invaluable clinical and surgical skills and providing guidance and support on her professional journey. She would like to extend a special thank you to her fellowship director, Seenu M. Hariprasad, MD, for teaching the medical side of patient care and emphasizing efficiency and cost-consciousness. Every time Dr. Mackin is in the OR, she hears Dr. Hariprasad's voice, urging her to make every second of the surgery count. Dr. Hariprasad also taught her the importance of industry collaboration. Working closely with industry allows clinicians to bring the interests of patients to the forefront of clinical discovery and ensures that everyday clinical experiences can lead to safer and more effective therapies for the community at large.

AN EXPERIENCE TO REMEMBER

During Dr. Mackin's first night of attending call, she took care of a monocular patient with an acute retinal detachment in his good eye. The surgery went well, and the patient regained his sight and independence. She was honored to use her skills to make such a difference and provide sight-saving care at that time and every day since. Many of her patients travel more than an hour to see a retina specialist, and it is rewarding to care for a community in need. ■

Anna Mackin, MD, is a vitreoretinal surgeon at Vistar Eye Center, a multispecialty ophthalmology practice in Roanoke, Virginia. She cares for urban and rural communities within a large geographic area. Vistar Eye Center is affiliated with Virginia Tech Carilion School of Medicine and frequently has medical students rotate in the clinic and OR. Dr. Mackin has no relevant financial disclosures and can be reached at **anna.g.mackin@gmail.com**.

HIGHLIGHTS FROM THE 22ND DUKE AVS COURSE

Experts from around the world shared clinical pearls on retinal vein occlusion, intraoperative OCT, and more.

BY NITA VALIKODATH, MD, MS; XIAO YI ZHOU, MD; YUXI ZHENG, MD; AND GRANT A. JUSTIN, MD

The Duke Advanced Vitreous Surgery (AVS) Course, initiated by Robert Machemer, MD, boasts a series of excellent lectures and interactive panel discussions with vitreoretinal surgery leaders from all over the world. It takes place every other year in Durham, North Carolina, and is open to all retina specialists. The course places an emphasis on a diverse range of vitreoretinal surgery and medical retina topics, including retinal detachment, novel drugs and devices, trainee presentations, management of intraocular tumors and uveitis, and pediatric retina. Furthermore, the course takes pride in the international diversity of its panel members, this year with faculty from Singapore, Poland, Canada, Brazil, and Croatia. Here, we share key highlights from the meeting, including an update on treatments for retinal vein occlusion (RVO) and intraoperative OCT (iOCT).

RVO UPDATES

Jorge Rocha, MD, PhD, a Retina World Congress board director, traveled from Brazil to present on new concepts in RVO (Figure 1). He started his presentation by highlighting the history of our understanding of RVO and prior treatments, explaining that, in the past, we thought the pathophysiology of RVO was related to either an existing thrombus, an inflammatory process, a structural or anatomic crossing, or some combination of these.

Dr. Rocha then shared past surgical management options for RVO, including arteriovenous sheathotomies to decompress branch RVOs (BRVOs) and manually remove pressure on the vein. He discussed past studies of radial optic neurotomies for the management of central RVO, which were incredibly delicate surgeries with initial data suggesting some positive results.

With the invention of intravitreal anti-VEGF agents, many of these surgeries became less popular. However, Dr. Rocha emphasized that in the RETAIN study looking at outcomes of patients with RVO treated with ranibizumab (Lucentis, Genentech/Roche), 56% still required regular injections at 48 months. His point was that there is still an opportunity to better understand the pathophysiology and improve treatment approaches for RVOs. Unanswered questions remain about why a BRVO sometimes self-resolves, how young patients without atherosclerosis or dyslipidemia develop RVO, and why we rarely find a thrombus on histopathology.

Dr. Rocha proposed that endothelin-1 may play a role in vein dysregulation and explain, in part, the pathophysiology of RVOs. Endothelin-1, typically produced by endothelial cells, is a potent vasoconstrictor that induces growth and migration of cells and regulates the blood-retinal barrier. Several studies have suggested that endothelin-1 is a risk factor for RVOs by inducing vein dysregulation; this makes it a potential target for future treatment of RVOs.

The following discussion was lively regarding whether there is any room for the use of endothelin-1 antagonists currently being used as treatment for other medical conditions, such as pulmonary hypertension, to treat RVOs.

DETAILS ON INTRAOPERATIVE OCT

Lejla Vajzovic, MD, an associate professor with tenure at Duke University and the AVS course director, gave a riveting talk on the evolution of iOCT in macular surgery. She also shed light on the next generation of this revolutionary technology (Figure 2).

DUKE AVS COURSE

Figure 1. Jorge Rocha, MD, PhD, traveled from Brazil to share his expertise in the treatment of RVOs.

Figure 2. Lejla Vajzovic, MD, discussed the growth of iOCT and where the technology is headed in the future.

Figure 3. Thomas Aaberg Jr, MD, provided important clinical pearls, while sharing from what he calls his "graveyard of cases."

Dr. Vajzovic first delved into the history of iOCT. She detailed how this technology evolved from a handheld device to technology that is incorporated into surgical microscopes. She gave a special acknowledgment to Cynthia A. Toth, MD, who is a pioneer in developing this technology. Although significant strides have been made in iOCT, Dr. Vajzovic highlighted some of the limitations that persist with current commercially available devices. For example, these systems predominantly use spectral domain technology, which is slower and yields lower-resolution images compared with swept-source technology. Furthermore, the intricacies of using these devices necessitate the assistance of an additional pair of hands.

Researchers at Duke University have developed a prototype microscope-integrated OCT (MIOCT) that uses swept-source technology. The swept-source MIOCT is considerably faster and has deeper penetration, offering valuable insight into our understanding of the surface of the retina and areas underneath the retina. Dr. Vajzovic shared her experience using this technology, particularly for complex cases. She noted that it is particularly useful in gene therapy delivery cases because she can observe where the fluid is being delivered. She is now working on obtaining volumetric data to quantify the amount of fluid being delivered.

Dr. Vajzovic expresses her optimism for the future of iOCT, emphasizing that commercially available devices are evolving to become more efficient and user-friendly for surgeons. Data provided by iOCT can teach the field so much, similar to what we have gained from OCT in the clinical setting, she said.

CASE COMPENDIUM

Finally, Thomas Aaberg Jr, MD, gave an important and insightful talk that consisted of his graveyard of cases and shared lessons that everyone in the audience could implement into their practices (Figure 3). His talk was truly humbling and reminded us that we are human, and errors will happen. Pearls from his talk included the following:

- Focus during surgery without succumbing to distractions.
- Ensure that you are well-rested.
- Have a supportive environment to help you cope with difficult situations.

The AVS is a fantastic meeting with significant learning opportunities for faculty and fellows. Don't miss the 23rd Duke AVS meeting in 2025! ■

GRANT A. JUSTIN, MD
- Vitreoretinal Surgeon, Research Director, Walter Reed National Military Medical Center, Bethesda, Maryland
- Vitreoretinal Surgery Fellow Alumnus, Duke University Eye Center, Durham, North Carolina
- grant.a.justin@gmail.com
- Financial disclosure: None

NITA VALIKODATH, MD, MS
- Assistant Professor of Ophthalmology, Kellogg Eye Center, University of Michigan, Ann Arbor, Michigan
- Vitreoretinal Surgery Fellow Alumna, Duke University Eye Center, Durham, North Carolina
- nita.valikodath1@gmail.com
- Financial disclosure: None

YUXI ZHENG, MD
- Ophthalmology Resident, PGY4, Duke University Eye Center, Durham, North Carolina
- yuxizhengmd@gmail.com
- Financial disclosure: None

XIAO YI ZHOU, MD
- Vitreoretinal Surgery Fellow, Duke University Eye Center, Durham, North Carolina
- Financial disclosure: None

THE VBS DEBATES IN BRIEF

Presenters battled over the utility of new therapies, technologies, and business models.

BY RACHEL S. MOGIL, MD, AND VIET CHAU, MD

The annual Vit-Buckle Society (VBS) meeting is known for its top-notch education, innovative presentations, and themes. During this year's debates, experts sparred over medical and surgical topics, helping attendees better understand the latest innovations in the field.

SURGICAL DEBATES

Moderated by Joseph M. Coney, MD, FACS, FASRS; Chirag D. Jhaveri, MD; and Katherine E. Talcott, MD, the first round touched on the latest technology and techniques.

Heads-up Displays

The first session discussed the use of 3D heads-up displays in the OR. Opposing views were presented by Jaya B. Kumar, MD, (pro) and Dr. Talcott (con). Dr. Kumar began by explaining that the heads-up surgery systems provide safer illumination of the retina and improved visualization. The displays have excellent resolution and contrast, allow for better posturing, and make switching between surgeons more efficient. Furthermore, it is an excellent educational tool.

According to Dr. Talcott, heads-up displays require headgear and can cause neck pain because the head is constantly turned. Positioning is difficult in a cramped OR, and moving the units between cases can increase OR turnover time. The videos still have some lag also. The numerous color filters are unnecessary, and the colors themselves are oversaturated. She added that the digitized images, while helpful, can compromise the view of the instruments. She noted that viewing the periphery can be challenging, as is depressing for assistants. While 3D heads-up displays offer great views of the macula and are helpful for teaching, Dr. Talcott indicated that they cannot replace standard microscopes just yet.

Polling indicated that the audience agreed with Dr. Kumar!

Macular Displacement

Rajeev H. Muni, MD, MSc, FRCSC, ("yes, it is") and Michael N. Cohen, MD, ("no, it's not") debated whether retinal displacement, possible in up to 35% of retinal detachment (RD) repair cases, matters. Dr. Muni is adamant that it does because the resultant metamorphopsia and aniseikonia affect patients' quality of life. The ALIGN trial found that vitrectomy was associated with a greater risk of displacement and worse aniseikonia compared with pneumatic retinopexy (PnR). PnR decreases the incidence of macular displacement due to the reduction in contact force.

Dr. Cohen contended that the percentage of displacement after RD repair varies widely. Wills Eye Hospital conducted a comparative case series and found that among 200 patients, only 15% displaced after vitrectomy and 17% after scleral buckle, which are comparable with the rates of displacement in the Canadian PnR arm. Importantly, the displacement had no measurable effect on vision (although aniseikonia was not assessed due to the retrospective nature of the study).

Dr. Cohen won this debate by a hair.

ICG Versus Brilliant Blue

Lastly, Ferhina S. Ali, MD, MPH, ("go green!") and Prethy Rao, MD, MPH, ("go blue!") debated the merits of ICG versus brilliant blue for internal limiting membrane (ILM) staining (Figure 1). Dr. Ali explained that ICG provides better visualization and maneuverability of the ILM than brilliant blue. ICG causes biomechanical changes of the ILM, making it more rigid and easier to peel, she said. Toxicity from ICG is rare, and brilliant blue also has reports of toxicity in the literature. A single vial of brilliant blue may be cheaper than an entire bottle of ICG, but one bottle of ICG can be used for multiple cases, making it more cost effective.

Dr. Rao noted that brilliant blue is the only FDA approved dye for ophthalmic use. She added that ICG toxicity can lead to reduced visual acuity, visual field defects, and retinal pigment epithelium changes and, if injected subretinally, can cause outer retinal toxicity and decreased ERG responses. Brilliant blue comes in easy-to-use pre-filled vials with, theoretically, less risk of endophthalmitis compared with ICG. Polling results were 32% versus 68% in Dr. Rao's favor.

MEDICAL RETINA DEBATES

The next debate session, moderated by Carl D. Regillo, MD, and Priya Vakharia, MD, included a look at new therapies and the effect of private equity (PE) on the field.

VIT-BUCKLE SOCIETY

Figure 1. Prethy Rao, MD, MPH, (right) discusses her use of brilliant blue with panelists (from left to right) Ferhina S. Ali, MD, MPH; Joseph M. Coney, MD, FACS, FASRS; Katherine E. Talcott, MD; and Chirag D. Jhaveri, MD.

Figure 2. Philip Storey, MD, MPH, (left) and Esther L. Kim, MD, (middle left) sit down with Carl D. Regillo, MD, (middle right) and Priya Vakharia, MD, (right) to discuss the pros and cons of PE in retina—with a little superhero flair.

Biosimilars

The first debate was between Maura Di Nicola, MD, arguing that biosimilar drugs are better, and Nika Bagheri, MD, arguing that reference drugs are better. Dr. Di Nicola noted that biosimilars are strictly regulated by the FDA, and the rigorous approval process eases safety or efficacy concerns. Ophthalmology has had positive experiences using anti-TNF-alpha biosimilars. Similarly, ranibizumab biosimilars have demonstrated comparable efficacy to reference drugs. More than 30,000 biosimilar injections had been performed at the time of the meeting without any reported complications, she said. In addition, the lower cost and accessibility can benefit the entire health care system.

Dr. Bagheri pointed out that a biosimilar's safety profile may not be the same as the reference drug, and real-world data is important for assessing safety. In addition, she emphasized that millions of patients worldwide have responded well to the tried-and-true anti-VEGF reference drugs, whereas the biosimilars have only been injected on the scale of thousands. The audience agreed with Dr. Bagheri on this interesting and timely debate.

Dry AMD Injections

For the second debate, Lejla Vajzovic, MD, was assigned the position that dry AMD injections are not sustainable. She said that the greatest challenge is identifying the right patient. A monocular patient with a VA of 20/40 and fovea-involving geographic atrophy (GA) may not need much convincing, whereas patients with extrafoveal GA and no symptoms may be less inclined to opt for treatment. OCT allows for monitoring response to wet AMD therapy, but there is no robust method of detecting treatment response to GA therapy. Dr. Vajzovic stressed the need for better prognostication and risk factors to help stratify patients who progress faster or respond better to these medications.

David Xu, MD, highlighted the unmet need for GA therapy. Even in patients well-treated for wet AMD, post-hoc analyses demonstrate a 30% increased risk of atrophy progression over 2 years, given loss of vascular maintenance, he said. He pointed out that data from the OAKS and DERBY trials, as well as the GATHER1 and GATHER2 trials, showed similar benefits in decrease of GA progression, which increased with extended duration of treatment.

PE For Young Retinal Specialists

For the last debate, Philip Storey, MD, MPH, and Esther L. Kim, MD, discussed PE (Figure 2). Dr. Storey felt that PE's strength is the unity between retina specialists and health care business minds. The infrastructure allows for collective bargaining, leading to decreased costs and increased margins. He said that PE provided him flexible personal and professional autonomy. A majority of PE gives equity to its physicians, the path to partnership only requires 3 years, and salary remains in the top 1% in the nation, he said. In addition, research funding in his practice has tripled, allowing involvement in more than 30 prospective clinical trials.

Dr. Kim said that financial profit is PE's singular objective, which misaligns with physician objectives of patient care. PE aims for a 30% return on investments in 2 to 5 years, with the goal of reselling over and over, effectively turning doctors into commodities. Full partners who initially sold the practice benefit from the upfront cash, but at the cost of future earnings and practice autonomy. Non-partner physicians usually receive no financial benefit, losing out on ownership prospects and throttling their earning potential. The audience overwhelmingly agreed with Dr. Kim on this hot topic.

See you next year at VBS 2024 in Miami! ■

VIET CHAU, MD
- Resident, Bascom Palmer Eye Institute, Miami
- vxc422@med.miami.edu
- Financial disclosure: None

RACHEL S. MOGIL, MD
- Vitreoretinal Surgery Fellow, Mayo Clinic, Rochester, Minnesota
- mogil.rachel@mayo.edu
- Financial disclosure: None

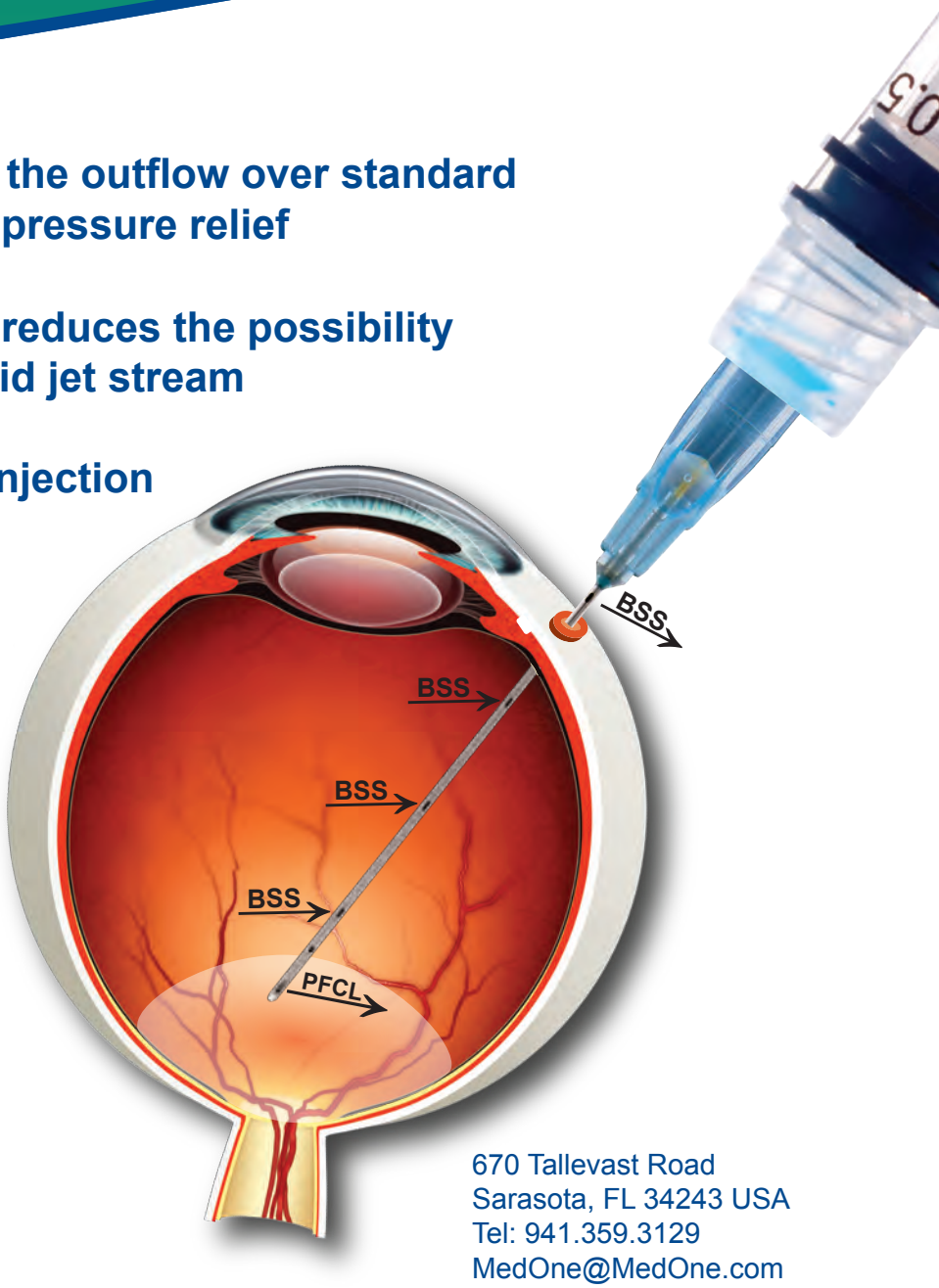
Works Best Under Pressure!

DualBore SideFlō® Cannulas

Optimized for simultaneous relief of pressure during injection of surgical liquids such as perfluorocarbon or staining dye in small gauge surgery.

- **Multiple egress vents double the outflow over standard DualBore cannulas for faster pressure relief**
- **Innovative side-port delivery reduces the possibility of retinal injury caused by fluid jet stream**
- **Maintains stable IOP during injection**
- **Available in 23g, 25g & 27g**

Patent #9937300



MedOne®

www.medone.com

670 Tallevast Road
Sarasota, FL 34243 USA
Tel: 941.359.3129
MedOne@MedOne.com

UNCOVERING THE TRUTH BEHIND CHOROIDAL FOLDS

Elucidating the root cause of this rare pathology will guide your management strategy.

BY MICHAEL K. NGUYEN, BA; MRITTIKA SEN, MD; AND CAROL L. SHIELDS, MD

Choroidal folds are undulations in the Bruch membrane located under the retina, often accompanied by retinal pigment epithelium (RPE) and inner choroidal undulations, which can be a sign of ocular or extraocular abnormalities. These findings can occur unilaterally or bilaterally and can present with or without symptoms.[1] Choroidal folds appear as hyper- and hypofluorescent lines on fluorescein angiography but can also be visualized on autofluorescent photography as hyper- and hypoautofluorescent linear folds.[2]

The underlying cause of choroidal folds can be challenging to determine. A thorough evaluation is necessary to tailor management strategies for treatable conditions. In this article, we report a case of unilateral choroidal folds in an adult that were found to be secondary to a rare condition. We also discuss useful diagnostic tests and suggest potential therapies.

CASE REPORT

A 64-year-old White woman was referred to our center following an 8-year history of a bulging left eye that was initially attributed to thyroid eye disease from underlying hypothyroidism. The patient did not have any other ophthalmic or systemic complaints. VA was 20/40 OD and 20/30 OS. IOP and color vision were normal in each eye. Refraction was +4.50 D OD and +6.00 D OS.

On fundoscopy, horizontal choroidal folds were discovered throughout the macula in the left eye. On wide-angle fundus imaging, the folds were oriented horizontally, which was confirmed on fundus autofluorescence (Figure 1). The vertical section on OCT demonstrated distinct choroidal folds at the level of the choroid and RPE (Figure 2). MRI of the left orbit and left side of the brain revealed a cystic mass in the lacrimal gland fossa (Figure 3A), suggestive of an orbital dermoid cyst with an intraosseous component superotemporally compressing the left globe and giving rise to the choroidal folds (Figure 3B).

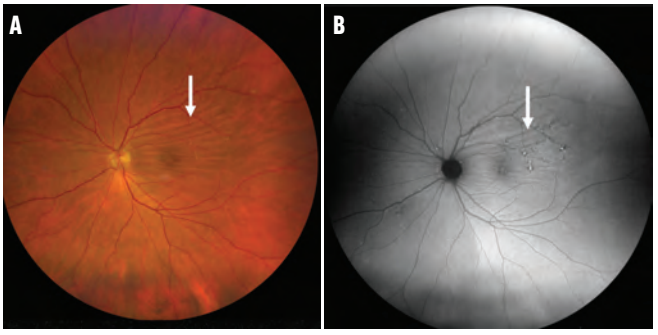


Figure 1. Fundus photography shows horizontal choroidal folds through the macula (A, arrow). Fundus autofluorescence provides another view of the choroidal folds with alternating hyper- and hypoautofluorescence (B, arrow).

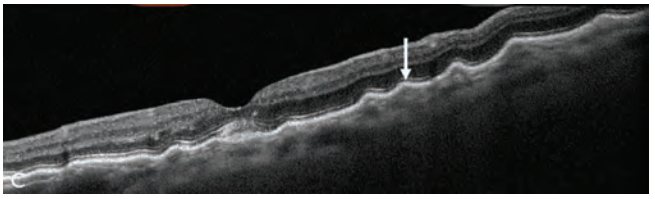


Figure 2. The vertical section (arrow) on OCT reveals RPE/Bruch membrane undulations.

Observation, rather than surgical resection with serial imaging, was advised because the patient was asymptomatic.

POSSIBLE CAUSES

Choroidal folds are rare and occur at the level of Bruch membrane/choriocapillaris, appearing as organized parallel lines with globe compression, circumferential lines in the juxtapapillary region with optic disc elevation, or randomly

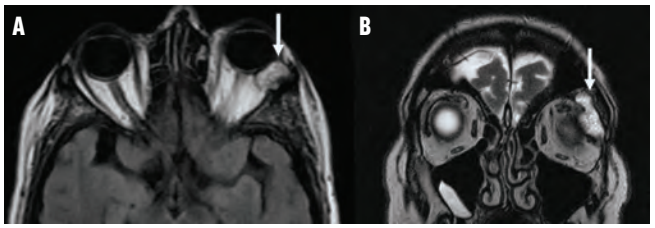


Figure 3. Axial view MRI (T1 weighted, no fat suppression) reveals an orbital dermoid cyst superotemporally (A, arrow) with globe compression. Coronal view MRI (T2 weighted) shows the dermoid cyst with an intraosseous component (B, arrow).

oriented lines, in the case of hypotony.

Jaworski et al proposed four distinct causes for the formation of choroidal folds: deformation of the sclera due to optic nerve traction, thickening or shrinkage of the sclera, decreased scleral rigidity, and contraction of the sub-RPE in neovascularization.[4] On ophthalmoscopy, choroidal folds appear as alternating bright and dark parallel streaks or lines that vary in length and width, typically in the post-equatorial region and predominantly involving the macular region. The less-pigmented lines correspond to RPE thinning, while the darkly pigmented intervening lines represent RPE compression.[5]

ASSOCIATED CONDITIONS

Choroidal folds can be associated with several ocular and extraocular pathological conditions. In a retrospective comparison study of unilateral versus bilateral chorioretinal folds, Leahey et al found that unilateral folds were due to scleritis (17%), hypotony (13%), vascular occlusion (13%), intraocular tumors (13%), AMD (10%), optic nerve edema (7%), retinal detachment (7%), hyperopia (3%), orbital tumor (3%), trauma (3%), optic atrophy (3%), and orbital bone compression (3%).[5] Furthermore, they found that bilateral folds were due to AMD (29%), hyperopia (25%), idiopathic (21%), hypotony (8%), scleritis (4%), thyroid eye disease (4%), uveitis (4%), and choroiditis (4%).[5]

Diagnosis and characterization of choroidal folds often requires functional analysis of the eye, tonometry, and imaging, such as color fundus photography, fluorescein angiography, ICG angiography, autofluorescence, OCT, and ultrasonography.[3,5] Currently, OCT is the most specific tool to enable differentiation of choroidal folds from retinal folds secondary to other causes, such as epiretinal membrane and complications post-retinal detachment surgery.[1,6]

In this case, MRI was key to establishing the cause of the choroidal folds with the delineation of an orbital dermoid cyst with globe compression. Orbital dermoid cyst is traditionally a childhood cystic tumor, often requiring surgical removal. In a retrospective study of 197 consecutive orbital and periorbital dermoid cysts from an ocular pathology laboratory over a 32-year period, Shields et al found that the mean age at surgical excision was 17 years; moreover, only 9% of the cysts were first diagnosed in patients 50 years of age and older, with the oldest patient being 85 years of age.[7] A dermoid cyst can originate superotemporally (72%), superonasally (17%), or in other locations (11%) within the orbit. Orbital dermoid cysts are classically managed with surgical excision, cyst aspiration and sclerotherapy, or observation.[8]

Our decision to follow the patient with serial imaging (OCT) was based on the chronic and asymptomatic nature of her disease.

FIND THE ROOT CAUSE

Choroidal folds are an important clinical sign that suggests the presence of a possible underlying ocular or orbital disease. The evaluation of the cause of choroidal folds should include taking a detailed medical history, clinical assessment, and imaging. Treatment should be individualized for each patient, depending on the underlying pathology. ■

Support provided in part by the Eye Tumor Research Foundation, Philadelphia, PA (CLS). The funders had no role in the design and conduct of the study, in the collection, analysis and interpretation of the data, and in the preparation, review or approval of the manuscript. Carol L. Shields, MD, has had full access to all the data in the study and takes responsibility for the integrity of the data.

1. Grosso D, Borrelli E, Sacconi R, Bandello F, Querques G. Recognition, diagnosis and treatment of chorioretinal folds: current perspectives. *Clin Ophthalmol*. 2020;14:3403-3409.
2. Cangemi FE, Trempe CL, Walsh JB. Choroidal folds. *Am J Ophthalmol*. 1978;86(3):380-387.
3. Newell FW. Choroidal folds. The seventh Harry Searls Gradle Memorial lecture. *Am J Ophthalmol*. 1973;75(6):930-942.
4. Jaworski A, Wolffsohn JS, Napper GA. Aetiology and management of choroidal folds. *Clin Exp Optom*. 1999;82(5):169-176.
5. Leahey AB, Brucker AJ, Wyszynski RE, Shaman P. Chorioretinal folds. A comparison of unilateral and bilateral cases. *Arch Ophthalmol*. 1993;111(3):357-359.
6. Heimann H, Bopp S. Retinal folds following retinal detachment surgery. *Ophthalmologica*. 2011;226(Suppl 1):18-26.
7. Shields JA, Kaden IH, Eagle RC, Jr, Shields CL. Orbital dermoid cysts: clinicopathologic correlations, classification, and management. The 1997 Josephine E. Schueler Lecture. *Ophthalmic Plast Reconstr Surg*. 1997;13(4):265-276.
8. Bagnis A, Cutolo CA, Corallo G, Musetti D, Nicolo M, Traverso CE. Chorioretinal folds: a proposed diagnostic algorithm. *Int Ophthalmol*. 2019;39(11):2667-2673.

MICHAEL K. NGUYEN, BA
- Medical Student, Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia
- michael.k.nguyen91@gmail.com
- Financial disclosure: None

MRITTIKA SEN, MD
- Fellow, Ocular Oncology Service, Wills Eye Hospital, Thomas Jefferson University, Philadelphia
- mrittika@shields.md
- Financial disclosure: None

CAROL L. SHIELDS, MD
- Director of the Ocular Oncology Service, Wills Eye Hospital, Thomas Jefferson University, Philadelphia
- Editorial Advisory Board Member, *Retina Today*
- carolshields@gmail.com
- Financial disclosure: None

HIGH-ALTITUDE RETINOPATHY: A REVIEW

Although rare and generally self-limiting, this condition may be associated with more serious disease.

BY MOHAMMAD JOURIEH, MD, AND LUJAIN JOURIEH

Millions travel to high-altitude destinations each year without fully understanding the potential medical risks involved. High-altitude illnesses, including acute mountain sickness (AMS), high-altitude cerebral edema (HACE), high-altitude pulmonary edema, and high-altitude retinopathy (HAR), are associated with the hypobaric nature of high altitudes. These conditions are commonly observed at altitudes greater than 2,500 m (8,200 ft) in non-acclimatized individuals shortly after ascent and may be caused by hypobaric hypoxia-induced compensatory mechanisms to boost delivery of oxygen.[1,2]

HAR DEFINED

HAR was first described in 1969 by Singh et al,[3] who noted increased dilatation and tortuosity of retinal vasculature, along with scattered dot-blot and flame-shaped hemorrhages, in 24 (1.3%) of 1,925 patients who were diagnosed with AMS after ascending to between 3,353 m and 5,486 m above mean sea level.[3]

HAR is usually asymptomatic and self-limiting, with most manifestations resolving spontaneously after descent.[4] Typically, HAR occurs in individuals who ascend above 2,500 m but can occur at as low as 2,000 m.[5-7] Symptomatic patients may experience unilateral or bilateral decreased vision, scotoma, and/or sudden onset of floaters after 8 to 24 hours of high-altitude exposure (see *Case Example of HAR*).[4,8] Severe manifestations rarely occur, but isolated cases of anterior ischemic optic neuropathy, branch retinal artery occlusion, central retinal vein occlusion, cilioretinal artery occlusion, and cystoid macular edema have been reported with poor visual recovery.[9,10-14]

RISK AND INCIDENCE

Risk factors for HAR include rapid ascent, high maximum altitude, high baseline IOP, genetic susceptibility, and use of NSAIDs.[7,15] HAR has been reported more frequently in individuals of young age, and its prevalence varies widely. McFadden et al noted retinal hemorrhages in 56% of 39 healthy individuals after a stay at 5,360 m,[16] whereas Barthelmes et al reported an incidence of up to 79% of 28 climbers during a high-altitude expedition.[17]

PATHOPHYSIOLOGY

Various theories have been proposed to elucidate the pathogenesis of HAR. Hypobaric hypoxia experienced at a high altitude induces various compensatory mechanisms aimed to maintain oxygen delivery, and it is thought that inadequate autoregulatory response of the retinal vascular system is the primary cause of HAR.[17,18] That is, hypoxia is assumed to cause increased retinal blood flow and intravenous pressure secondary to intracranial pressure, variations in hematocrit levels, extreme physical exertion, and Valsalva maneuvers during mountain climbing at high elevation. A hypoxic vasodilatation exposed to increased retinal venous pressure leads to a predisposition to intraretinal hemorrhages.[9,17] Reduced IOP at high altitudes may also contribute to the progression of intraretinal hemorrhages.[19] Moreover, the increase of cerebral vascular blood flow and disruption of the blood-brain barrier caused by hypoxia can lead to cerebral edema, which results in optic disc swelling.[20]

INVESTIGATING THE MECHANISMS

Xin et al conducted a randomized study that explored the effects of hypobaric hypoxia on the retinas of rats to investigate whether resveratrol has a protective effect on hypoxic damage.[21] The study concluded that hypobaric hypoxia increased thioredoxin 1 and thioredoxin 2 expression in the retina, and resveratrol treatment significantly reversed these findings ($P < .05$ and $P < .05$, respectively). Therefore, resveratrol may be beneficial as a treatment

CASE EXAMPLE OF HAR

A large preretinal hemorrhage occurred 1 day after exposure to high elevation.

BY E. ANNE SHEPHERD, MD; NARYAN SABHERWAL, MD; AND MATHEW MACCUMBER, MD, PHD

A 32-year-old healthy woman presented with sudden vision loss in her left eye. She saw a "gray thumb print" with her left eye that occurred in the early morning. She denied physical exertion at the time of the vision loss; however, the day before, she had been skiing on trails at an elevation of roughly 3,962 m (13,000 ft) with limited hydration because her water bottle had frozen.

The patient's BCVA was 20/20 OD and 20/400 OS with no improvement with pinhole. She had no afferent pupillary defect, and her IOPs were 13 mm Hg OD and 11 mm Hg OS. Her motility and confrontational fields were full. Her anterior segment examination was normal.

Examination of the posterior segment demonstrated a normal right eye, while the left eye had slightly tortuous vessels, a large preretinal/sub-internal limiting membrane (ILM) hemorrhage, a superior subretinal hemorrhage, and a flame-shaped retinal hemorrhage along the inferior arcade (Figure 1). Fluorescein angiography demonstrated normal arterial and venous filling times, without evidence of leakage. No macroaneurysm was identified.

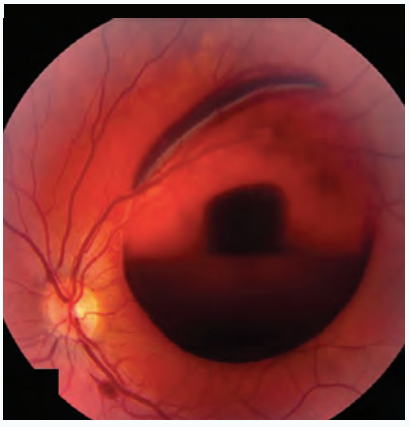


Figure 1. On fundus photography, the left eye demonstrated slight venous tortuosity, a large preretinal/sub-ILM hemorrhage, a superior subretinal hemorrhage, and a small flame-shaped hemorrhage along the inferotemporal arcade.

We decided to observe the patient closely and referred her to her primary care physician for systemic workup of blood pressure and altered coagulability, which was normal. When she returned 1 week later, her preretinal hemorrhage had mildly worsened.

After discussion with the patient, she was treated with Nd:YAG laser of the posterior hyaloid/ILM to release the hemorrhage (Figure 2). After treatment, a break in the ILM can be seen on OCT (Figure 3). At the 1-week follow-up, the patient's VA improved to 20/40, with further improvement to 20/30 upon resolution of mild inferior vitreous hemorrhage.

To our knowledge, our patient experienced the largest documented retinal hemorrhage due to high-altitude retinopathy occurring 1 day after returning from a high altitude. Low oxygen saturation and higher-than-usual hematocrit potentially increased her risk of HAR during and after descent.

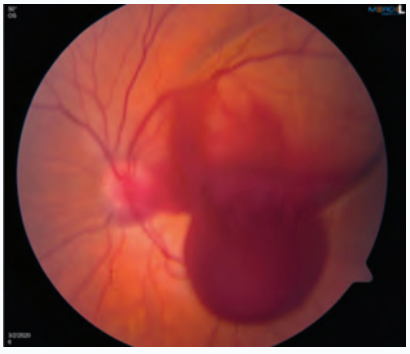


Figure 2. After Nd:YAG laser to the posterior hyaloid, a release of the hemorrhage can be seen.

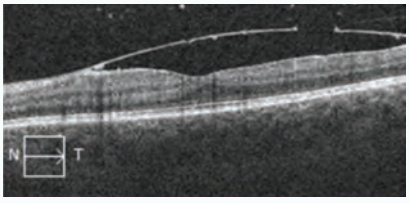


Figure 3. OCT of the left eye after Nd:YAG laser reveals a small break in the ILM.

E. ANNE SHEPHERD, MD
- Rush University Medical Center, Department of Ophthalmology, Chicago
- Financial disclosure: None

NARYAN SABHERWAL, MD
- Rush University Medical Center, Department of Ophthalmology, Chicago
- Illinois Retina Associates, Chicago
- Financial disclosure: None

MATHEW MACCUMBER, MD, PHD
- Rush University Medical Center, Department of Ophthalmology, Chicago
- Illinois Retina Associates, Chicago
- mmaccumber@illinoisretina.com
- Financial disclosure: None

for HAR by exerting an antioxidative role and modulating genes associated with hypoxia-induced stress; it may also regulate apoptosis-related cytokines.[21]

In 2022, Xin et al used a low-pressure oxygen cabin mimicking 5,000 m altitude to evaluate whether pyroptosis is involved in the mechanism of retinal dysfunction in rat retinas.[22] Hypobaric hypoxia significantly increased the expression of proinflammatory cytokines, including interleukin-1 beta and interleukin-18, indicating that pyroptosis is involved in the pathogenesis of HAR.

A recent study looked at the molecular mechanism of HAR. Su et al used an integrated bioinformatics analysis and a hypoxia-induced cell culture to identify genes *FOS, IL10, IL7R,* and seven different miRNAs as candidate biomarkers of HAR, which may help explain an individual's increased susceptibility to this condition.[23]

ASSESSMENT AND DIAGNOSTIC IMAGING

Patients with HAR usually have a history of ascent to a high-altitude location or even air travel with or without visual symptoms.[6,24] Fundus photography may show an increase in the diameter of retinal vessels with tortuosity of arterioles and venules, along with diffuse dot-blot and flame-shaped hemorrhages, usually involving the midperiphery. Cotton-wool spots, Roth spots, vitreous hemorrhages, and papilledema may occasionally be seen as well.[4,8,17,25]

OCT may detect a significant increase in retina nerve fiber layer thickness in the temporal and nasal quadrants of the optic disc, along with an increase in the ganglion cell layer thickness in the superior macula. In one report, these changes were temporary and returned to baseline upon descent.[26] Another study showed an increase in temporal and superior retina nerve fiber layer thickness following high-altitude exposure.[27]

Fluorescein angiography may show bilateral leakage of retinal vessels peripherally, favoring venules more than arterioles, and optic disc staining. These findings resolve completely after descent to baseline altitude.[28] The reduction in retinal function may also be detected by multifocal electroretinography, showing reduced responses in the macula that recover with time upon descent.[29]

One case reported an increase in choroidal thickness (up to 530 µm) on OCT in a patient with HAR, suggesting that the hypoxia-induced increase in retinal blood flow could be associated with an increase in the choroidal blood flow and an increase in choroidal thickness.[30] However, more studies are required to confirm choroidal changes in HAR.

TREATMENT AND PROGNOSIS

Although no evidence-based treatment exists for HAR and no active intervention is typically required, some reports suggest the use of steroids, nonsteroidal antiinflammatory drugs, diuretics, and supplemental oxygen, although without consistent evidence of effectiveness.[31] Hyperbaric oxygen therapy has also been suggested.[10]

The prognosis is favorable, with patients generally regaining their full vision in the weeks after descent. Visual impairment is rare, although it may occur in severe manifestations of HAR (eg, cilioretinal artery occlusion,[10] central retinal vein occlusion[12]). Recommendations for prevention include a slow ascent (no more than 300 m a day), allowing time for acclimatization, and immediate descent to baseline altitude if symptoms are progressing.[32]

A POSSIBLE SIGN OF TROUBLE

Whether HAR is related to life-threatening conditions at high altitude is still a matter of debate. Clarke et al reported retinal hemorrhages as common findings due to the acclimatization process and denied their association with impending cerebral edema.[33] Other findings suggest that vasogenic cerebral edema and altered autoregulation of the cerebral blood flow may correlate with AMS and HACE.[34,35] Thus, early diagnosis may alert physicians to recommend immediate descent to avoid further progression of HAR or more serious, potentially fatal high-altitude illness.[36]

Further studies are required to investigate the significance of HAR and whether it is a useful warning sign of potentially fatal conditions on the spectrum of high-altitude illnesses. ■

1. Fuehrer J, McGowan J, Huecker MR. High altitude cardiopulmonary diseases. In:StatPearls. Updated April 9, 2023. Accessed June 27, 2023. www.ncbi.nlm.nih.gov/books/NBK442011
2. West JB. English translation of nomenclature, classification, and diagnostic criteria of high altitude disease in China. *High Alt Med Biol*. 2010;11(2):169-172.
3. Singh I, Khanna PK, Srivastava MC, Lal M, Roy SB, Subramanyam CS. Acute mountain sickness. *N Engl J Med*. 2010;280(4):175-184.
4. Bhende MP, Karpe AP, Pal BP. High altitude retinopathy. *Indian J Ophthalmol*. 2013;61(4):176-177.
5. Mahesh SP, Mathura JRJr. Retinal hemorrhages associated with high altitude. *N Engl J Med*. 2010;362(16):1521-1521.
6. Nieto Estrada VH, Molano Franco D, Medina RD, Gonzalez Garay AG, Marti-Carvajal AJ, Arevalo-Rodriguez I. Interventions for preventing high altitude illness: part 1. commonly-used classes of drugs. *Cochrane Database Syst Rev*. 2017;2017(6).
7. Russo A, Agard E, Blein JP, et al. [High altitude retinopathy: report of 3 cases]. *J Fr Ophthalmol*. 2014;37(8):629-634.
8. Shrestha A, Suwal R, Shrestha B. Vitreous hemorrhage following high-altitude retinopathy. *Case Rep Ophthalmol Med*. 2021;2021:7076190.
9. Mishra A, Luthra S, Baranwal VK, Shyamsunder K. Bilateral cystoid macular oedema due to high altitude exposure: an unusual clinical presentation. *Med J Armed Forces India*. 2013;69(4):394.
10. Gokce G, Metin S, Erdem U, et al. Late hyperbaric oxygen treatment of cilioretinal artery occlusion with nonischemic central retinal vein occlusion secondary to high altitude. *High Alt Med Biol*. 2014;15(1):84-88.
11. Feng X, Wang L, Wang H, Qi H, Zhang J, Wang Y. Branch retinal artery occlusion secondary to high-altitude exposure and diabetic retinopathy: a case report. *BMC Ophthalmol*. 2020;20(1):281.
12. Lee KM, Yoo SJ, Woo SJ. Central retinal vein occlusion following hypobaric chamber exposure. *Aviat Space Environ Med*. 2013;84(9):986-989.
13. Gupta A, Singh S, Ahluwalia TS, Khanna A. Retinal vein occlusion in high altitude. *High Alt Med Bio*. 2011;12(4):393-397.
14. Bandyopadhyay S, Singh R, Gupta V, Gupta A. Anterior ischaemic optic neuropathy at high altitude. *Indian J Ophthalmol*. 2002;50(4):324-325.
15. Barry PW, Pollard AJ. Altitude illness. *BMJ*. 2003;326(7395):915-919.
16. Mcfadden DM, Houston CS, Sutton JR, Powles ACP, Roberts RS, Gray GW. High-altitude retinopathy. *JAMA*. 1981;245(6):581-586.
17. Barthelmes D, Bosch MM, Merz TM, et al. Delayed appearance of high altitude retinal hemorrhages. *PLoS One*. 2011;6(2):e11532.
18. Mullner-Eidenbock A, Rainer G, Strenn K, Zidek T. High-altitude retinopathy and retinal vascular dysregulation. *Eye (Lond)*. 2000;14(5):724-729.
19. Somner JEA, Morris DS, Scott KM, MacCormick IJC, Aspinall P, Dhillon B. What happens to intraocular pressure at high altitude? *Invest Ophthalmol Vis Sci*. 2007;48(4):1622-1626.
20. Bosch MM, Barthelmes D, Merz TM, et al. High incidence of optic disc swelling at very high altitudes. *Arch Ophthalmol*. 2008;126(5):644-650.
21. Xin X, Dang H, Zhao X, Wang H. Effects of hypobaric hypoxia on rat retina and protective response of resveratrol to the stress. *Int J Med Sci*. 2017;14(10):943-950.
22. Xin X, Yang K, Liu H, Li Y. Hypobaric hypoxia triggers pyroptosis in the retina via NLRP3 inflammasome activation. *Apoptosis*. 2022;27(3-4):222-232.
23. Su T, Gu C, Draga D, et al. Integrative analysis of miRNA–mRNA network in high altitude retinopathy by bioinformatics analysis. *Biosci Rep*. 2021;41(1).
24. Okudo AC, Babalola OE. A case of high-altitude retinopathy following long distance air travel to Abuja, Nigeria: Case report. *East Afr Med J*. 2022;99(4):4771-4775.
25. Petrocinio RR, Gomes ED. Lipid subhyaloid maculopathy and exposure to high altitude. *Aerosp Med Hum Perform*. 2016;87(10):898-900.
26. Tian X, Zhang B, Jia Y, Wang C, Li Q. Retinal changes following rapid ascent to a high-altitude environment. *Eye (Lond)*. 2018;32(2):370-374.
27. Ascaso FJ, Nerín MA, Villén L, Morandeira JR, Cristóbal JA. Acute mountain sickness and retinal evaluation by optical coherence tomography. *Eur J Ophthalmol*. 2011;22(4):580-589.
28. Willmann G, Fischer MD, Schatz A, Schommer K, Gekeler F. Retinal vessel leakage at high altitude. *JAMA*. 2013;309(21):2210-2212.
29. Pavlidis M, Stupp T, Georgalas I, Georgiadou E, Moschos M, Thanos S. Multifocal electroretinography changes in the macula at high altitude: a report of three cases. *Ophthalmologica*. 2005;219(6):404-412.
30. Hirukawa-Nakayama K, Hirakarta A, Tomita K, Hiraoka T, Inoue M. Increased choroidal thickness in patient with high-altitude retinopathy. *Indian J Ophthalmol*. 2014;62(4):506-507.
31. Plant T, Aref-Adib G. Travelling to new heights: practical high altitude medicine. *Br J Hosp Med (Lond)*. 2013;69(6):348-352.
32. Bezruchka S. High altitude medicine. *Med Clin North Am*. 1992;76(6):1481-1497.
33. Clarke C. Acute mountain sickness: medical problems associated with acute and subacute exposure to hypobaric hypoxia. *Postgrad Med J*. 2006;82(973):748-753.
34. Hackett PH, Yarnell PR, Hill R, Reynard K, Heit J, McCormick J. High-altitude cerebral edema evaluated with magnetic resonance imaging: clinical correlation and pathophysiology. *JAMA*. 1998;280(22):1920-1925.
35. Jansen GFA, Kagenaar DA, Basnyat B, Odoom JA. Basilar artery blood flow velocity and the ventilatory response to acute hypoxia in mountaineers. *Respir Physiol Neurobiol*. 2002;133(1-2):65-74.
36. Seth RK, Adelman RA. High-altitude retinopathy and optical coherence tomography findings. *Semin Ophthalmol*. 2010;25(1-2):13-15.

MOHAMMAD JOURIEH, MD
- Ophthalmologist, M. M. Krasnov Scientific Research Institute of Eye Diseases, Moscow, Russia
- jourieh.mo@gmail.com
- Financial disclosure: None

LUJAIN JOURIEH
- Dentistry Student, Al Andalus University for Medical Sciences, Tartus, Syria
- Financial disclosure: None

LASER PHOTOCOAGULATORS

DIVERSE LINE OF LASERS

MC-500/500VIXI

- MULTICOLOR LASER (532/577/647nm)
- 22 preprogrammed scan patterns
- Auto Forward function for automated positioning of the scan pattern
- **LPM (Low Power Mode)** for minimally invasive photocoagulation

GYC-500/500VIXI

- 532nm GREEN LASER
- 22 preprogrammed scan patterns
- Auto Forward function for automated positioning of the scan pattern

Now optional with YC-200 YAG laser and YC-200 S plus YAG/SLT laser!

YLC-500/500VIXI

- 577nm YELLOW LASER
- 22 preprogrammed scan patterns
- Auto Forward function for automated positioning of the scan pattern
- **LPM (Low Power Mode)** for minimally invasive photocoagulation

LEARN MORE: **info@nidek.com** or **usa.nidek.com**

NIDEK

THE ART OF EYE CARE

Contact Us Today!

877.200.9892

52 YEARS ANNIVERSARY

August 15, 2023
2023-0022

What to Look for With MODY

Maturity-onset diabetes of the young–a rare monogenic variant–can present with a severe form of diabetic retinopathy.

BY SAHAL SALEH, MD; TEDI BEGAJ, MD; JEREMY WOLFE, MD; AND SANDEEP RANDHAWA, MD

Extensive literature exists detailing the effect of both type 1 diabetes mellitus (DM; mediated by insulin deficiency due to autoimmune destruction of pancreatic beta cells) and type 2 DM (mediated by insulin resistance) on the retina.[1] However, there is a paucity of data on the pathologic retinal changes due to maturity-onset diabetes of the young (MODY).

MODY is a rare cause of DM contributing to approximately 1% of all cases.[2] It can manifest in childhood, adolescence, or early adulthood.[2] Unlike type 1 or 2 DM, MODY is monogenic, with at least 14 known gene mutations. The four most common are in *hepatic nuclear factor 1 alpha* (*HNF1A*), *HNF4A*, *HNF1 beta*, and *glucokinase* (*GCK*). Each mutation affects insulin production differently, which determines the systemic manifestations and treatment approach. For example, *GCK*-MODY has minimal insulin-level perturbations and systemic microvascular sequelae, while *HNF1A*-MODY causes worse pancreatic beta cell dysfunction, decreased insulin production, and more severe systemic sequelae.[3]

Herein, we present a rare case of a young "healthy" patient with a family history of MODY and rapid onset of proliferative diabetic retinopathy (PDR).

THE CASE

A 32-year-old White man was referred for progressive decrease in vision in his right eye. He denied any previous medical history except for a diagnosis of diabetes 6 months prior. His brother and several family members over two generations were diagnosed with diabetes in their 20s and 30s. His brother had been diagnosed with MODY (genetically confirmed, unknown mutation) 5 years prior. Initially, the patient had a reported hemoglobin A1c of > 10% that had an excellent response to metformin and glipizide.

On examination, BCVA was 20/800 OD and 20/25 OS, with no relative afferent pupillary defect, normal IOPs, and no neovascularization of the iris. Dilated fundus examination revealed cotton-wool spots, dot-blot hemorrhages, microaneurysms, and neovascularization elsewhere in the right eye and early neovascularization elsewhere, cotton-wool spots, and dot-blot hemorrhages in the left eye (Figure 1). OCT imaging showed significant macular edema and disruption of the subfoveal ellipsoid zone (EZ) in the right eye and minimal cystoid macular edema in the left eye.

Fluorescein angiography (FA) was notable for large swaths of hypofluorescence suggestive of peripheral capillary nonperfusion, leakage from neovascularization, and blockages from the dot-blot hemorrhages in the right eye (Figure 2). Critically, there was also an enlarged foveal avascular zone (FAZ). In the left eye, there was a lesser but still significant amount of peripheral capillary nonperfusion, areas of leakage from neovascularization, and a normal FAZ.

Given the PDR and macular edema, the patient underwent anti-VEGF injections in each eye at presentation, followed by panretinal photocoagulation in each eye.

At the 1-year follow-up, VA had improved to 20/100 OD and 20/20 OS. The macular edema and peripheral neovascularization had resolved. OCT imaging showed significant

AT A GLANCE

- Maturity-onset diabetes of the young (MODY) contributes to roughly 1% of all diabetes cases.
- The underlying genetic mutations play an important role in the phenotypic manifestations of MODY-associated retinopathy, which underscores the importance of genetic testing.
- Chronic hyperglycemia in MODY can lead to microvascular damage with subsequent decreased perfusion and increased risk of neovascularization.

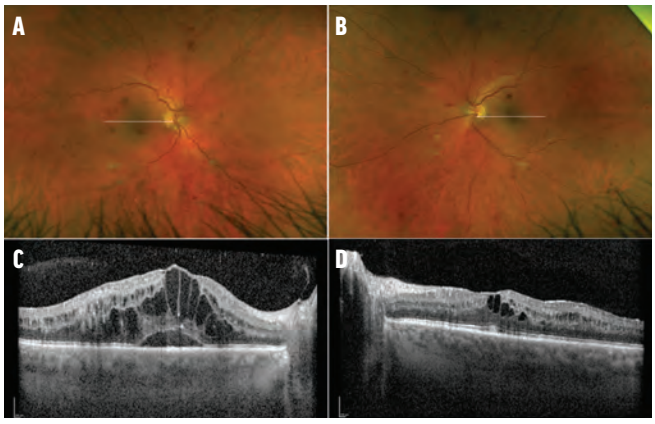


Figure 1. Widefield imaging reveals dot-blot hemorrhages in all quadrants, hard exudates, cotton-wool spots, and neovascularization elsewhere in the right eye (A). The left eye has less severe proliferative retinopathy with dot-blot hemorrhages, cotton-wool spots, and early neovascularization elsewhere (B). The white lines correspond to the OCT segmentation at the fovea. OCT of the right eye shows significant macular edema and disruption of the fovea (C). The left eye has minimal cystoid macular edema (D).

diffuse perifoveal attenuation of the EZ in the right eye and scattered macular exudates with subtle subfoveal attenuation of the EZ in the left eye (Figure 3).

DISCUSSION

MODY is a rare form of diabetes caused by a single genetic mutation.[4] Unlike type 1 or 2 DM, there is no autoimmune pancreatic beta cell death nor insulin resistance. MODY should be suspected in patients younger than age 30 with persistent hyperglycemia, clinical features not usual for type 1 or 2 DM, and a family history of diabetes. After obtaining various serologies to rule out ancillary disorders, genetic testing is ultimately necessary to confirm the diagnosis.[5,6]

There are currently 14 known gene mutations that cause MODY,[7] but *HNF1A* and *GCK* account for roughly 80% of cases.[8] *HNF1A* is a transcription factor prominent in hepatic and pancreatic tissues that helps regulate beta cell function.[9] Mutations in *HNF1A* cause progressive beta cell dysfunction, reduced glucose-stimulated insulin secretion, and low renal threshold for glucosuria.[9] *GCK* catalyzes adenosine triphosphate-dependent phosphorylation of glucose to produce glucose-6-phosphate, which is the rate-limiting reaction of glucose metabolism.[2] Mutations in *GCK* have minimal clinical effects and rarely require treatment, except in pregnancy.[2,10] In contrast to *HNF1A*-MODY, microvascular complications are much less prevalent in *GCK*-MODY.[9]

Like both type 1 and 2 DM, chronic hyperglycemia in MODY can lead to microvascular damage with subsequent decreased perfusion and increased risk of neovascularization. In one study, investigators developed an *HNF1A*-MODY porcine model and monitored the development of DR using fundus photography and fluorescein angiography. They found that *HNF1A*-MODY eyes developed greater vascular tortuosity, decreased blood vessel density, and thickening

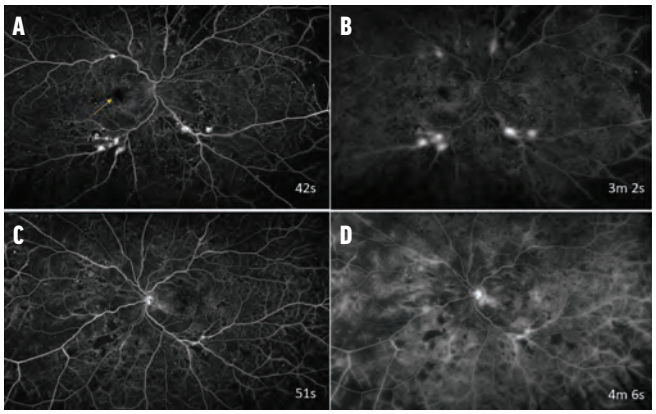


Figure 2. The early frame widefield FA of the right eye shows an enlargement of the FAZ (A, yellow arrow), significant peripheral nonperfusion and vessel attenuation, and early leakage corresponding to areas of neovascularization elsewhere. The later frame delineates the neovascularization elsewhere and demonstrates a persistent FAZ enlargement (B). The left eye shows microaneurysms and peripheral nonperfusion but no evidence of FAZ enlargement (C). The late frame demonstrates the overall capillary attenuation, given the patchy staining throughout the retina (D).

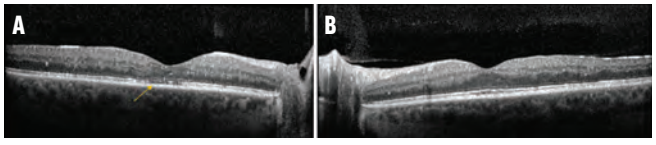


Figure 3. OCT of each eye at 1 year. The right eye shows persistent subfoveal EZ attenuation (yellow arrow) and foveal thinning (A). The left eye shows resolution of the macular edema (B).

of capillary basement membranes compared with wild-type pig eyes.[11] The data overall suggest a similar mechanism as vascular complications due to type 1 or type 2 DM.

The underlying genetics of MODY contribute to their differences in retinal manifestations. There is a paucity of data on MODY-induced DR. In a case series from 2015, only one of 51 patients with *GCK*-MODY had findings of mild NPDR. In contrast, 15 of 63 patients with *HNF1A*-MODY had findings of DR, including nine patients with PDR with high-risk characteristics.[12] A case report of a 32-year-old man with presumed MODY developed PDR early, but after treatment and glucose control, his retinopathy was stable for approximately 30 years without progression.[13] The underlying mutations play an important role in the phenotypic manifestations of DR, underscoring the importance of genetic testing.

Our patient's clinical course provides further insight into this rare form of diabetes. First, he exhibited findings of advanced disease at presentation. Despite annual follow-ups, he developed PDR in a relatively short amount of time. However, he had a robust systemic response to metformin and sulfonylureas with improvement in hemoglobin A1c from > 10% to 7% within several months.

At 1 year, VA had improved to 20/100 OD, which, although better than presentation, represents the significant changes of hyperglycemic microvascular complications and resultant macular ischemia. At the most recent visit, OCT

(Continued on page 32)

Assessing DR With Ultra-Widefield Imaging

Clinicians can use new technology to track disease severity and progression.

BY HARNAINA K. BAINS, BS; VENKATKRISH M. KASETTY, MD; AND DENNIS M. MARCUS, MD



Since the landmark Early Treatment Diabetic Retinopathy Study (ETDRS), the Diabetic Retinopathy Severity Scale (DRSS) has been the established method for grading diabetic retinopathy (DR) severity.[1,2] Although this has been a reliable metric to determine baseline DR status and likelihood of progression, the DRSS has not been updated to account for imaging advances, such as ultra-widefield (UWF) technologies.

UWF images are defined as a single image, centered on the fovea, that captures beyond the posterior pole and includes anatomy anterior to the vortex veins in all four quadrants.[3] These images capture approximately 82% of the retinal surface, including the midperipheral and peripheral retina.[4] Imaging of the peripheral retina allows for better assessment of DR lesions and assessment of retinal nonperfusion on UWF fluorescein angiography (FA), which cannot be captured from color fundus photographs alone.[5-8] Prior single-center studies have demonstrated predominantly peripheral lesions (PPLs) in DR, portending a higher baseline DR severity and an increased risk of progression.[5-17]

Diabetic Retinopathy Clinical Research (DRCR) Retina Network Protocol AA is a 4-year prospective observational study evaluating the ability of PPLs to predict DR progression and severity for eyes with nonproliferative DR (NPDR) without center-involving diabetic macular edema. Herein, we discuss the results of this study and the utility of UWF imaging in classifying DR severity and predicting progression.

PREDOMINANTLY PERIPHERAL LESIONS

PPLs are defined as lesions primarily (> 50%) located outside the ETDRS 7-standard-field images (Figure 1). Overall, PPLs were common in the Protocol AA cohort. Among the 544 study eyes with gradable color UWF images, PPLs were present at baseline in 41% and 46% of eyes on UWF color photography and UWF FA, respectively. Of the 542 eyes with gradable UWF color images and UWF FA, 25% had PPLs present at baseline on both UWF color imaging and UWF FA, 20% had PPLs on UWF FA only, and 16% had PPLs on UWF color images only, leaving 39% of eyes without evidence of PPLs on either imaging modality.[18]

Hemorrhages and microaneurysms were the most common PPLs seen in 81% and 91% of UWF color images and UWF FA, respectively. PPLs were most likely in peripheral fields 3, 4, and 6. Baseline DRSS levels from ETDRS fields on UWF color imaging showed that 45%, 40%, 26%, and 43% of patients with mild, moderate, moderately severe, and severe NPDR, respectively, met the study's primary objective (DRSS worsening by 2 or more steps) over the 4-year study period.[18] It is unclear why these rates of DR progression are not consistent with the expected increase in progression rates usually seen with worsening baseline DRSS level; however, prior DRCR studies have demonstrated consistency between digital and film photographs, which were originally used in the ETDRS.[19]

AT A GLANCE

- Imaging of the peripheral retina allows for better assessment of diabetic retinopathy (DR) lesions and assessment of retinal nonperfusion on ultra-widefield fluorescein angiography.
- Protocol AA is a 4-year study evaluating the ability of predominantly peripheral lesions (PPLs) to predict DR severity and progression.
- PPLs and higher nonperfusion areas on ultra-widefield fluorescein angiography can serve as predictors for DR progression.

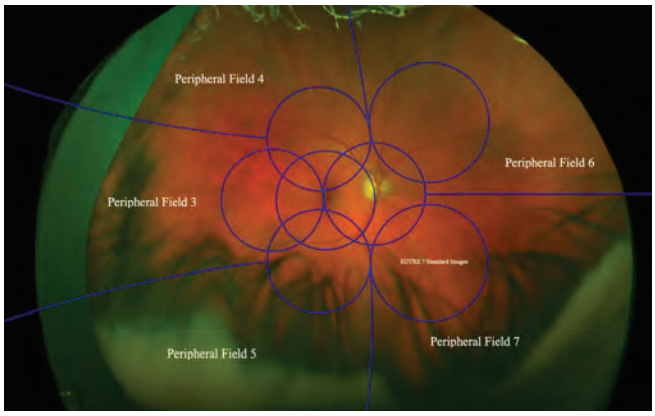


Image courtesy of Dennis Marcus, MD

Figure 1. This UWF fundus color photograph demonstrates the ETDRS 7-standard-field images (blue circles) and peripheral fields 3-6.

Over the 4-year study period, the risk of DR progression was associated with PPLs seen on UWF FA, but not with those seen on UWF color photography (Figure 2). Eyes with PPLs on UWF FA had a 1.7-fold increased risk of DR progression compared with eyes without PPLs on UWF FA. Specifically, peripheral hemorrhages and microaneurysms and intraretinal microvascular abnormalities on UWF FA were associated with an increased risk of DRSS worsening.[18]

RETINAL NONPERFUSION INDEX

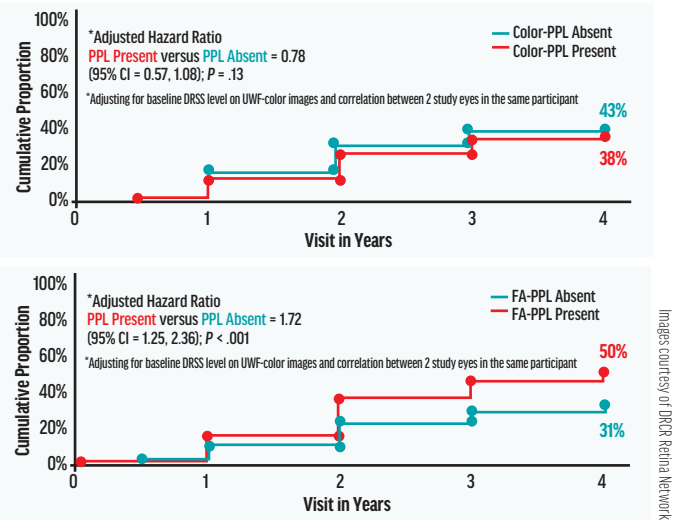
Protocol AA also assessed the association between retinal nonperfusion and PPL presence and DR severity worsening. The area of nonperfusion (mm^2) and the nonperfusion index (NPI, the area of nonperfusion divided by the total gradable area) were the primary metrics evaluated (Figure 3). In this cohort of 508 eyes with NPDR and gradable UWF FA nonperfusion at baseline, only 9% of eyes had no nonperfusion.[20]

In the study, 26%, 43%, 38%, and 46% of eyes in the no, low, medium, and high nonperfusion subgroups, respectively, had worsening DR by at least 2 steps or required treatment. This suggests that increasing NPI is a significant risk factor for progression and may be useful in DR monitoring (Figure 4).[20]

Furthermore, higher levels of nonperfusion in the ETDRS fields 6 and 7, midperiphery and posterior pole, and superior, inferior, and nasal peripheral retina were all significantly associated with a higher risk of progression. Similarly, greater NPI was associated with an increased risk for progression to proliferative DR and the development of vitreous hemorrhage.[20]

CLINICAL PEARLS

The 4-year longitudinal results of Protocol AA highlight the advantage of UWF color photography and UWF FA in managing patients with diabetes. PPLs and higher nonperfusion areas on UWF FA can serve as predictors for DR progression and are beneficial tools to assess patients with NPDR. However, the advantages of UWF FA should be weighed against the drawbacks of increased cost, time, and risks associated with FA, especially in patients with NPDR



Images courtesy of DRCR Retina Network

Figure 2. The proportion of eyes with PPLs on UWF color photography (top) and UWF FA (bottom) over 4 years in Protocol AA.[18]

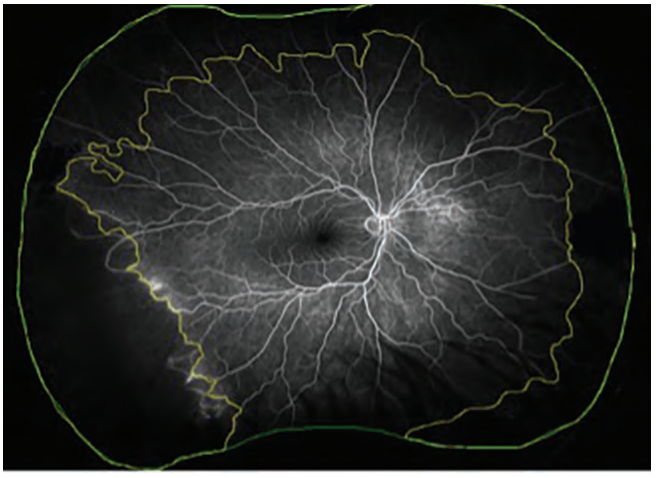


Image courtesy of DRCR Retina Network

Figure 3. UWF FA demonstrates the total gradable area and area of nonperfusion used in calculating NPI. Area of nonperfusion is measured between the yellow and green lines. The total gradable area is measured within the green line.

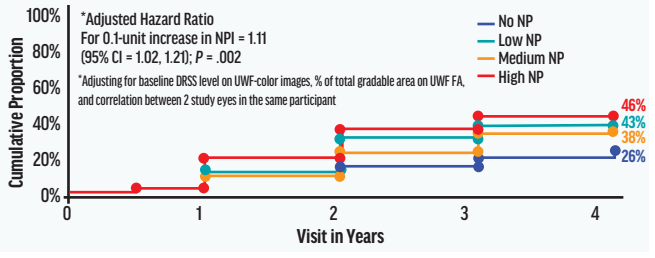


Image courtesy of DRCR Retina Network

Figure 4. The proportion of eyes with no, low, medium, and high levels of nonperfusion through 4 years of follow-up in Protocol AA.[20]

for whom FA is not routinely obtained at baseline. However, UWF FA provides more information than that observed on clinical examination and color fundus photography.

We recommend using baseline UWF FA for patients with NPDR who are at a higher risk for disease progression, such as those with long-standing disease, poor glycemic control,

long-term insulin use, dyslipidemia, and other vasculopathic risk factors. It can also be a useful tool when counseling patients about the need to better control their diabetes. ■

1. ETDRS Research Group. Grading diabetic retinopathy from stereoscopic color fundus photographs--an extension of the modified Airlie House classification. ETDRS report number 10. *Ophthalmology*. 1991;98(5 Suppl):786-806.
2. Wilkinson C, Ferris F, Klein R, et al. Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales. *Ophthalmology*. 2003;110(9):1677-1682.
3. Choudhry N, Duker J, Freund K, et al. Classification and guidelines for widefield imaging: recommendations from the International Widefield Imaging Study Group. *Ophthalmol Retina*. 2019;3(10):843-849.
4. Shoughy S, Arevalo J, Kozak I. Update on wide- and ultra-widefield retinal imaging. *Indian J Ophthalmol*. 2015;63(7):575-551.
5. Ashraf M, Shokrollahi S, Salongcay R, Aiello L, Silva P. Diabetic retinopathy and ultrawide field imaging. *Semin Ophthalmol*. 2020;35(1):56-65.
6. Silva P, Cavallerano J, Haddad N, et al. Peripheral lesions identified on ultrawide field imaging predict increased risk of diabetic retinopathy progression over 4 years. *Ophthalmology*. 2015;122(5):949-956.
7. Wessel M, Aaker G, Parlitsis G, Cho M, D'Amico D, Kiss S. Ultra-wide-field angiography improves the detection and classification of diabetic retinopathy. *Retina*. 2012;32(4):785-791.
8. Silva P, Dela Cruz A, Ledesma M, et al. Diabetic retinopathy severity and peripheral lesions are associated with nonperfusion on ultrawide field angiography. *Ophthalmology*. 2015;122(12):2465-2472.
9. Silva P, Cavallerano J, Sun J, Noble J, Aiello L, Aiello L. Nonmydriatic ultrawide field retinal imaging compared with dilated standard 7-field 35-mm photography and retinal specialist examination for evaluation of diabetic retinopathy. *Am J Ophthalmol*. 2012;154(3):549-559.e2.
10. Kernt M, Hadi I, Pinter F, et al. Assessment of diabetic retinopathy using nonmydriatic ultra-widefield scanning laser ophthalmoscopy (Optomap) compared with ETDRS 7-field stereo photography. *Diabetes Care*. 2012;35(12):2459-2463.
11. Rasmussen M, Broe R, Frydkjaer-Olsen U, et al. Comparison between Early Treatment Diabetic Retinopathy Study 7-field retinal photos and non-mydriatic, mydriatic and mydriatic steered widefield scanning laser ophthalmoscopy for assessment of diabetic retinopathy. *J Diabetes Complications*. 2015;29(1):99-104.
12. Aiello L, Odia I, Glassman A, et al. Comparison of Early Treatment Diabetic Retinopathy Study standard 7-field imaging with ultrawide-field imaging for determining severity of diabetic retinopathy. *JAMA Ophthalmol*. 2019;137(1):65-73.
13. Silva P, Cavallerano J, Tolls D, et al. Potential efficiency benefits of nonmydriatic ultrawide field retinal imaging in an ocular telehealth diabetic retinopathy program. *Diabetes Care*. 2014;37(1):50-55.
14. Silva P, Cavallerano J, Sun J, Soliman A, Aiello LM, Aiello LP. Peripheral lesions identified by mydriatic ultrawide field imaging: distribution and potential impact on diabetic retinopathy severity. *Ophthalmology*. 2013;120(12):2587-2595.
15. Price L, Au S, Chong N. Optomap ultrawide field imaging identifies additional retinal abnormalities in patients with diabetic retinopathy. *Clin Ophthalmol*. 2015;9:527-531.
16. Talks S, Manjunath V, Steel D, Peto T, Taylor R. New vessels detected on wide-field imaging compared to two-field and seven-field imaging: implications for diabetic retinopathy screening image analysis. *Br J Ophthalmol*. 2015;99(12):1606-1609.
17. Neubauer A, Kernt M, Haritoglou C, Priglinger S, Kampik A, Ulbig M. Nonmydriatic screening for diabetic retinopathy by ultra-widefield scanning laser ophthalmoscopy (Optomap). *Graefes Arch Clin Exp Ophthalmol*. 2008;246(2):229-235.
18. Marcus D, Silva P, Liu D, et al. Association of predominantly peripheral lesions on ultra-widefield imaging and the risk of diabetic retinopathy worsening over time. *JAMA Ophthalmol*. 2022;140(10):946-954.
19. Gangaputra S, Almukhtar T, Glassman AR, et al. Comparison of film and digital fundus photographs in eyes of individuals with diabetes mellitus. *Invest Ophthalmol Vis Sci*. 2011;52(9):6168-6173.
20. Silva P, Marcus D, Liu D, et al. Association of ultra-widefield fluorescein angiography-identified retinal nonperfusion and the risk of diabetic retinopathy worsening over time. *JAMA Ophthalmol*. 2022;140(10):936-945.

HARNAINA K. BAINS, BS
- MS4, Texas Tech Health Sciences Center El Paso, Paul L. Foster School of Medicine, El Paso, Texas
- naina.bains@ttuhsc.edu
- Financial disclosure: None

VENKATKRISH M. KASETTY, MD
- PGY4, Henry Ford Hospital, Detroit
- vkasett1@hfhs.org
- Financial disclosure: None

DENNIS M. MARCUS, MD
- Vitreoretinal Surgeon, Managing Physician, Southeast Retina Center, PC; Director of Clinical Research, Eye Health America; Professor of Clinical Ophthalmology, Medical College of Georgia, Augusta University, all in Augusta, Georgia
- dmarcus@southeastretina.com
- Financial disclosure: Consultant (Annexon, Clearside, Coherus, Genentech/Roche, Regeneron, Regenxbio, Vantage Biosciences, Vial); Research Grants (Alexion, Amgen, Annexon, Apellis, Clearside, Gemini, Genentech/Roche, Graybug, Gyroscope, Ionis, Iveric Bio/Astellas, Kodiak, Mylan, Oculis, Opthea, Outlook, Oxurion, Regeneron, Regenxbio, Stealth, Topcon, Xplore)

(Continued from page 29)

imaging demonstrated stable perifoveal attenuation of the outer retinal layers in the right eye. The patient underwent genetic testing, which revealed a single exon deletion in *HNF4A*, a known autosomal dominant pathogenic variant.

IMPORTANT CLINICAL PEARLS

Although type 1 and 2 DM are the main drivers of DR, less common types such as monogenic forms of MODY can also present to our clinics. Obtaining a thorough history can be difficult, but it is invaluable. MODY-associated DR is rare, and the phenotypic changes depend on the specific mutation. Early genetic screening of these patients and their family can help with understanding the prognosis, direct treatment, and guide the timing for follow-up visits to mitigate the development of severe microvascular complications. ■

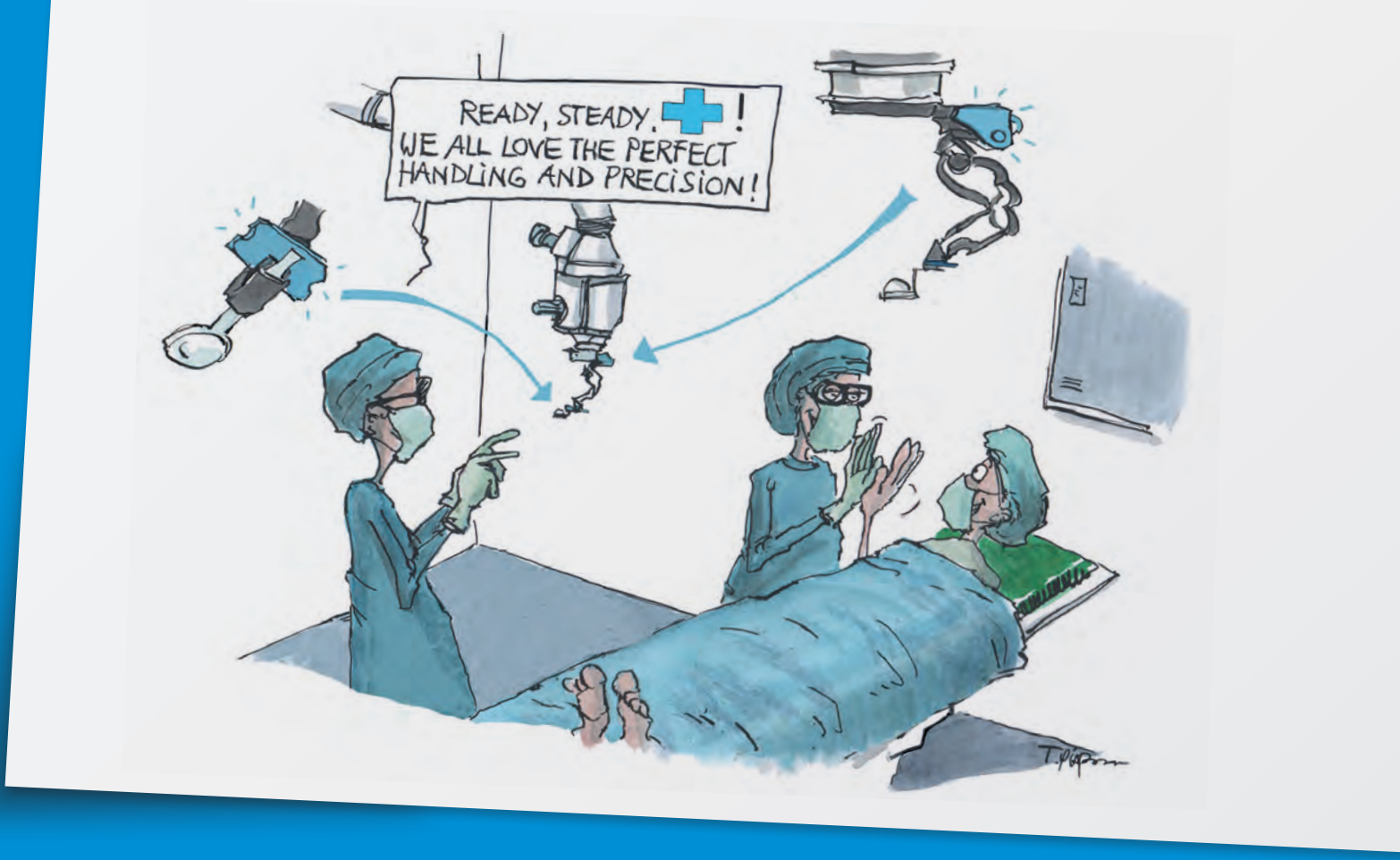
1. Teo ZL, Tham YC, Yu M, et al. Global prevalence of diabetic retinopathy and projection of burden through 2045: systematic review and meta-analysis. *Ophthalmology*. 2021;128(11):1580-1591.
2. Anik A, Çatli G, Abaci A, Böber E. Maturity-onset diabetes of the young (MODY): an update. *J Pediatr Endocrinol Metab*. 2015;28(3-4):251-263.
3. Naylor R, Johnson AK, Gaudio D del. Maturity-onset diabetes of the young overview. *GeneReviews*. May 2018. Accessed June 1, 2023. www.ncbi.nlm.nih.gov/books/NBK500456
4. Fajans SS, Cloutier MC, Crowther RL. Clinical and etiologic heterogeneity of idiopathic diabetes mellitus. *Diabetes*. 1978;27(11):1112-1125.
5. Fajans SS, Bell GI. MODY: History, genetics, pathophysiology, and clinical decision making. *Diabetes Care*. 2011;34(8):1878-1884.
6. Nkonge KM, Nkonge DK, Nkonge TN. The epidemiology, molecular pathogenesis, diagnosis, and treatment of maturity-onset diabetes of the young (MODY). *Clin Diabetes Endocrinol*. 2020;6(1):20.
7. Urakami T. Maturity-onset diabetes of the young (MODY): current perspectives on diagnosis and treatment. *Diabetes Metab Syndr Obes*. 2019;12:1047-1056.
8. Shields BM, Hicks S, Shepherd MH, Colclough K, Hattersley AT, Ellard S. Maturity-onset diabetes of the young (MODY): How many cases are we missing? *Diabetologia*. 2010;53(12):2504-2508.
9. Valkovicova T, Skopkova M, Stanik J, Gasperikova D. Novel insights into genetics and clinics of the *HNF1A*-MODY. *Endocr Regul*. 2019;53(2):110-134.
10. Rudland VL. Diagnosis and management of glucokinase monogenic diabetes in pregnancy: current perspectives. *Diabetes Metab Syndr Obes*. 2019;12:1081-1089.
11. Takase K, Yokota H, Ohno A, et al. A pilot study of diabetic retinopathy in a porcine model of maturity onset diabetes of the young type 3 (MODY3). *Exp Eye Res*. 2023;227:109379.
12. Szopa M, Wolkow J, Matejko B, et al. Prevalence of retinopathy in adult patients with *GCK*-MODY and *HNF1A*-MODY. *Exp Clin Endocrinol Diabetes*. 2015;123(9):524-528.
13. Tymms DJ, Reckless JPD. Proliferative diabetic retinopathy in a patient with maturity-onset diabetes of the young (MODY). *Diabetic Medicine*. 1989;6(5):451-453.

TEDI BEGAJ, MD
- Vitreoretinal Surgeon, Associated Retinal Consultants/Beaumont Health, Royal Oak, Michigan
- Tbegaj@arcpc.net
- Financial disclosure: None

SANDEEP RANDHAWA, MD
- Vitreoretinal Surgeon, Associated Retinal Consultants/Beaumont Health, Royal Oak, Michigan
- Srandhawa@arcpc.net
- Financial disclosure: None

SAHAL SALEH, MD
- Resident, Beaumont Eye Institute, Department of Ophthalmology, Royal Oak, Michigan
- sahal.saleh@corewellhealth.org
- Financial disclosure: None

JEREMY WOLFE, MD
- Vitreoretinal Surgeon, Associated Retinal Consultants/Beaumont Health, Royal Oak, Michigan
- Jwolfe@arcpc.net
- Financial disclosure: None



BIOM® ready+

Get ready for the extra plus in your O.R.

Experience fundus viewing at its best! As the name suggests, the new BIOM® ready+ offers quite a few plus points:

- **Adjustable lens retainer**
  To optimally centre the fundus image
- **Newly designed pivot joint**
  For even greater mechanical stability
- **Ideal for 3D Heads-up systems**
  Its optic never shows the slightest trace of use

www.oculussurgical.com +49 641 2005-298 855-SDI-BIOM (Toll Free, US Only)

OCULUS® SURGICAL

Your Complex TRD Questions Answered

Patients with diabetic eye disease require careful pre- and postoperative planning–and perhaps some intraoperative creativity.

A CONVERSATION WITH ROBERTO DIAZ-ROHENA, MD; DUNCAN FRIEDMAN, MD, MPH; JUAN RUBIO, MD; AND MOISES CHICA, MD

Diabetic tractional retinal detachment (TRD) repair can be one of the most challenging surgical scenarios. Patient-specific factors, instrumentation, and even access to therapeutics all affect how you approach each case. *Retina Today* sat down with several experts from the San Antonio area to discuss their various techniques for tackling complex TRD and combined rhegmatogenous retinal detachment (RRD) surgeries.

RETINA TODAY: WHAT ARE SOME OF THE CHALLENGES THAT ARISE DURING COMPLEX DIABETIC TRD SURGERY?

Moises Chica, MD: Bleeding is the biggest concern for these surgeries, and you must work fast on tamponade when avulsing fibrovascular proliferation. You must stay on top of bleeders as they happen—and always keep a view. If visualization is a problem due to bleeding, I prefer to work under air. I use a soft tip to press lightly on a bleeding vessel, and I always consider panretinal photocoagulation (PRP) before I tackle a macular TRD. Lastly, patients need to be prepared for postoperative vitreous hemorrhage. I get preoperative widefield fluorescein angiography to document the extent of the ischemia, educate patients on the severity of their disease, and set appropriate expectations for surgery.

Roberto Diaz-Rohena, MD: I don't want surprises, so I also get wide-angle photographs whenever possible. I check for ischemia and thin areas that may develop a hole or already have a retinal hole. The biggest frustration is trying to peel these very taut adherent membranes. I use a 27-gauge cutter for segmentation, but some membranes are so fused to the retina that you can't separate them. Because you can't delaminate or segment them, you are faced with tough decisions about whether to be aggressive with the membrane or leave it alone and continue your case.

Duncan Friedman, MD: It's all about progression. I am often surprised by how advanced these membranes are. If the patient has some traction in the preretinal space that is limited to the posterior pole, the case should go smoothly. But if the patient presents with advanced, progressive, tacked-on membranes that are already pulling the retina up into a "tabletop" or "wolf-jaw" configuration, the case will be much more challenging.

I agree that visualization is key. You can see the membranes if there is no hemorrhage, but often it's behind a sheet of blood, and you are entering the unknown. It can be

AT A GLANCE

- Vitreous hemorrhage is a significant problem during surgical repair of diabetic tractional retinal detachments (TRDs).
- Preoperative injection of an anti-VEGF agent can reduce the risk of postoperative complications–but surgeons must be careful of crunch.
- Some surgeons consider adding a buckle for support in some cases of combined rhegmatogenous RD/TRD.
- Performing panretinal photocoagulation in patients with a TRD or combined rhegmatogenous RD/TRD can help to reduce the risk of intraoperative hemorrhage.

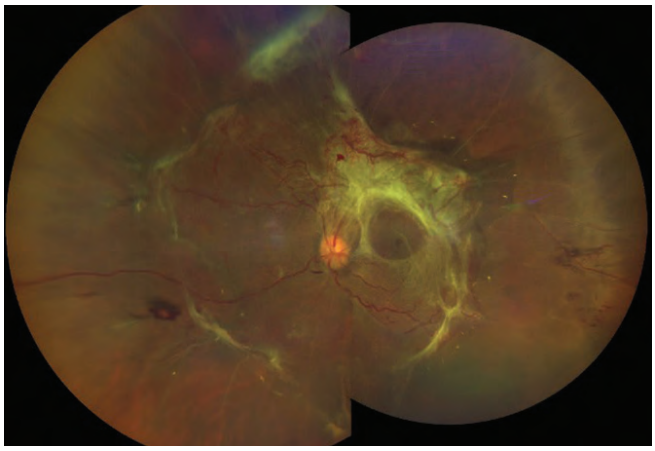


Figure. This 35-year-old Black man presented with uncontrolled diabetes and a hemoglobin A1c of 13. He was not adherent to follow-ups and eventually presented with a TRD in the left eye with a VA of counting fingers.

frustrating to see it get to that point. Screening for diabetic eye disease in everyone could make a significant difference.

Juan Rubio, MD: So many patients still have uncontrolled diabetes who are noncompliant with treatment, and even if the operation goes well, they can show up the next day with these postoperative complications, such as severe hemorrhage. It can be disheartening (Figure).

RT: HOW DO YOU LIMIT COMPLICATIONS?

Dr. Chica: Preoperatively, I inject an anti-VEGF agent a few days before surgery, and I consider cataract removal for patients presenting with a cataract and a nonurgent TRD. Intraoperatively, I carefully consider my choice of tamponade depending on the patient. If I used silicone oil, I consider adding an inferior peripheral iridotomy.

Postoperatively, I watch for neovascularization of the iris and keep a glaucoma colleague at the ready, monitor the hemorrhage with B-scan to check for redetachments, and educate the patient. I ask them to limit the use of anticoagulation medications (eg, heparin-free dialysis) if possible and avoid the Valsalva maneuver for a few weeks by limiting lifting and taking medications to reduce coughing or constipation.

Dr. Diaz-Rohena: I am in the OR on Mondays and tend to inject an anti-VEGF agent the prior Thursday or Friday. When the patient comes in then, I ensure that no issues will cancel the surgery and expect them in the OR on Monday. If I feel that the membranes are particularly taut, I might add a half dose of the anti-VEGF agent on the day of surgery.

Dr. Rubio: I operate on Wednesdays, and depending on the patient, I will inject them the Friday before. A select few patients might do well with an injection the day before.

Dr. Friedman: I always worry about crunch if patients miss surgery. After you do the injection, you're on the clock, and it may be a problem if you cannot operate in a timely fashion.

Dr. Diaz-Rohena: Crunch is a real problem. There's always a controversy about it, but I have seen it and try to ensure that I don't let a patient go too long between the anti-VEGF injection and surgery.

Dr. Rubio: Because I can access it in the hospital, I also like to add an anti-VEGF injection at the end of surgery. For most patients with severe diabetes, it can help reduce the risk of postoperative complications.

Dr. Friedman: I'd like to use it at the end of the case, but access is an issue. During my fellowship, I used it routinely to stop postoperative hemorrhage and it worked wonders; I usually saw a clear eye at 1 week compared with patients who did not get an anti-VEGF injection at the end of surgery. Unfortunately, my ORs don't stock it, and I can't carry a syringe of an anti-VEGF agent in my pocket.

Dr. Diaz-Rohena: I also try to have cataracts removed before bringing a patient to the OR. I can better manipulate the eye with the lens out of the way. It also avoids the potential development of a cataract If I use a gas bubble. It's much easier to visualize any postoperative hemorrhage.

DR. DIAZ-ROHENA: WHAT TAMPONADE DO YOU USE TO REDUCE THE RISK OF POSTOPERATIVE HEMORRHAGE?

Dr. Rubio: I'll use a fluid-air exchange or SF_6 gas. But now that we're using 25-gauge instruments, do you routinely suture your sclerotomies for patients with diabetes? I find that hypotony can be an issue, and with these patients, I want an eye that's not hypotonus after surgery. Depending on the patient and the type of surgery, they may wake up and experience nausea or a blood pressure spike, and I feel better having the sclerotomy sutured up.

Dr. Friedman: Having at least some air tamponade helps promote the clotting cascade and close small bleeds, which is why I prefer at least a partial air tamponade on most vitrectomies. I haven't sutured a 25-gauge sclerotomy in years.

Dr. Diaz-Rohena: When I use 23-gauge instruments, I suture to maintain the IOP. But with the 27-gauge surgery, I don't feel the need because it seems to close on its own.

RT: HOW ARE YOU INTEGRATING PRP?

Dr. Diaz-Rohena: I perform PRP on all my patients with diabetes who have proliferative disease, but with TRDs or combined RRD/TRD cases, I do as much laser as possible without getting too close to the traction to avoid causing contraction. Putting in some laser before surgery reduces the risk of intraoperative hemorrhage.

Dr. Friedman: If it is a nasal TRD, and most of the retina is still attached, I want to get as much laser in as I can. Often, they've already got vitreous hemorrhage, and you can't see anything, but if I have a view, getting the laser in before going to the OR is to the patient's benefit.

Dr. Rubio: For many patients, the eye with a TRD is their good eye, and they already have complications in the other eye. I make sure that the other eye is stable by doing as much PRP in both eyes before I take them to surgery.

IZERVAY™ (avacincaptad pegol intravitreal solution) 2 mg

INDICATION

IZERVAY™ (avacincaptad pegol intravitreal solution) is indicated for the treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD)

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

- IZERVAY is contraindicated in patients with ocular or periocular infections and in patients with active intraocular inflammation.

WARNINGS AND PRECAUTIONS

- Endophthalmitis and Retinal Detachments
  - Intravitreal injections, including those with IZERVAY, may be associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering IZERVAY in order to minimize the risk of endophthalmitis. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately.

NOW APPROVED

for the treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD).

To learn more and stay up to date, visit IZERVAYecp.com

- Neovascular AMD
  - In clinical trials, use of IZERVAY was associated with increased rates of neovascular (wet) AMD or choroidal neovascularization (7% when administered monthly and 4% in the sham group) by Month 12. Patients receiving IZERVAY should be monitored for signs of neovascular AMD.
- Increase in Intraocular Pressure
  - Transient increases in intraocular pressure (IOP) may occur after any intravitreal injection, including with IZERVAY. Perfusion of the optic nerve head should be monitored following the injection and managed appropriately.

ADVERSE REACTIONS

- Most common adverse reactions (incidence ≥5%) reported in patients receiving IZERVAY were conjunctival hemorrhage, increased IOP, blurred vision, and neovascular age-related macular degeneration.

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

IVERIC BIO
An Astellas Company

IZERVAY™ (avacincaptad pegol intravitreal solution)
Rx only

Brief Summary: This information is not comprehensive. Visit IZERVAYecp.com to obtain the FDA-approved product labeling or call 609-474-6755.

1 INDICATIONS AND USAGE
IZERVAY is indicated for the treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD).

2 DOSAGE AND ADMINISTRATION
2.1 General Dosing Information
IZERVAY must be administered by a qualified physician.

2.2 Recommended Dosage
The recommended dose for IZERVAY is 2 mg (0.1 mL of 20 mg/mL solution) administered by intravitreal injection to each affected eye once monthly (approximately every 28 ± 7 days) for up to 12 months.

2.4 Injection Procedure
Only 0.1 mL (2 mg) should be administered to deliver a single dose. Any excess volume should be disposed.

Prior to the intravitreal injection, patients should be monitored for elevated intraocular pressure (IOP) using tonometry. If necessary, ocular hypotensive medication can be given to lower the IOP.

The intravitreal injection procedure must be carried out under controlled aseptic conditions, which includes the use of surgical hand disinfection, sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent). Adequate anesthesia and a broad-spectrum topical microbicide should be given prior to the injection.

Inject slowly until the rubber stopper reaches the end of the syringe to deliver the volume of 0.1 mL. Confirm delivery of the full dose by checking that the rubber stopper has reached the end of the syringe barrel.

Immediately following the intravitreal injection, patients should be monitored for elevation in intraocular pressure (IOP). Appropriate monitoring may consist of a check for perfusion of the optic nerve head or tonometry.

Following intravitreal injection, patients should be instructed to report any symptoms suggestive of endophthalmitis (e.g., eye pain, redness of the eye, photophobia, blurring of vision) without delay.

Each vial and syringe should only be used for the treatment of a single eye. If the contralateral eye requires treatment, a new vial and syringe should be used and the sterile field, syringe, gloves, drapes, eyelid speculum, filter needle, and injection needle should be changed before IZERVAY is administered to the other eye. Repeat the same procedure steps as above.

Any unused medicinal product or waste material should be disposed of in accordance with local regulations.

3 DOSAGE FORMS AND STRENGTHS
Intravitreal solution: 20 mg/mL clear to slightly opalescent, colorless to slightly yellow solution in a single-dose vial.

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

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

5 WARNINGS AND PRECAUTIONS
5.1 Endophthalmitis and Retinal Detachments
Intravitreal injections may be associated with endophthalmitis and retinal detachments. Proper aseptic injection techniques must always be used when administering IZERVAY in order to minimize the risk of endophthalmitis. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay, to permit prompt and appropriate management.

5.2 Neovascular AMD
In clinical trials, use of IZERVAY was associated with increased rates of neovascular (wet) AMD or choroidal neovascularization (7% when administered monthly and 4% in the sham group) by Month 12. Patients receiving IZERVAY should be monitored for signs of neovascular AMD.

5.3 Increase in Intraocular Pressure
Transient increases in intraocular pressure (IOP) have been observed after an intravitreal injection, including with IZERVAY. Perfusion of the optic nerve head should be monitored following the injection and managed as needed.

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

- Ocular and periocular infections
- Active intraocular inflammation
- Endophthalmitis and retinal detachments
- Neovascular AMD
- Increase in intraocular pressure

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 the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of avacincaptad pegol was evaluated in 733 patients with AMD in two sham-controlled studies (GATHER1 and GATHER2). Of these patients, 292 were treated with intravitreal IZERVAY 2 mg (0.1 mL of 20 mg/mL solution). Three hundred thirty-two (332) patients were assigned to sham.

Adverse reactions reported in ≥2% of patients who received treatment with IZERVAY pooled across GATHER1 and GATHER2, are listed below in Table 1.

Table 1: Common Ocular Adverse Reactions (≥2%) and greater than Sham in Study Eye

Adverse Drug Reactions	IZERVAY N=292	Sham N=332
Conjunctival hemorrhage	13%	9%
Increased IOP	9%	1%
Choroidal neovascularization	7%	4%
Blurred Vision*	8%	5%
Eye pain	4%	3%
Vitreous floaters	2%	<1%
Blepharitis	2%	<1%

* Blurred vision includes visual impairment, vision blurred, visual acuity reduced, visual acuity reduced transiently.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
There are no adequate and well-controlled studies of IZERVAY administration in pregnant women. The use of IZERVAY may be considered following an assessment of the risks and benefits.

Administration of avacincaptad pegol to pregnant rats and rabbits throughout the period of organogenesis resulted in no evidence of adverse effects to the fetus or pregnant female at intravenous (IV) doses 5.1 times and 3.2 times the human exposure (based on AUC) at the maximum recommended human dose (MRHD) of 2 mg once monthly, respectively.

In the U.S. general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15%-20%, respectively.

Animal Data
An embryo fetal developmental toxicity study was conducted with pregnant rats. Pregnant rats received daily intravenous (IV) injections of avacincaptad pegol from day 6 to day 17 of gestation at 0.1, 0.4, 1.2 mg/kg/day. No maternal or embryofetal adverse effects were observed at any dose evaluated. An increase in the incidence of a non-adverse skeletal variation, described as short thoracolumbar (ossification site without distal cartilage) supernumerary ribs, was observed at all doses evaluated. The clinical relevance of this finding is unknown. Plasma exposures at the high dose were 5.1 times the MRHD, based on Area Under the Curve (AUC).

An embryo fetal developmental toxicity study was conducted with pregnant rabbits. Pregnant rabbits received daily IV injections of avacincaptad pegol from day 7 to day 19 of gestation at 0.12, 0.4, 1.2 mg/kg/day. No maternal or embryofetal adverse effects were observed at any dose evaluated. Plasma exposure in pregnant rabbits at the highest dose of 1.2 mg/kg/day was 3.2 times the human exposure at the MRHD, based on AUC.

8.2 Lactation
There is no information regarding the presence of avacincaptad pegol in human milk, the effects of the drug on the breastfed infant or on milk production.

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

8.4 Pediatric Use
Safety and effectiveness of IZERVAY in pediatric patients have not been established.

8.5 Geriatric Use
Of the total number of patients who received IZERVAY in the two clinical trials, 90% (263/292) were ≥65 years and 61% (178/292) were ≥75 years of age. No significant differences in efficacy or safety of avacincaptad pegol 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 following IZERVAY administration, patients are at risk of developing neovascular AMD, endophthalmitis, elevated intraocular pressure and retinal detachments. If the eye becomes red, sensitive to light, painful, or if a patient develops a change in vision, instruct the patient to seek immediate care from an ophthalmologist.

Patients may experience temporary visual disturbances and blurring after an intravitreal injection with IZERVAY and the associated eye examinations. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

Manufactured by:
IVERIC bio, Inc., An Astellas Company. Parsippany, NJ 07054

RT: WHAT IS YOUR APPROACH TO COMBINED RRD/TRD?

Dr. Friedman: With combined detachment, you must take a stepwise approach. First, you take down all the anterior-posterior vitreous adhesion. Next, isolate the posterior traction and islands of tangential traction. Finally, address the rhegmatogenous component. At this point, if I know where the break is, I make sure that all tangential traction is off that break. I use that as a retinotomy, hit it with endo-cautery, and then drain as much as possible to get the eye as dry as possible. I then laser some more and treat it like an RRD, at which point I would put in a gas.

Dr. Diaz-Rohena: In addition, I always teach the residents to avoid pulling. When working on these tractional membranes, I gently lift them with the 25-gauge or 27-gauge beveled cutters to access that space and then cut, not pull. Pulling will lead to more tears.

Dr. Friedman: You must find your dissection plane—it's not just one sheet most of the time. The membrane often consists of little fronds sticking up and causing fibrovascular proliferation, almost like a tent over the posterior retina. You must find an inroad and dissect along that plane with your cutter or peel along that plane and isolate those islands of traction to release everything to gain more access.

DR. RUBIO: HOW MUCH PFO DO YOU USE?

Dr. Diaz-Rohena: PFO is like mercury; it finds its way into the strangest areas. It's heavy, so if you have a thin retina with traction, the PFO can make a hole, and the next thing you know, it's under the retina, which is a disaster.

Rather than PFO, I used to do Healon dissection; however, with these new cutters, I've been using it less. Still, with particularly adherent membranes, I may consider using some Healon to dissect. For the same reason, I don't particularly appreciate using oil because it can have some proinflammatory properties. I might have a case or two that requires oil, but I try to use gas more than oil.

Dr. Friedman: I don't use PFO unless I have to, especially for TRDs. I prefer oil with multiple breaks; if the retina's tearing and there's a lot of bleeding, I will use oil.

Dr. Chica: With combined RRD/TRD cases with inferior pathology, I consider using medium-term PFO to tamponade for 2 to 3 weeks.

RT: WHEN WOULD YOU END THE CASE EARLY?

Dr. Friedman: I would say two scenarios. One is if there is too much bleeding that cannot be controlled. If the blood is clotting at the back of the eye, it's a real challenge, and I might consider achieving as much hemostasis as possible and then exiting the eye. The second scenario would be if I see pliable membranes causing a bullous subretinal component with no counter traction. If I have already released the anterior-posterior traction and I've got good PRP in the eye, I would consider ending the case to let the subretinal fluid drain and create counter traction. I can bring the patient back to the OR in 1 to 2 weeks.

Dr. Rubio: If I have been in the eye for a long time and relieved the tractional attachment but the patient still has membranes, I feel comfortable putting in silicone oil, ending the case, and coming back another day. Sometimes the subretinal fluid dries up, and I can go back and deal with the remaining membranes later.

Dr. Diaz-Rohena: If I start to make more tears and holes as I try to clear up the membranes, it's time to stop. I can put in an air or gas bubble, see how much that spreads the retina out, and return to fix the problem.

Dr. Chica: There are a few scenarios in which I consider stopping early and reevaluating the approach: in the setting of intractable bleeding or choroidal hemorrhage and if the patient is unstable. In addition, if the macula is attached before surgery, I will stop the case if I see an iatrogenic break leading to an RRD that threatens the macula.

DR. RUBIO: DOES ANYONE USE SCLERAL BUCKLES?

Dr. Diaz-Rohena: Rarely; I can't think of the last time I put a buckle on an RRD/TRD case.

Dr. Friedman: I think that's too much to do with the eye in one day. I have had cases that have come back that have been phakic and experienced anterior loop traction. For those I might consider an encircling band (style 42), but that's not the first surgery.

Dr. Chica: I do use a buckle for support in some cases of combined RRD/TRD. Then, if peeling and buckling is unsuccessful and I still have traction, I consider a retinectomy. ■

MOISES CHICA, MD
- Vitreoretinal Surgeon, Retina Consultants of Texas, San Antonio
- moises.chica@gmail.com
- Financial disclosure: None

ROBERTO DIAZ-ROHENA, MD
- Head, Retina Department, San Antonio Veterans Affairs Clinic, San Antonio
- Veterans Affairs Site Director for the University of Texas Health - San Antonio Ophthalmology Residency Program, San Antonio
- rdiazmd60@gmail.com
- Financial disclosure: None

DUNCAN FRIEDMAN, MD, MPH
- Vitreoretinal Surgeon, Central Texas Retina Institute, San Antonio
- duncan.friedman@gmail.com
- Financial disclosure: None

JUAN RUBIO, MD
- Vitreoretinal Surgeon, Retina Associates of South Texas, San Antonio
- jrubeosis@gmail.com
- Financial disclosure: None acknowledged

An Algorithmic Approach to DME

With a solid framework, clinicians can treat patients efficiently and effectively.

BY MICHAEL J. ALLINGHAM, MD, PHD

Patients with diabetic eye disease can be some of the most challenging patients to care for in the retina clinic. Nonetheless, clinicians shouldn't have to start from scratch when formulating a treatment plan for each new patient with diabetic macular edema (DME). Most patients with DME fit into one of three typical presentations of disease, and a flexible, evidence-based treatment algorithm can help clinicians care for patients efficiently and effectively.

START WITH IMAGING

The first step is to do a thorough clinical examination and perform OCT and fluorescein angiography (FA), unless it's contraindicated. Although FA is used less frequently with the advent of OCT angiography (OCTA), it remains an important imaging tool in terms of staging disease and tracking retinopathy. These imaging results will guide the initial treatment decisions based on whether the patient has focal, diffuse, or mixed leakage (Figure).

FOCAL LEAKAGE

The most obvious patients to identify are those who have predominantly focal leakage—this constitutes a minority (5% to 10%) of patients in our practice. On clinical examination and FA, patients with focal leakage have a relatively small number of microaneurysms that are responsible for most of the leakage and swelling of the macula. These cases often do well with appropriately applied focal laser therapy, as it is a durable treatment that can save patients from ongoing injections.

In addition, research suggests that microaneurysm-mediated leakage is less responsive to anti-VEGF therapy than diffuse leakage.[1] For example, FA before and after anti-VEGF injections for DME demonstrates a more rapid resolution of leakage when it is diffuse, but frequently shows persistent leakage when it is focal.

DIFFUSE/MIXED LEAKAGE

Most patients with DME present with either diffuse leakage or a mixture of both focal and diffuse leakage. Both groups do well with anti-VEGF injections as the first-line treatment. In my practice, we start with three monthly injections as a unit of treatment, adapted from the more complex 4-2-1-1-1-1 treatment plan used by the Diabetic Retinopathy Clinical Research (DRCR.net) Retina Network Protocol I.[2]

A single anti-VEGF injection rarely resolves the DME; in fact, studies show that most patients need eight or nine injections over the first year of treatment to reach the OCT criteria for withholding therapy.[3]

Because managing diffuse and mixed DME frequently requires long-term treatment, clinicians should consider performing OCT at each injection visit, particularly early in the process to ensure patients require ongoing therapy. Rarely (but it does happen), a patient may experience rapid resolution after a few injections and only require close monitoring. If the patient shows improvement with anti-VEGF injections, clinicians should treat until the patient's OCT

AT A GLANCE

- Most presentations of diabetic macular edema fit into one of three categories, and implementing a flexible, evidence-based treatment algorithm can be efficient and effective.
- Cases of pure focal leakage, while rare, often do well with appropriately applied focal laser treatment.
- Mixed and diffuse leakage often do well with initial therapy with anti-VEGF agents; unresponsive patients may require steroids or grid laser.

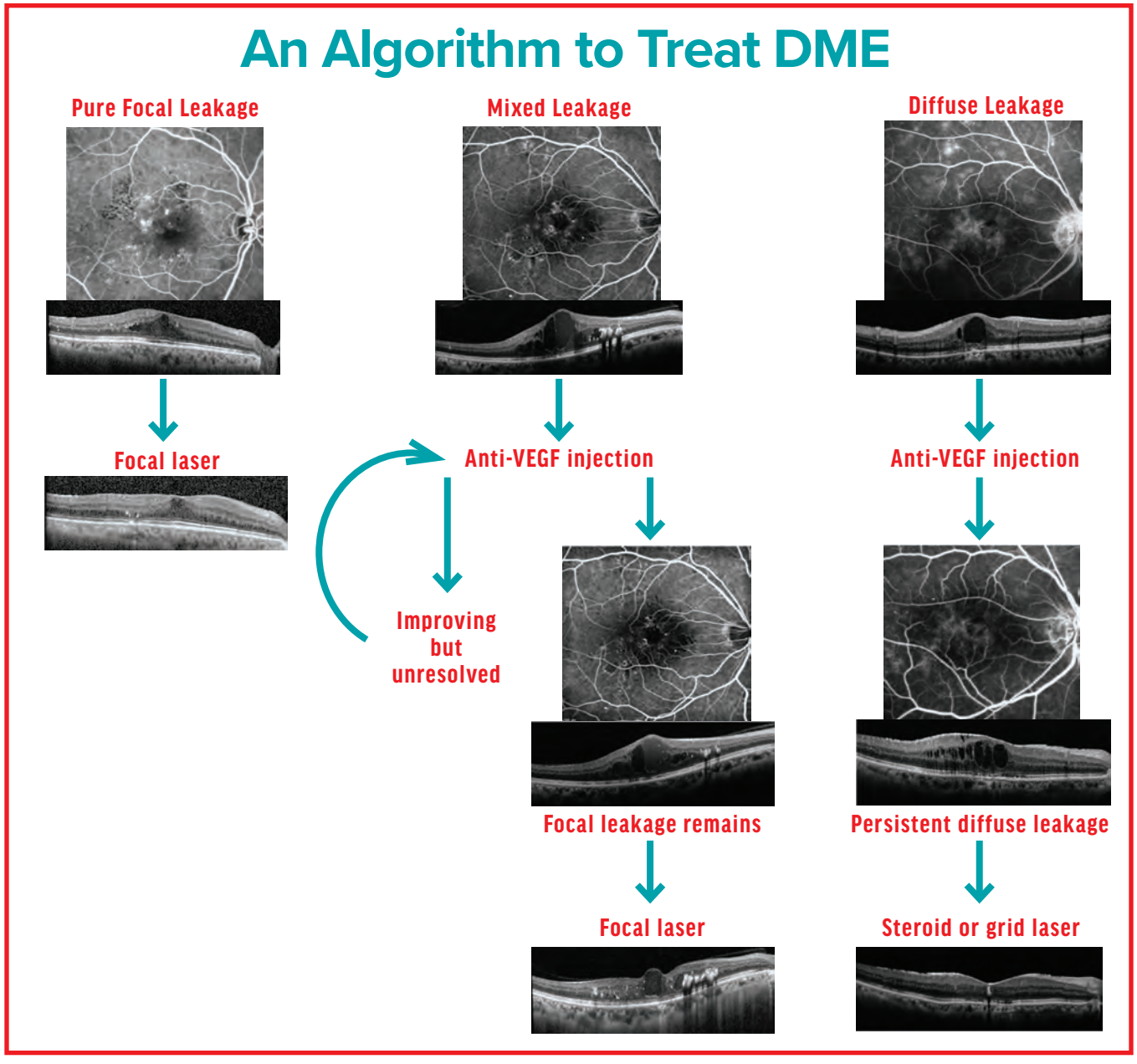


Figure. This algorithm, coupled with a careful assessment of the patient's individual needs, can help clinicians effectively treat DME based on the initial presentation and treatment response.

shows resolution of fluid, vision has improved, and the fovea returns to its expected morphology. Patients with resolved DME still require frequent follow-up and imaging.

Cases of mixed leakage with incomplete response to anti-VEGF therapy may benefit from repeat FA and laser to address the microaneurysms.[2,3] After all, anti-VEGF trials are often trials of anti-VEGF therapy plus rescue laser. In Protocol T, 40% of patients required rescue laser therapy, even with treatment with aflibercept (Eylea, Regeneron).[2,3]

Although many retina specialists may hesitate to add laser therapy, combination treatments are evidence-based and can benefit DME patients with focal and mixed leakage.[2,3]

For patients with diffuse leakage who do not improve on anti-VEGF therapy, the second line of treatment is either steroid or grid laser. I tend to avoid repeat anti-VEGF injections if the patient doesn't respond; instead, I often pivot to steroids. At Duke, we have excellent glaucoma colleagues with whom we collaborate before treating with steroids in cases where IOP response is a significant concern.

I often start with intravitreal dexamethasone (Ozurdex, Allergan/Abbvie) as the first steroid test because it is relatively short acting, and any steroid response is usually manageable with topical medications. For patients who do well with dexamethasone, I frequently move them to a

THE BIRTH OF AN ALGORITHM

The faculty at Duke Eye Center in Durham, North Carolina, led by Scott W. Cousins, MD, designed this treatment algorithm to help trainees and young attendings quickly understand what care most patients with DME need. Without an artificial intelligence platform to evaluate, with 100% accuracy, whether a patient would do well with any given therapy, this algorithm is the next best thing. The Duke faculty continuously update the algorithm as new therapies are approved and new research advances the field's understanding of the disease.

fluocinolone acetonide intravitreal implant (Iluvien, Alimera Sciences). When I dose a patient with a short-acting steroid, I also seek prior authorization for the fluocinolone acetonide implant so that I have it as an option at follow-up.

If patients are not good candidates for steroids, grid laser is an option, but it is often reserved as a salvage treatment.

INCORPORATING NEW THERAPIES

Treatment burden is a significant issue for this patient population, with patients averaging approximately 15 to 16 anti-VEGF injections over a 2-year period.[3] Thus, longer-duration therapies are a welcome advancement. However, clinicians rarely use a treat-and-extend approach for patients with diabetes, and a more pulsatile treatment approach tends to work well. In Protocol T, patients required an average of eight or nine injections in the first year, three or four in the second year, and one or two in the third year.[3]

Clinicians and researchers are still working to determine which patients with diabetes might benefit from treatment with longer-acting or dual-action therapies, such as faricimab (Vabysmo, Genentech/Roche), the port delivery system with ranibizumab (Lucentis, Genentech/Roche), or 8 mg aflibercept (Eylea HD, Regeneron).

At 2 years, patients with DME treated with faricimab every 8 weeks in YOSEMITE and RHINE experienced a mean BCVA change of +10.7 and +10.9 ETDRS letters, respectively; those treated with a personalized treatment interval up to every 16 weeks had a mean BCVA change of +10.7 and +10.1 ETDRS letters, respectively.[4] The researchers noted that more patients achieved resolution of their DME and an absence of intraretinal fluid with faricimab compared with aflibercept every 8 weeks through week 100.[4] Faricimab may be useful for patients who do not achieve a good response with traditional anti-VEGF agents and who have glaucoma or are known steroid responders.

The 2-year results of the phase 3 PHOTON trial of 8 mg aflibercept showed that 89% of patients with DME in the treatment arm maintaining ≥ 12-week dosing through 2 years, 83% maintaining ≥ 16-week dosing, and 43% met the criteria for ≥ 20-week dosing by week 96.[5]

FUTURE ADVANCES

Given the treatment burden, researchers are looking at novel approaches to therapy, some of which are promising.

RGX-314 (Regenxbio) is a gene therapy that enables virus-mediated production of an anti-VEGF Fab fragment in ocular tissues. The phase 2 ALTITUDE is a dose-escalation study for diabetic retinopathy that is underway.[6]

OPT-302 (Opthea), an anti-VEGF therapy that targets VEGF-C and -D, is under investigation as a combination therapy with available anti-VEGF agents. The phase 2 data of patients with refractory DME treated with combination therapy showed that 52% of patients experienced improved VA ≥ 5 letters at 12 weeks compared with baseline.[7]

APX3330 (Ocuphire Pharma) is an oral therapy in phase 2 for the treatment of diabetic retinopathy. Preliminary data suggest that, at 24 weeks, no patients treated with APX3330 had a binocular ≥ 3-step worsening of DRSS from baseline compared with 16% of patients treated with placebo.[8]

These therapies, if successful, have the potential to improve patient care and disrupt the current DME treatment algorithm.

THE ART OF TREATMENT

While the treatment algorithm outlined in this article serves as a useful guide for an increasingly complex therapeutic landscape, the art of medicine remains paramount. There will always be patients for whom treatment burden, cost of therapy, or specific complications such as glaucoma surgery are an overriding concern. These patient concerns will help to inform the treatment approach, and, ultimately, physicians must tailor therapy to the individual patient. ■

1. Allingham MJ, Mukherjee D, Lally EB, et al. A quantitative approach to predict differential effects of anti-VEGF treatment on diffuse and focal leakage in patients with diabetic macular edema: a pilot study. *Transl Vis Sci Technol*. 2017;6(2):7.
2. Bressler SB, Odia I, Glassman AR, et al. Changes in diabetic retinopathy severity when treating diabetic macular edema with ranibizumab: DRCR.net Protocol I 5-year report. *Retina*. 2018;38(10):1896-1904.
3. Wells JA, Glassman AR, Ayala AR, et al. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema two-year results from a comparative effectiveness randomized clinical trial. *Ophthalmology*. 2016;123(6):1351-1359.
4. Lim JI, Wells JA; Eichenbaum DA; et al. Efficacy, durability, and safety of faricimab in diabetic macular edema: 2-year results from the phase 3 YOSEMITE and RHINE trials. *Invest Ophthalmol Vis Sci*. 2022;63:3850.
5. Two-year results for aflibercept 8 mg from PHOTON trial demonstrate durable vision gains at extended dosing intervals in DME [press release]. Eyewire+. June 27, 2023. Accessed July 3, 2023. bit.ly/46uMk6x
6. RGX-314 gene therapy administered in the suprachoroidal space for participants with diabetic retinopathy (DR) without center involved-diabetic macular edema (CI-DME) (ALTITUDE). November 17, 2022. Accessed July 3, 2023. bit.ly/45w0x8H
7. A dose ranging study of OPT-302 with aflibercept for persistent diabetic macular edema. Updated June 22, 2022. Accessed July 3, 2023. bit.ly/3YIntZx
8. Ocuphire presents APX3330 ZETA-1 clinical data in late-breaker session at the American Diabetes Association's Annual Conference [press release]. Ocuphire. June 27, 2023. Accessed July 3, 2023. bit.ly/3sdF0N6

MICHAEL J. ALLINGHAM, MD, PHD
- Assistant Professor of Ophthalmology, Duke University, Duke Eye Center, Durham, North Carolina
- mike.allingham@duke.edu
- Financial disclosure: Consultant (Alimera, Eclipse Life Sciences, Iveric Bio/Astellas, Notal, Pulsar Life Sciences); Grant Support (Stealth Biotherapeutics); Scientific Advisory Board (Alimera, Ocuphire)

YoungMD Connect | RETINA

Unparalleled Access to Thought Leaders in Retina

Calling all trainees and new-to-practice ophthalmologists:

Participate in monthly mentoring sessions & enjoy unequaled access to retina thought leaders and peer mentors.

Scan the QR code for 20% off one-year membership (less than $30).

Discount automatically applied.

MENTORS:

Anton Orlin, MD
Monday, October 16
8:15PM ET

Thomas Albini, MD
Tuesday, December 5
8:15PM ET

PEER MENTORS:

Jordan Deaner, MD
Tuesday, September 19
8:15PM ET

Deepak Sambhara, MD
Monday, November 27
8:15PM ET

YoungMD Connect Members Gain Exclusive Access To:

- ✔ **MENTORING SESSIONS** to build connections with thought leaders.
- ✔ **EDUCATIONAL WORKSHOPS** to complement your clinical training.
- ✔ ***BOOKMARKED* EDITORIAL FORUM** to read the latest articles in eye care.
- ✔ **RESOURCES** to build new skills.
- ✔ **JOB BOARD** to land your first job or make a change.
- ✔ **IN-PERSON EVENTS** to fasttrack your networking opportunities and engage with industry.

YMDC is made possible with industry support from:

VISIONARY: Allergan an AbbVie company | Johnson & Johnson VISION

FOUNDATIONAL: Apellis | Dompé | LUMIBIRD MEDICAL | REGENERON

PARTNER: Alcon | Vision Innovation Partners | STAARSURGICAL

GUIDING: BAUSCH + LOMB | Genentech A Member of the Roche Group | GLAUKOS TRANSFORMING VISION | ZEISS

Brought to you by: bmc vision | RT

Behind the Curtain:
Anti-VEGF Responses in DME

Exploring phenotypes for response to therapy in patients with diabetic macular edema.

BY CONNOR ERICKSEN, MD, AND JARED S. NIELSEN, MD, MBA, FASRS


Anti-VEGF treatments such as bevacizumab (Avastin, Genentech/Roche), ranibizumab (Lucentis, Genentech/Roche), 2 mg aflibercept (Eylea, Regeneron), faricimab-svoa (Vabysmo, Genentech/Roche), and now 8 mg aflibercept (Eylea HD, Regeneron) have revolutionized the way we treat center-involving diabetic macular edema (CI-DME). However, despite adequate treatment, many patients may not achieve 20/20 vision or may have residual fluid. For example, strong responses for patients starting with a baseline VA of 20/30 may be different in terms of letters gained or reduction in intraretinal fluid because of a ceiling effect. The magnitude of response to treatment will differ for each patient depending on their starting point (Figures 1 and 2).

What makes some patients strong responders when it comes to vision gains and fluid reduction and others weak? To help answer this question, we must first uncover what determines a strong versus a weak response. Once we have a treatment response paradigm, we can determine if patient-specific or other parameters influence a strong response.

THE INITIAL DATA

Researchers from the Diabetic Retinopathy Clinical Research (DRCR) Retina Network, led by Jennifer K. Sun, MD, MPH, set out to determine how to better characterize these responses and published their results in *Retina*.[1] They conducted a retrospective review of patients treated with anti-VEGF therapy in the DRCR Protocols I, T, and V and evaluated several outcomes after treatment. The anti-VEGF treatments used included ranibizumab in Protocol I; bevacizumab, ranibizumab, and 2 mg aflibercept in Protocol T; and 2 mg aflibercept in Protocol V. All eyes were treated using the DRCR treatment protocol, which included change in visual acuity ETDRS letters; change in visual acuity ETDRS letters under the curve; gains of at least 5, 10, or 15 letters; change in central subfield thickness (CST); change in CST relative to baseline; and reduction in CST of at least 50 µm, 100 µm, or 200 µm.[1]

The baseline characteristics of the patients were mostly similar with a few differences. There were slightly more men (54%) than women, and 32% were non-White race or Hispanic ethnicity. In terms of the anti-VEGF agent received, 51% received ranibizumab, 28% received 2 mg aflibercept, and 21% received bevacizumab. Approximately a quarter (26%) had excellent baseline vision (20/25 to 20/32), half (51%) had good vision (20/40 to 20/63), and another quarter (23%) had poorer baseline vision (20/80 to 20/320). In terms of DME above the DRCR thresholds for CI-DME, about one-third of patients had mild edema (0 µm to < 75 µm over the threshold), one-third had moderate edema (75 µm to < 175 µm over the threshold), and one-third had severe edema (> 175 µm over the threshold).[1]

There was a varied response in improving visual acuity and reducing CST at 24 weeks. Interestingly, approximately half of the patients with initial excellent visual acuity (20/25 to 20/32) gained at least 5 letters, half of the patients with initial good acuity (20/40 to 20/63) gained at

AT A GLANCE

- The Diabetic Retinopathy Clinical Research Retina Network researchers have proposed definitions for strong and weak phenotypic responses to anti-VEGF therapy for diabetic macular edema (DME), both in terms of letter gains and reductions in central subfield thickness (CST).
- These new definitions can be used to inform patients with DME and future investigations into DME treatment responses.
- At 104 weeks, only 69% of patients with DME who initially had a strong visual acuity and CST response maintained that response.

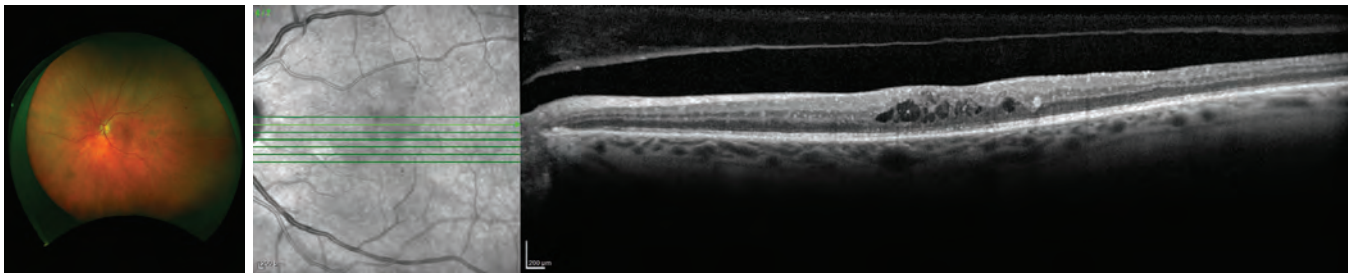


Figure 1. A 59-year-old man with type 2 diabetes presented with CI-DME in the left eye. His VA was 20/40, and CST on spectral-domain OCT measured 348 µm.

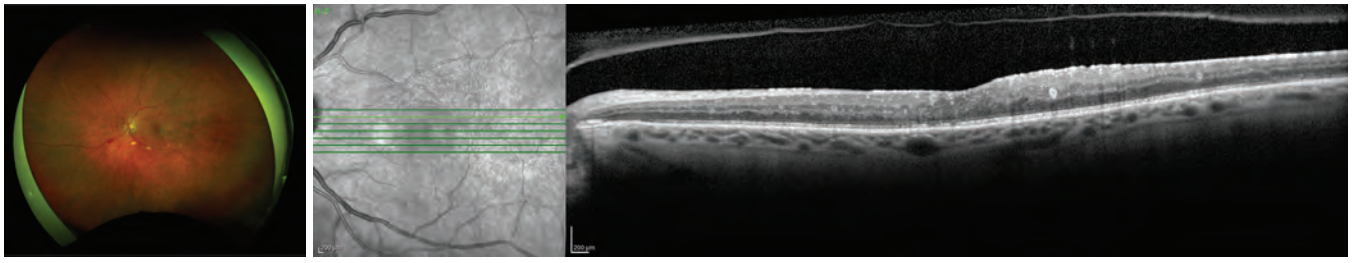


Figure 2. Four weeks after a single anti-VEGF injection of 2 mg aflibercept, the patient exhibited a strong response with a VA of 20/20-2 and CST of 294 µm.

TABLE 1. STRONG RESPONSE BASED ON VISUAL ACUITY GAINS

Baseline VA	Strong Response to Anti-VEGF Treatment
20/25 to 20/32	Gain of at least 5 letters
20/40 to 20/63	Gain of at least 10 letters
20/80 to 20/320	Gain of at least 15 letters

least 10 letters, and half of the patients with initial poorer visual acuity (20/80 to 20/320) gained at least 15 letters. These patients were defined as having a strong response in terms of visual acuity gains (Table 1).[1]

As for the reduction in CST at 24 weeks, approximately half of the patients with mild, moderate, and severe baseline DME had a fluid reduction of at least 50 µm, 100 µm, and 200 µm, respectively. These patients were defined as having a strong response in terms of fluid reduction (Table 2).[1]

Overall, at 24 weeks, 32% of patients were determined to have a strong response in terms of visual acuity gain and CST reduction, 18% had a strong visual acuity response but a weak CST response, 21% had a weak visual acuity response but a strong CST response, and 29% had a weak visual acuity and CST response.[1]

ONGOING TREATMENT

What happens as patients continue to get treatment? Do all patients who initially have strong visual acuity and CST responses maintain that later in their treatment course? The latest data suggests otherwise. At 104 weeks, only 69% of patients who initially had a strong visual acuity and CST response maintained that response. Of those with an

TABLE 2. STRONG RESPONSE BASED ON FLUID REDUCTION

Baseline CI-DME	Strong Response to Anti-VEGF Treatment
0 µm to < 75 µm over DRCR threshold	Reduction in fluid of at least 50 µm
75 µm to < 175 µm over DRCR threshold	Reduction in fluid of at least 100 µm
> 175 µm over DRCR threshold	Reduction in fluid of at least 200 µm

initial strong visual acuity and CST response, 7% converted to a weak visual acuity and weak CST phenotype. Of those with an initial weak visual acuity and weak CST response, 40% stayed that way at 104 weeks while 21% converted to a strong phenotype.[1]

Even considering visual acuity and CST gains separately, patients experienced changes in phenotype with time. In those with a strong visual acuity response at 24 weeks (regardless of CST response), 77% maintained that response at 104 weeks. Of patients with an initial weak visual acuity response at 24 weeks (regardless of CST response), 40% had a strong response at 104 weeks. As for CST gains, 81% of patients with an initial strong response at 24 weeks (regardless of visual acuity response) maintained that response at 104 weeks. Of patients with an initial weak CST response at 24 weeks (regardless of visual acuity response), 42% converted to a strong response phenotype at 104 weeks.[1]

The total number of anti-VEGF injections received varied based on the protocol but had no clear relationship to the treatment response.

(Continued on page 51)

A Broader Approach to Diabetes: Take 2 Minutes for Plants

A brief nutritional intervention in the retina practice can positively affect the long-term health of patients with type 2 diabetes.

BY BRITTANY LONG, BS, AND ALLISON MENEZES, MD


Although current treatments for diabetic retinopathy (DR) can improve vision and delay the progression of DR, they do not affect the progression of diabetes—which requires changes in diet and lifestyle.[1,2] This article outlines the research supporting the benefits of a plant-based diet for patients with type 2 diabetes and a single-center case series investigating the effect of a 2-minute nutritional intervention in the retina practice.

THE EVIDENCE

A recent study of the global burden of type 2 diabetes estimated that 70% (14 million) of new cases can be attributed to dietary factors, such as the intake of insufficient whole grains, excessive refined rice and wheat, and excess processed meat.[2]

Large observational cohort studies indicate that a plant-based diet is associated with reduced mortality, cardiovascular disease, diabetes, and hypertension.[3-5] One prospective cohort study in Taiwan reported that vegetarians and non-vegetarians who converted to a vegetarian diet had a 35% and 53% reduction in the risk of diabetes, respectively, compared with non-vegetarians.[6]

Interventional trials also demonstrate the benefits of plant-based dietary patterns. One randomized controlled study showed that a low-fat vegan diet improved glycemic control in patients with type 2 diabetes more effectively than the standard American Diabetes Association diet at that time.[7] A 2014 meta-analysis and systematic review established that a vegetarian diet is associated with a significant reduction in hemoglobin A1c and improved glycemic control for individuals with type 2 diabetes.[8] More recently, two intervention studies demonstrated that plant-based diets and exercise were more effective at improving glycemic control and sometimes reversing the effects of type 2 diabetes compared with typical diabetes care.[9,10]

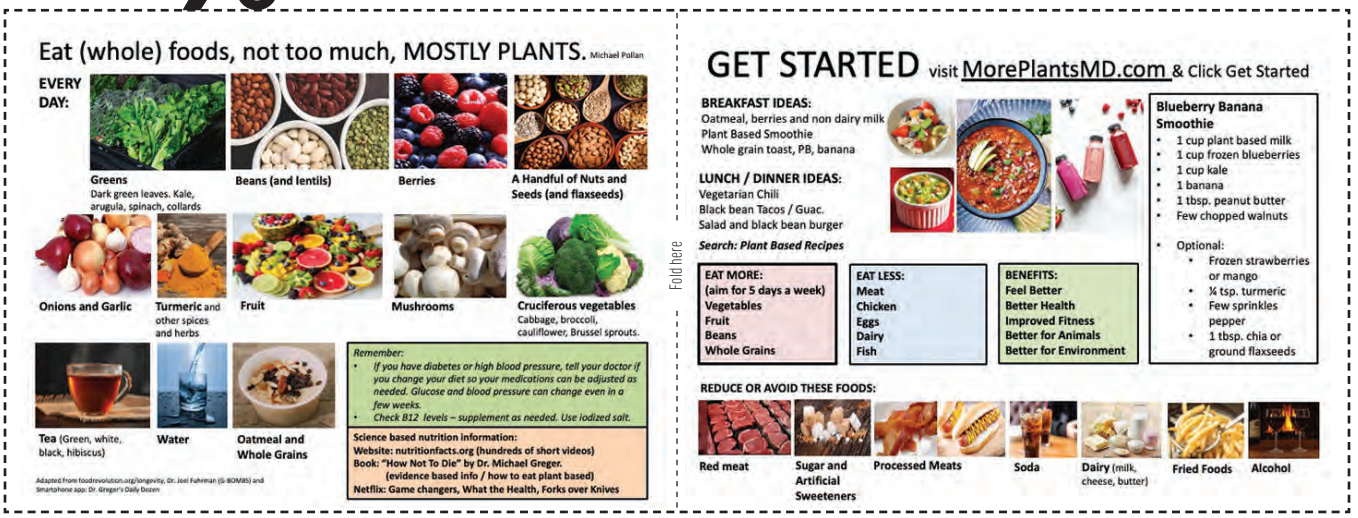
Evidence from these and other studies demonstrates the benefits of a plant-based diet in improving glycemic control and reducing mortality and microvascular and macrovascular complications of diabetes.[11]

Results from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study and the UK Prospective Diabetes Study (UKPDS), both of which studied patients with type 2 diabetes, showed that good glycemic control reduces the incidence and risk of progression of DR.[12] In the ACCORD study, strict glycemic control resulted in a 1/3 reduction in the risk of DR progression. In the ACCORD follow-on study (ACCORDION), even when hemoglobin A1c levels became equivalent once the initial study had been completed, the risk of DR progression over the subsequent 4 years was reduced from 12.7% in the standard treatment group to 5.8% in the intensive treatment group.[12]

We designed a study within our practice to determine if

AT A GLANCE

- Plant-based diets are associated with reduced cardiovascular disease, hypertension, and diabetes.
- The authors designed a study to evaluate whether a brief discussion of plant-based nutrition with patients with type 2 diabetes could motivate them to change their diet and improve their glycemic control.
- The study found that, of 283 consecutive patients with type 2 diabetes, 21% incorporated a more plant-based diet, 80% of whom had improved glycemic control, which has been shown to prevent or delay diabetic retinopathy.



To access this card online, follow the QR code or visit www.moreplantsmd.com/nutr-card.

Figure 1. This nutrition card can help clinicians highlight to patients the key foods to eat or avoid in their daily diets.

a brief plant-based nutritional intervention in a retina practice could motivate patients with diabetes to meaningfully improve their glycemic control, thereby improving their health and reducing the risk of long-term complications.

STUDY DESIGN AND METHODS

We conducted a consecutive case series of prospectively collected established patients with type 2 diabetes from a single retina practice. The inclusion criteria were patients treated with medication for their diabetes, with no dementia, and who lived at home so they could implement dietary changes. The study continued for 6 months.

All patients with diabetes had previously received a 2-minute discussion on the benefits of whole food plant-based nutrition and an 8x11 informational card describing foods to eat, foods to avoid, and where to access evidence-based nutrition information (Figure 1). Patients were encouraged to eat primarily vegetables, fruits, beans, and whole grains 5 days a week, with flexibility for some animal products on weekends. Patients were also informed that the implementation of these recommendations could improve glucose levels within 16 days.[13] As such, it was important for them to check glucose levels regularly and notify their primary care physician if levels decreased so that medications could be adjusted.

During follow-up visits, patients were surveyed as to whether they had changed their diet and whether their glycemic control or weight had changed. Age, duration of diabetes, and level of DR were documented. For patients who indicated that they adopted a more plant-based diet, they self-reported the duration and percent of plants in their diet and any change in hemoglobin A1c levels, fasting glucose levels, medications, and weight.

A PLANT-BASED DIET IS ASSOCIATED WITH REDUCED MORTALITY, CARDIOVASCULAR DISEASE, DIABETES, AND HYPERTENSION.

Days of plant-based eating included consuming vegetables, fruits, legumes, and whole grains with minimal red meat, chicken, fish, eggs, or dairy products. Whole foods rather than processed foods were emphasized. Patients who reported improved hemoglobin A1c, reduced diabetes medications, or improved fasting glucose measurements (without additional medications) were designated to have improved glycemic control.

Results

Over 6 months, 283 consecutive established patients with type 2 diabetes were identified. Of these, 60 patients (21%) changed their diets to include more plants (with at least 2 days per week designated as plant based). The average age and duration of diabetes in patients who chose their usual

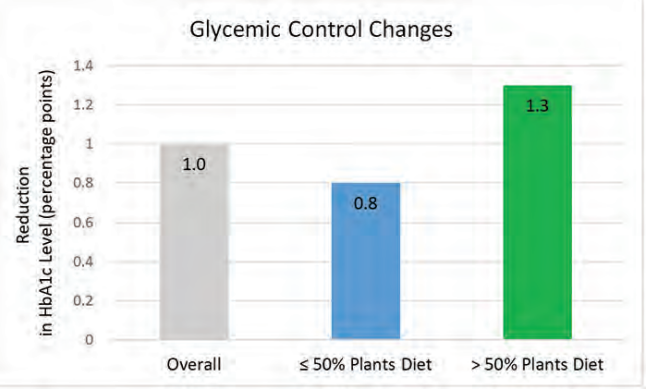


Figure 2. Study results of 60 patients with diabetes who focused on a plant-based diet suggest that patients who had a plant-based diet more than 50% of the time experienced a higher reduction in hemoglobin A1c percentage points compared with patients who had a plant-based diet less than 50% of the time.

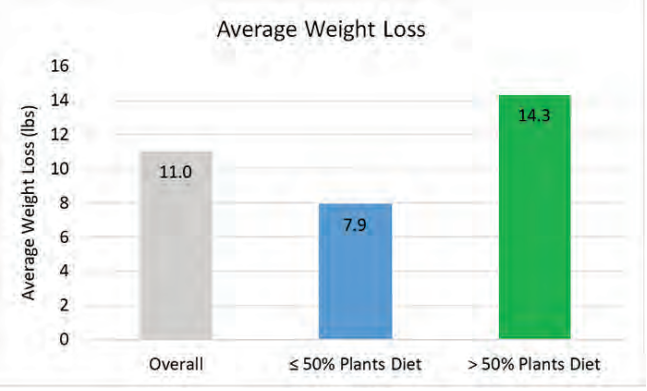


Figure 3. Study results of 60 patients with type 2 diabetes who focused on a plant-based diet showed that those who stayed with a plant-based diet more than 50% of the time experienced more weight loss than patients who had a plant-based diet less than 50% of the time.

diet or who adopted a more plant-based diet were similar. Of the 60 patients who chose a more plant-based diet, 24 (40%) had nonproliferative DR, 11 (18%) had proliferative DR, and 26 (43%) had diabetic macular edema (DME). There was no significant change in retinopathy noted in the short duration of this study other than less DME with anti-VEGF therapy.

Of the 60 patients who changed to a more plant-based diet (range: 15% to 100% plant-based), 80% improved their hemoglobin A1c by an average of 1.0 percentage points (range: 0 to 4.0; Figure 2). Weight loss was reported in 68% of these patients with an average loss of 11 lbs (range: 0 to 98 lbs; Figure 3). As expected, patients who ate a plant-based diet more than 50% of the week had better results, with an average improved hemoglobin A1c of 1.3 percentage points and weight loss of 14.3 lbs.

One patient with type 2 diabetes for 15 years was on 175 units of insulin and had DME. He adopted a 100% whole food plant-based diet, and within 3 months, his hemoglobin A1c decreased from 9 to 5.2 percentage points. Within a year, he had lost 98 lbs and discontinued all medications for diabetes and hypertension. He required intermittent intravitreal anti-VEGF injections for a year and none thereafter.

Limitations and Future Recommendations

The limitations of our study are evidenced by self-reported findings and the results from a single health care provider. Future studies should use a larger sample size, blinded interviewers, objective glucose and weight measurements, and multiple providers. If these findings are reproducible, then this brief, consistent nutritional intervention could be applicable across multiple medical specialties to scale the message of the benefits of plant-based eating for our patients' health and the reduction of risk and progression of DR.

KEY TAKEAWAYS

After receiving brief nutritional information, 21% of patients in our study were motivated to adopt a more plant-based diet. This resulted in improved glycemic control in 80% of patients and weight loss in 68% of these patients, suggesting that retina specialists have an opportunity to positively affect the long-term health of patients and, ultimately, reduce the complications of diabetes with a simple, brief intervention. ■

1. Kherani S, Kim JE. A DRCR Retina Network Update A to Z. *Retina Today*. 2022;16(6):42-44.
2. O'Hearn M, Lara-Castor L, Cudhea F, et al. Incident type 2 diabetes attributable to suboptimal diet in 184 countries. *Nature Medicine*. 2023;29:982-995.
3. Shan Z, Li Y, Baden MY, et al. Association between healthy eating patterns and risk of cardiovascular disease. *JAMA Intern Med*. 2020;180(8):1090-1100.
4. Hu Y, Liu G, Yu E, et al. Low-carbohydrate diet scores and mortality among adults with incident type 2 diabetes. *Diabetes Care*. 2023;46(4):874-884.
5. Appel LJ, Moore TJ, Obarzanek E, et al. A clinical trial of the effects of dietary patterns on blood pressure. *N Engl J Med*. 1997;336(16):1117-1124.
6. Chiu THT, Pan WH, Lin MN, Lin CL. Vegetarian diet, change in dietary patterns, and diabetes risk: a prospective study. *Nutr Diabetes*. 2018;8(1):12.
7. Barnard ND, Cohen J, Jenkins DJA, et al. A low-fat vegan diet improves glycemic control and cardiovascular risk factors in a randomized clinical trial in individuals with type 2 diabetes. *Diabetes Care*. 2006;29(8):1777-1783.
8. Yokoyama Y, Barnard ND, Levin SM, Watanabe M. Vegetarian diets and glycemic control in diabetes: a systematic review and meta-analysis. *Cardiovasc Diagn Ther*. 2014;4(5):373-382.
9. Hanick C, Peterson CM, Sabate J, Davis BC. Effects of a plant-based intensive lifestyle intervention in adults with type 2 diabetes: a randomized controlled trial. *Diabetes*. 2022;71(Supp 1):551-P.
10. Tripathi P, Kadam N, Sharma B, et al. Effectiveness of an intensive lifestyle modification program on type 2 diabetes remission in Indian population. *Diabetes*. 2023;72(Supp 1):1790-P.
11. McMacken M, Shah S. A plant-based diet for the prevention and treatment of type 2 diabetes. *J Geriatr Cardiol*. 2017;14(5):342-354.
12. Ferris III FL, Nathan DM. Preventing diabetic retinopathy progression. *Ophthalmology*. 2016;123(9):1840-1842.
13. Anderson JW, Ward K. High-carbohydrate, high-fiber diets for insulin-treated men with diabetes mellitus. *Am J Clin Nutr*. 1979;32(11):2312-2321.

BRITTANY LONG, BS
- MD Candidate 2025, Florida State University College of Medicine, Tallahassee, Florida
- bal20bs@med.fsu.edu
- Financial disclosure: None

ALLISON MENEZES, MD
- Retina Specialist, Coastal Eye Institute, Sarasota, Florida
- Assistant Professor, Florida State University, College of Medicine, Sarasota Campus, Florida
- Affiliate Staff, Sarasota Memorial Health Care System, Sarasota, Florida
- allison.menezes@gmail.com; www.moreplantsmd.com
- Financial disclosure: None

FROM RESIDENT TO FELLOW: WHAT TO KNOW

Seasoned retina fellows and attendings discuss how to better prepare for the first year of fellowship.

BY ANAND D. GOPAL, MD

July marked the beginning of fellowship for rising vitreoretinal trainees across the country. I sat down with several colleagues to discuss the transition from residency to fellowship and offer advice for making the most of the first year of fellowship.

– Anand D. Gopal, MD

DR. GOPAL: WHAT WAS THE TRANSITION LIKE FROM RESIDENT TO RETINA FELLOW?

Jordan D. Deaner, MD: This transition can be daunting. You are still a trainee but are frequently asked to act as an attending, which means staffing residents and treating non-surgical retinal disease independently. You can prepare for much of this. Spend as much time in the retina clinic and ORs as you can. Increase your confidence by performing as many lasers, injections, and procedures as possible before fellowship.

Louis Z. Cai, MD: As a retina fellow, there is a lot more pressure to know what is going on. Your retina knowledge is only as good as what you learned in residency. It's okay not to know, but it's important to know where to get information and to have a framework for approaching complex situations. For me, the hardest part of transitioning to retina fellowship was learning the logistics and expectations of a new institution (eg, where to get supplies, where to send clinic patients, and how to navigate OR scheduling). Leaning on the residents and other fellows was very helpful during this time.

Austen Knapp, MD: You end residency feeling pretty good about your skills and knowledge in cataract surgery and general ophthalmology. Then, once in fellowship, you must try something relatively new all over again with a higher level of responsibility. However, having a strong foundation in general ophthalmology and medical retina is tremendously helpful. It's a humbling experience but so worth it!

DR. GOPAL: HOW DID YOU PREPARE FOR THE RETINA OR?

Dr. Deaner: Know everything you can about the patient you are operating on. Know the indications and standard steps for the planned surgery. Nothing impresses me more than when my trainee can tell me the history of a complex patient and the steps of surgery. When you get the chance to operate, be confident but cautious. Slow, intentional movements show me that you are technically good but also thoughtful. These actions make me confident that you are ready to progress and do more advanced portions of the surgery.

Aditya S. Rali, MD: When I was a resident, a vitreoretinal fellow gave me a 25-gauge pars plana vitrectomy instrumentation set (that was opened for a case but unused) to play with to get a feel for the instruments. It may sound silly, but at the start of fellowship I would sit at my desk and mimic the movements I struggled with in the OR. Overall, most of the attendings understand that vitreoretinal surgery is hard. If you have done your homework for each case and show that you're thinking through the cases, you should be fine.

Dr. Knapp: Simulating vitreoretinal surgery in a wet lab environment is challenging. However, one of my mentors told me, "Suture, suture, suture." This is extremely practical advice. As vitreoretinal surgeons, we do a great deal of work with the anterior segment, including suturing. Getting involved with retina cases during residency is also helpful in familiarizing yourself with the equipment and the steps of retina surgery. Simple things like knowing the microscope, how the foot pedals work, and the basic principles of each surgery you are doing go a long way early on.

IT'S OKAY NOT TO KNOW, BUT IT'S IMPORTANT TO KNOW WHERE TO GET INFORMATION AND TO HAVE A FRAMEWORK FOR APPROACHING COMPLEX SITUATIONS.

DR. GOPAL: WHAT ARE YOUR TIPS FOR BALANCING LIFE OUTSIDE OF FELLOWSHIP?

Dr. Cai: You must think of time with friends and family as mandatory. So often as physicians we put aside our home life to focus on our careers, but the narrative should be reversed. Say yes to social engagements, even if all you want to do is finish up that paper at home. Schedule calls home just like you would schedule your patient follow-ups.

Dr. Deaner: Try your best to insulate your work and personal life from one another. When you are at work, try to be fully present. Dedicate your operating days and call days completely to work so that you aren't worrying about trying to meet a personal deadline outside of work. Similarly, when you are off work, keep it that way. During fellowship, this doesn't mean you won't have work to do on evenings or weekends but try to schedule it for a block of time and stick to it.

Asad F. Durrani, MD: The key is to make efficient use of your time. On lighter days or calls, I would try to get research done in between seeing patients. It is important to carve out protected time for pursuing your hobbies, exercising, and relaxing with loved ones to prevent burnout.

DR. GOPAL: HOW DID YOU PREPARE FOR THE WRITTEN AND ORAL BOARDS?

Dr. Deaner: For written boards, repetition is key. The greatest piece of advice I can give is to be present and pay attention during your residency didactic lectures. Finally, I did OphthoQuestions (Edcetera) during my downtime and then crammed questions starting a couple of weeks before the examination. For oral boards, find a single, reliable study partner. Learn the format of the examination and what is expected of you. Schedule a couple of hours once a week to review cases with your study partner and ramp up the frequency of your sessions leading up to the board examination. Just before the examination, my co-resident and I reviewed cases for a couple of hours every night.

Dr. Durrani: For written boards, I also used the OphthoQuestions. I started at the end of July and worked mostly on the weekends to complete the questions before the written boards. For oral boards, I started preparing 3 months before the examination, used Ophthalmology Clinical Vignettes, and practiced going through the cases with my co-fellow. I also used Case Reviews in Ophthalmology and the Oral Boards videos.

DR. GOPAL: WHAT DO YOU WISH YOU KNEW BEFORE STARTING FELLOWSHIP?

Dr. Deaner: First, the Dunning-Kruger effect is very real. You won't learn everything in fellowship. If anything, you will mostly learn how much there is to learn and grow. Take it in stride and learn as much as you can every day. I still read nearly every night. Second, vitreoretinal surgery fellowship is hard. It will test your intelligence, stamina, and resolve. There are super high highs and pretty low lows. Stay close to your classmates and co-fellows. Celebrate each other's wins and commiserate when the going gets tough. Our field is the most rewarding in ophthalmology, but it takes grit to succeed.

Dr. Cai: You will have hard times, especially in the OR, where you will question your ability to do surgery. You will have times when residents know more than you do about certain topics even though they are the ones staffing you. Trust your training and trust yourself. It's hard for everyone, and it's okay to have a little imposter syndrome. Even the greatest retina specialists were fellows at one point.

Dr. Durrani: I would have started on research earlier in my fellowship, as the abstract deadlines for all the major conferences come up quickly. I also wish I had been more mindful of ergonomics at the start of fellowship. It is easy to be so focused on excelling clinically that we forget to maintain good posture during stressful times early in fellowship.

DR. GOPAL: ANY FINAL PEARLS OR TIPS?

Dr. Cai: Enjoy spending time with the friends you have made during residency. When you start fellowship, be vulnerable and learn from as many people as you can, not just your attendings. You're going to be sending patients to the wrong clinic or messing up the electronic consent documentation, and it will be okay.

Dr. Deaner: Keep in contact with your mentors from residency. The retina world is small, and they will be great resources when you are looking for a future job. Do some reading in advance (you will have more time as a senior resident than as a fellow). The Duke Manual of Vitreoretinal Surgery and Vitreoretinal Surgery Online (vrsurgeryonline.com) are great references. Michels Retinal Detachment and Ryan's Retina are the classics. Finally, enjoy

your year as a senior resident!

Dr. Knapp: Take the trips, spend time with your people, read one new thing every day, ask for help when you need it (not after the fact), be open to feedback, learn new things in new ways, and invest in your relationships and yourself.

Dr. Rali: You want to come into fellowship with a solid foundation of surgical and medical retina knowledge. At the same time, it is also important to enjoy the end of residency. Residency and fellowship can both be a grind, so it's nice to be refreshed before starting fellowship. As for the first few months of fellowship, it can be a challenging time; vitreoretinal surgery is different from the surgeries we typically master in residency, but everyone goes through the same learning curve. No one is born knowing how to do vitreoretinal surgery, so stay patient and keep at it. It becomes a lot more fun once you start improving! ■

LOUIS Z. CAI, MD
- Vitreoretinal Surgery Fellow, Bascom Palmer Eye Institute, Miami
- Financial disclosure: None

JORDAN D. DEANER, MD
- Uveitis and Vitreoretinal Surgery, Mid Atlantic Retina, Wills Eye Hospital, Philadelphia
- Assistant Professor of Ophthalmology, Thomas Jefferson University, Philadelphia
- jdeaner@midatlanticretina.com
- Financial disclosure: Consultant (Alimera)

ASAD F. DURRANI, MD
- Vitreoretinal Surgery Fellow, Wills Eye Hospital Retina Service, Mid Atlantic Retina, and Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia
- adurrani@midatlanticretina.com
- Financial disclosure: None

ANAND D. GOPAL, MD
- Vitreoretinal Surgery Fellow, Wills Eye Hospital Retina Service, Mid Atlantic Retina, and Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia
- agopal@midatlanticretina.com
- Financial disclosure: None

AUSTEN KNAPP, MD
- Vitreoretinal Surgery Fellow, Byers Eye Institute, Stanford, Palo Alto, California
- Financial disclosure: None

ADITYA S. RALI, MD
- Vitreoretinal Surgery Fellow, Retina Group of Washington, Reston, Virginia
- Financial disclosure: None

(Continued from page 45)

CLINICAL IMPLICATIONS

The current study provides some valuable insights and tools to assist retina specialists in managing CI-DME.

First, the authors propose definitions for strong and weak phenotypic responses in terms of letter gains and reductions in CST. These definitions account for the baseline vision and CST to ensure they are more applicable to all patients, even those with good starting vision and limited DME.

Second, this assists in counseling patients who are starting treatment. Based on the above data, clinicians can advise patients that there is approximately a 50% chance that they will have a strong response after treatment for approximately 6 months. Clinicians can further counsel patients that if they have a strong response in terms of vision acuity, there is approximately a 75% chance they will maintain that for 2 years of treatment. If they don't have an initial strong visual acuity response at 6 months, there is a 40% chance they will start to have a strong response at 2 years, highlighting that eyes with an initial suboptimal response can improve substantially with continued treatment. These numbers can help patients better understand what the future may hold and what they can expect in terms of visual acuity gains.

Third, the definitions of strong and weak responders to anti-VEGF therapy for DME can be used to inform future investigations into DME treatment responses, thus functioning as a powerful research tool.

This analysis does not delve into patient-specific characteristics, such as age or hemoglobin A1c, which may inform why some patients have a strong response and others don't; these definitions could be applied to future research efforts to gauge which patients will be strong and which will be weak responders to therapy.

Overall, this report adds to the growing body of knowledge about CI-DME and patient response to anti-VEGF therapy. It may prove particularly useful when it comes to prognosticating outcomes after treatment. ■

1. Sun JK, Beaulieu WT, Melia M, et al. Defining "strong" versus "weak" response to antivascular endothelial growth factor treatment for center-involved diabetic macular edema. *Retina*. 2023;43(4):616-623.

CONNOR ERICKSEN, MD
- Vitreoretinal Fellow, Wolfe Eye Clinic, West Des Moines, Iowa
- cje2jc@gmail.com
- Financial disclosure: None

JARED S. NIELSEN, MD, MBA, FASRS
- Director, Retina Clinical Research, Retina Fellowship; Medical Director, Wolfe Surgery Center, West Des Moines, Iowa
- jnielsen@wolfeclinic.com
- Financial disclosure: Clinical Research (Alexion, Bayer, Clearside, Genentech/Roche, Gyroscope, Iveric Bio/Astellas, Kodiak Scientific, Novartis, NovoNordisk, Regeneron, Regenxbio); Consultant (Alcon, Apellis, Genentech/Roche, Iveric Bio/Astellas, Regeneron); Speaker (Apellis, Genentech/Roche, Iveric Bio/Astellas)

COINCIDENT PAMM AND AMN: FINDING THE MISSING LINK



Use OCT and OCT angiography to better understand macular ischemic changes in the Henle fiber layer.

BY RANIA ESTAWRO, MD; SHILO VOICHANSKI, MD; AND DAVID SARRAF, MD

OCT and OCT angiography (OCTA) have revolutionized our understanding of retinal diseases. The four macular capillary plexuses can now be readily identified with depth-resolved precision.[1] Recently, Cabral et al used high-resolution OCT to study macular perfusion and proposed a blood flow connectivity pattern consistent with reported histologic studies (Figure 1).[2]

With the technological progress of OCT, a new spectrum of macular ischemic changes can be identified and linked to a specific sequence of capillary plexus hypoperfusion.[3-5] In this article, we discuss two important, and not uncommon, OCT abnormalities: paracentral acute middle maculopathy (PAMM) and acute macular neuroretinopathy (AMN).

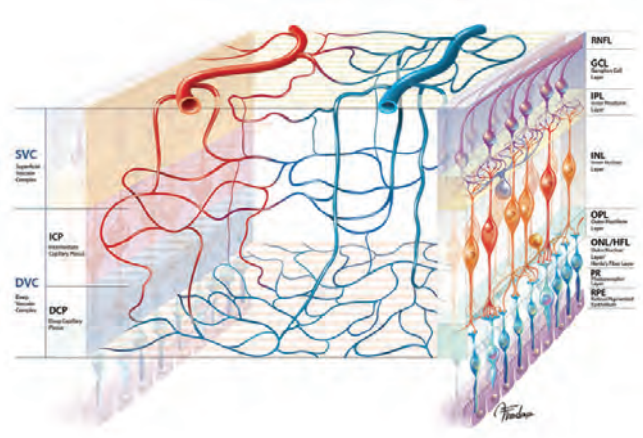


Image courtesy of Cabral et al

Figure 1. This schematic representation of the parafoveal vascular network demonstrates the most frequently observed connectivity patterns seen with high-resolution OCT. The superficial capillary plexus is directly supplied by the major arteries while the DCP receives its blood supply from smaller interconnected arterioles arising from the intermediate retinal capillary plexus. The DCP is the predominant level of venous outflow.[2]

PARACENTRAL ACUTE MIDDLE MACULOPATHY

PAMM is a spectral-domain OCT (SD-OCT) finding that is characterized by a hyperreflective band at the level of the inner nuclear layer (INL) with or without extension into the adjacent inner plexiform layer (IPL) and the outer plexiform layer (OPL).[3] PAMM can be focal, multifocal, or diffuse, and this pattern is best appreciated with en face OCT. These hyperreflective PAMM lesions represent acute infarction of the middle retinal layer or INL secondary to deep capillary plexus (DCP) hypoperfusion, which resolves to leave permanent INL thinning. PAMM can be the earliest sign of macular ischemia, referred to as the ischemic cascade described in association with retinal vascular occlusion (eg, central retinal artery or vein occlusion [CRVO]).[6,7]

At the initial stage of macular hypoperfusion, the middle retinal layers are at the greatest risk of infarction owing to their high metabolic demand and the vulnerable nature of the DCP. With more severe forms of occlusion, deep infarction progresses anteriorly to involve the inner retinal layer.[6]

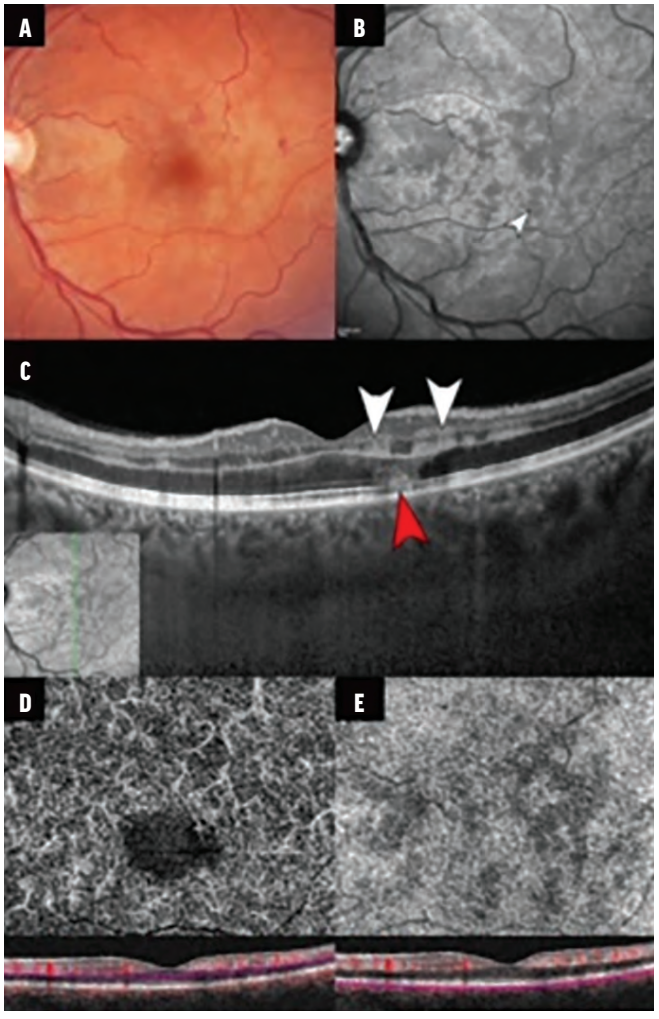
ACUTE MACULAR NEURORETINOPATHY

Bos and Deutman first reported AMN in 1975, and Fawzi et al further analyzed the condition using multimodal imaging in 2012.[3,8] The earliest lesions seen with OCT are associated with disruption of the OPL, followed by retrograde extension through the Henle fiber layer (HFL) with associated impairment of the ellipsoid zone (EZ) and interdigitation zone (IZ).

Hyperreflective lesions resolve over time and can leave outer nuclear layer (ONL) thinning with the potential to disrupt the junction between the outer photoreceptor segment and retinal pigment epithelium (RPE). Although the etiology of AMN is debatable, most studies correlate AMN with DCP ischemia.[3,4,9] Cabral et al localized AMN lesions to the center of the DCP vortices at the level of collecting venules using a complex OCTA analysis investigation.[10]

COINCIDENT PAMM AND AMN

Although PAMM and AMN are distinct entities,[11] they have overlapping features. Both are associated with



Images courtesy of Iovino et al

Figure 2. Color fundus photography shows perivenular retinal whitening in the macula with scattered retinal hemorrhages and venous dilation consistent with CRVO (A). NIR imaging shows perivenular hyporeflectivity corresponding to the PAMM lesions (B; white arrow). The vertical SD-OCT B-scan shows hyperreflective band-like lesions primarily involving the INL and extending into the adjacent IPL/OPL consistent with PAMM (C). Note the characteristic hyperreflective lesion, consistent with AMN, present in the ONL and radiating in the HFL. The NIR image indicates the location of the SD-OCT B-scan (C, inset). En face OCTA of the DCP shows multiple areas of absent decorrelation signal that colocalize with the PAMM lesions on OCT (D). The cross-sectional SD-OCT B-scan indicates the segmentation (pink lines) of the corresponding OCTA at the level of the DCP (D, inset). En face OCTA imaging of the choriocapillaris shows areas of flow signal loss presumably attributed to shadow artifacts from the overlying PAMM lesions (E). The cross-sectional SD-OCT B-scan indicates the segmentation (pink lines) of the corresponding OCTA at the level of the choriocapillaris (E, inset).[12]

paracentral scotomas, and each manifests as parafoveal hyperreflective lesions on OCT and hyporeflective lesions on near-infrared reflectance (NIR). Moreover, both entities are attributed to DCP hypoperfusion.[6,9,10] However, the acute lesions of PAMM characteristically appear in the INL, while AMN lesions start in the OPL. Additionally, PAMM lesions progress anteriorly and spare the outer retinal layers, while

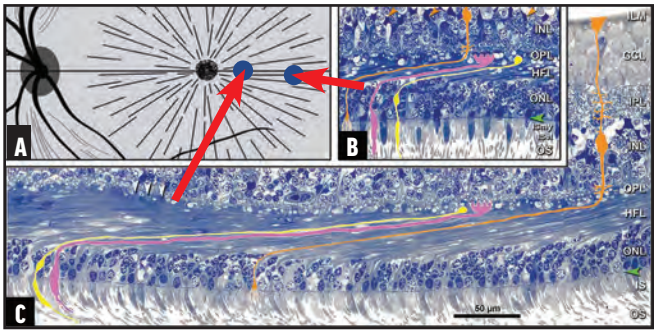


Image adapted from Li et al

Figure 3. The en face view of normal Henle fibers shows their radial dispersion from the foveal center (A). In the perifoveal area of the central section, the Henle fibers are longitudinally oriented but short (B). A Müller cell (orange), rod (yellow), and cone (pink) photoreceptor and the Müller cell bodies (arrowheads) are shown. Close to the fovea in the central section, the Henle fibers are longitudinally oriented and long (C).[14]

AMN lesions progress posteriorly and can cause permanent disruption of EZ and IZ.

Recently, Iovino et al reported coincident PAMM and AMN lesions in the same eye, implicating a common pathology (Figure 2).[12] The authors found an association of PAMM and AMN in eyes with retinal vein occlusion (CRVO, hemi-RVO) and Purtscher-like retinopathy. With Purtscher, all three levels of retinal impairment were identified in the affected eye, including inner retinal infarction (ie, cotton-wool spots), middle retinal infarction (ie, PAMM), and outer retinal disruption (ie, AMN). Impairment of the DCP can cause infarction not only to the middle retina and INL but can also, rarely, disrupt the contiguous HFL with retrograde disruption of the outer retina. This can lead to AMN, known as angular sign of HFL hyperreflectivity (ASHH) with OCT.[13]

THE MISSING LINK?

The HFL is comprised of bundles of unmyelinated photoreceptor axons intermingled with outer Müller cell processes with a 1 to 1 ratio.[13] It has a unique distribution within the macular area. At the foveal center, the HFL is short and vertical. In the perifoveal region, the obliqueness of the striations increases, and the HFL assumes an almost horizontal trajectory, giving rise to the typical Z-shape HFL pattern. Outside the perifovea, the obliqueness of the striations decreases, and the HFL again assumes an almost vertical pathway (Figure 3).[13,14]

The Müller cell bodies reside within the INL and receive their blood supply via the DCP.[15] Interestingly, histopathology of hypoperfused Müller cells shows cytoplasm swelling without enlargement of intercellular spaces.[16] Also, the DCP functions as the main source of blood supply to the synaptic layer of the OPL, which is connected to the contiguous HFL.[17] Thus, although photoreceptors receive most of their nutritional support from the choroidal circulation, impairment of the DCP can affect the photoreceptor inner segment and/or cause Müller cell disruption within the HFL.

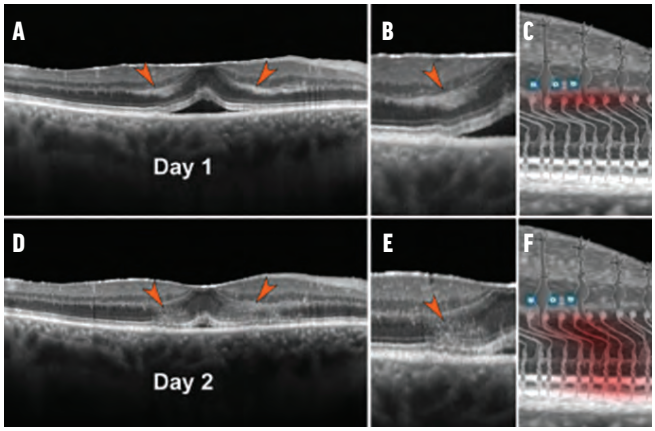


Image adapted from Ramtohul et al

Figure 4. SD-OCT horizontal B-scan through the fovea shows hyperreflective lesions (orange arrows) confined to the OPL and HFL (A, B). A schematic representation shows the presumed hyperacute damages in AMN, including DCP disruption and photoreceptor synapse and axon insults (C). Tracked OCT B-scan shows retrograde extension of the hyperreflective lesions to the ONL, EZ, and IZ (D, arrows). The angular configuration of the hyperreflective lesions is especially apparent in the temporal side of the fovea (E). Persistent DCP alteration can be observed in the schematic representation of the ASHH in AMN characterized by retrograde extension of the insult to the whole photoreceptor length (F).[13]

For follow-up imaging for figures 2 and 4, follow the QR code or visit *retinatoday.com*.

This might explain the potential retrograde extension of AMN lesions toward the outer retinal layers.[18]

OCTA studies show that PAMM is the result of DCP impairment,[19,20] and more recently Chu et al confirmed that PAMM was associated with reduced DCP and middle capillary plexus flow signals, and occasionally superficial capillary plexus as well, while the flow reduction in AMN was limited to DCP alone.[9] The DCP impairment in AMN may occur at the level of the capillary vortex or draining venule.[10]

The location of outer retinal changes associated with DCP ischemia appears to be influenced by the length and orientation of the HFL. Ramtohul et al proposed a novel OCT biomarker indicative of acute photoreceptor disruption involving the HFL, the ASHH of macular disease.[13] This sign unifies the pathoanatomy common to various disorders affecting the HFL including those that result from DCP impairment such as AMN (ie, retrograde disruption of the HFL) and those that result from anterograde disruption of the HFL such as trauma, laser, and acute posterior multifocal placoid pigment epitheliopathy (Figure 4).[13]

Thus, we presume that deep capillary retinal impairment can have two serious macular implications. The first and most common is PAMM, which represents INL infarction with the rare potential for anterograde progression following the predominantly vertical arrangement of the retinal capillary plexus.[6] The second is AMN, which may arise as a result of OPL ischemia with retrograde disruption of the Müller cell processes and/or photoreceptor axons comprising the HFL. ■

1. Campbell JP, Zhang M, Hwang TS, et al. Detailed vascular anatomy of the human retina by projection-resolved optical coherence tomography angiography. *Sci Rep*. 2017;7:42201.
2. Cabral D, Fradinho AC, Pereira T, et al. Macular vascular imaging and connectivity analysis using high-resolution optical coherence tomography. *Transl Vis Sci Technol*. 2022;11(6):2.
3. Fawzi AA, Pappuru RR, Sarraf D, et al. Acute macular neuroretinopathy: long-term insights revealed by multimodal imaging. *Retina*. 2012;32(8):1500-1513.
4. Sarraf D, Rahimy E, Fawzi AA, et al. Paracentral acute middle maculopathy: a new variant of acute macular neuroretinopathy associated with retinal capillary ischemia. *JAMA Ophthalmol*. 2013;131(10):1275-1287.
5. Long CP, Chan AX, Bakhoum CY, et al. Prevalence of subclinical retinal ischemia in patients with cardiovascular disease - a hypothesis driven study. *EClinicalMedicine*. 2021;33:100775.
6. Bakhoum MF, Freund KB, Dolz-Marco R, et al. Paracentral acute middle maculopathy and the ischemic cascade associated with retinal vascular occlusion. *Am J Ophthalmol*. 2018;195:143-153.
7. Zhao PY, Johnson MW, McDonald HR, Sarraf D. paracentral acute middle maculopathy and the ischemic cascade: toward interventional management. *Am J Ophthalmol*. 2022;234:15-19.
8. Bos PJ, Deutman AF. Acute macular neuroretinopathy. *Am J Ophthalmol*. 1975;80(4):573-584.
9. Chu S, Nesper PL, Soetikno BT, Bakri SJ, Fawzi AA. Projection-resolved OCT angiography of microvascular changes in paracentral acute middle maculopathy and acute macular neuroretinopathy. *Invest Ophthalmol Vis Sci*. 2018;59(7):2913-2922.
10. Cabral D, Ramtohul P, Zatreanu L, et al. Deep capillary plexus features in acute macular neuroretinopathy: novel insights based on the anatomy of Henle fiber layer. *Invest Ophthalmol Vis Sci*. 2022;63(13):4.
11. Rahimy E, Kuehlewein L, Sadda SR, Sarraf D. Paracentral acute middle maculopathy: What we knew then and what we know now. *Retina*. 2015;35(10):1921-1930.
12. Iovino C, Au A, Ramtohul P, et al. Coincident PAMM and AMN and insights into a common pathophysiology. *Am J Ophthalmol*. 2022;236:136-146.
13. Ramtohul P, Cabral D, Sadda S, Freund KB, Sarraf D. The OCT angular sign of Henle fiber layer (HFL) hyperreflectivity (ASHH) and the pathoanatomy of the HFL in macular disease. *Prog Retin Eye Res*. 2023;95:101135.
14. Li M, Huisingh C, Messinger J, et al. Histology of geographic atrophy secondary to age-related macular degeneration: a multilayer approach. *Retina*. 2018;38(10):1937-1953.
15. Bringmann A, Pannicke T, Grosche J, et al. Müller cells in the healthy and diseased retina. *Prog Retin Eye Res*. 2006;25(4):397-424.
16. Fine BS, Brucker AJ. macular edema and cystoid macular edema. *Am J Ophthalmol*. 1981;92(4):466-481.
17. Yu DY, Cringle SJ. Oxygen distribution and consumption within the retina in vascularised and avascular retinas and in animal models of retinal disease. *Prog Retin Eye Res*. 2001;20(2):175-208.
18. Pecen PE, Smith AG, Ehlers JP. Optical coherence tomography angiography of acute macular neuroretinopathy/paracentral acute middle maculopathy. *JAMA Ophthalmol*. 2015;133(12):1478-1480.
19. Scharf J, Freund KB, Sadda S, Sarraf D. Paracentral acute middle maculopathy and the organization of the retinal capillary plexuses. *Prog Retin Eye Res*. 2021;81:100884.
20. Nemiroff J, Phasukkijwatana N, Sarraf D. Optical coherence tomography angiography of deep capillary ischemia. *Dev Ophthalmol*. 2016;56:139-145.

RANIA ESTAWRO, MD
- International Retina Fellow, Retinal Disorders and Ophthalmic Genetics Division, Stein Eye Institute, University of California Los Angeles, Los Angeles
- Medical Retina Consultant, Retina Department, Al-Watany Eye Hospital, Cairo, Egypt
- Financial disclosure: Speaker (Allergan/AbbVie, Bayer, Genentech/Roche, Novartis)

DAVID SARRAF, MD
- Clinical Professor of Ophthalmology, Retinal Disorders and Ophthalmic Genetics Division, Stein Eye Institute, University of California Los Angeles, Los Angeles
- Greater Los Angeles VA Healthcare Center, Los Angeles
- dsarraf@ucla.edu
- Financial disclosure: Consultant (Amgen, Bayer, Endogena Therapeutics, Genentech/Roche, Iveric Bio/Astellas, Novartis, Optovue/Visionix); Research Grants (Amgen, Boehringer, Genentech/Roche, Heidelberg, Optovue/Visionix, Regeneron, Topcon)

SHILO VOICHANSKI, MD
- Medical Retina Fellow, Retinal Disorders and Ophthalmic Genetics Division, Stein Eye Institute, University of California Los Angeles, Los Angeles
- Vitreoretinal Division, Ophthalmology Department, Shaare Zedek Medical Center, Jerusalem, Israel
- Financial disclosure: None

The Importance of Intraocular Pressure Stability During Retinal Surgery

COURTNEY CRAWFORD, MD, FACS — VITREORETINAL SURGEON, STAR RETINA. BURLESON, TX; USA
MARTÍN CHARLES, MD — VITREORETINAL SURGEON, CIUDAD AUTÓNOMA DE BUENOS AIRES. BUENOS AIRES, ARGENTINA

Several important organ functions in the human body regulate themselves in order to preserve life. For example, body temperature is regulated within 2 degrees Celsius before organ systems begin to malfunction.[1] In a similar way, intraocular pressure (IOP) is also regulated within a narrow range, and if exceeded, can result in morbid sequelae. Acute intraoperative ocular hypotony can result in suprachoroidal hemorrhage, especially if the initial IOP is elevated.[2] Ocular hypertension can also have its consequences. Data from the cataract surgery literature indicate that postoperative and intraoperative elevated IOP can adversely affect visual outcomes in the form of post-cataract-extraction anterior ischemic optic neuropathy (PCE-AION), which develops within a few hours or days after the extraction,[3] or postoperative nonarteritic anterior ischemic optic neuropathy (NAION), characterized by sudden, painless, mostly irreversible, and generally nonprogressive visual loss.[4] IOP elevations of 45 mm Hg or higher have been documented to be associated with NAION.[5] A study by Findl determined that in healthy subjects, choroidal blood flow decreases when IOP is increased by as little as 10 mm Hg, and significantly with an increase of 20 mm Hg. Reduced blood flow velocity was also noted in the central retinal artery with elevated IOP.[6] Nevertheless, the ocular elements that ultimately suffer the consequences leading to compromised vision occur in the posterior segment, despite the abnormal intraoperative IOP occurring within the anterior segment. As opposed to the healthy subjects in the study by Findl, the effect of reduced perfusion from elevated IOP may have a further detrimental effect in unhealthy subjects who typically undergo vitreoretinal surgery and could experience compromised perfusion. Any factor that reduces circulation, such as elevated intraoperative IOP, can jeopardize vision.

INTRAOPERATIVE IOP MANAGEMENT OVER TIME

Retinal surgeons, for the most part, are knowledgeable about avoiding the extremes of IOP during surgery. There has been significant progress since the days of Machemer, who used gravity to infuse the eye with saline during vitrectomy. Some of today's modern surgical vitrectomy consoles utilize a version of Vented Gas-forced Infusion (VGFI) in which an increased pressure, as well as a rapid decrease of infusion pressure in the buffered saline solution (BSS) bottle, is possible via a surgeon-controlled foot pedal.[7] In 2014, Stalmans highlighted features of the EVA System (DORC International, Zuidland, The Netherlands), including Automatic Infusion Compensation (AIC), which compensates for the volume mismatch typically experienced when aspirating with the vitrector in vacuum mode at relatively high vacuum levels. The infusion pressure setting elevates by generating higher air pressure in the infusion bottle as the aspiration of the vitrector increases to prevent collapse; the bottle is vented back to baseline to prevent a rise in IOP when cutter aspiration stops.[8] VGFI-based systems are a significant improvement, but they are not perfect. Studies in human eyes have shown that IOP during vitrectomy using a gravity flow or a vented gas-forced infusion method ranged from 0-120 mm Hg.[9]

There has been an evolution of control systems over time that optimize operational efficiency, such as fuel delivery for a gasoline internal combustion engine. Prior to the use of fuel injection in modern vehicles, the air-fuel mixture delivered to the cylinders was regulated by a carburetor. Although this system worked fairly well for over 100 years, modern fuel injection systems use mass airflow and oxygen sensor data to provide information to a computer that sends duty-cycle information to fuel injectors to provide optimized engine efficiency and performance. This closed-loop operation uses feedback to continuously deliver optimal combustion efficiency. In a similar manner, the CONSTELLATION Vision System (Alcon LLC, Fort Worth, TX; USA, Figure 1) has a closed-loop pressure control system that can maintain constant IOP during vitrectomy within ±1-2 mm Hg regardless of aspiration flow rates.[10]

Figure 1. The CONSTELLATION Vision System

CONSTELLATION has a noninvasive flow sensor that uses ultrasound wave differential to detect the actual flow velocity that can, then, derive flowrate and other operational parameters.[11] This approach allows the IOP to be constantly controlled throughout the various operating conditions experienced during a case. Sugiura et al also concluded that CONSTELLATION IOP Control can attenuate IOP fluctuations during vitrectomy maneuvers with no significant difference in IOP fluctuations between gauge sizes.[12]

INTRAOPERATIVE IOP MANAGEMENT – SURGICAL CONSOLE PERFORMANCE

In 2020, Shinkai et al first reported on the variability of IOP during ex-vivo vitrectomy in Porcine eyes between the EVA AIC and the CONSTELLATION Vision System IOP Control. The experimental findings demonstrated that during core vitrectomy for the 25G and 27G cutters, there was less variability with the CONSTELLATION Vision System when compared to the EVA in vacuum mode. However, the least variability was with the 27G EVA in Flow Mode.[13] Although this study measured IOP variability, the time duration of IOP outside of the set range was not measured. To further evaluate intraoperative IOP performance, data from a video presentation at the 2023 American Society of Retina Specialists meeting in Seattle described an experiment undertaken to evaluate the IOP variability of these same two systems during simulated vitrectomy and described the time during which each system spent outside of the set range. The study was performed at vacuum setting of 250 mm Hg, 450 mm Hg and 650 mm Hg for both the 25- and 27-gauge TDC cutters (DORC International, Zuidland, The Netherlands) at 16,000 cuts per minute with the AIC settings that allowing IOP to be at 30 mm Hg during the aspiration of pure BSS. The CONSTELLATION Vision System was also tested using the same vacuum settings with the 25- and 27- gauge HYPERVIT cutters (Alcon LLC, Fort Worth, TX; USA) at 20,000 cuts per minute with IOP Control ON set to 30 mm Hg.[14]

The average IOP prior to aspiration, average IOP during the vitreous removal, and average IOP after full vitreous removal were determined and analyzed; statistical analysis was performed using ANOVA with a P-value set to 0.05.[14] The general appearance of the IOP pressure tracing for the 25G probes is shown on Figure 2. For CONSTELLATION, there is little IOP variation regardless of the engaged medium (vitreous or BSS) or the applied vacuum; the IOP ranged from 30.16 ± 0.17 to 31.55 ± 1.38 mm Hg. However, the EVA AIC shows a greater IOP variation dependent on both the applied vacuum as well as with the engaged medium, with IOP ranging from 30.43 ± 0.15 to 44.62 ± 1.24 mm Hg.[14] Figure 3 also shows that CONSTELLATION IOP Control also spend a longer duration of the time (from 63% to 93%) in the target range (27.5-32.5 mm Hg) than the EVA AIC (from 16% to 23%).[14]

Similarly, for the 27G probes, the general appearance of the IOP tracing is shown on Figure 4. For CONSTELLATION, little variation is seen regardless of the engaged medium or the applied vacuum, with IOP ranging from 30.19 ± 0.33 to 31.32 ± 1.06 mm Hg. However, the EVA AIC shows a greater IOP variation, ranging from 30.34 ±0.21 mm Hg to 38.18±0.76 mm Hg, dependent on both the engaged medium as well as with the applied vacuum.[14] Furthermore, Figure 5 shows that CONSTELLATION IOP Control also spends a longer duration of the time (from 69% to 93%) in the target range (27.5-32.5 mm Hg) than the EVA AIC (from 13% to 22%).[14]

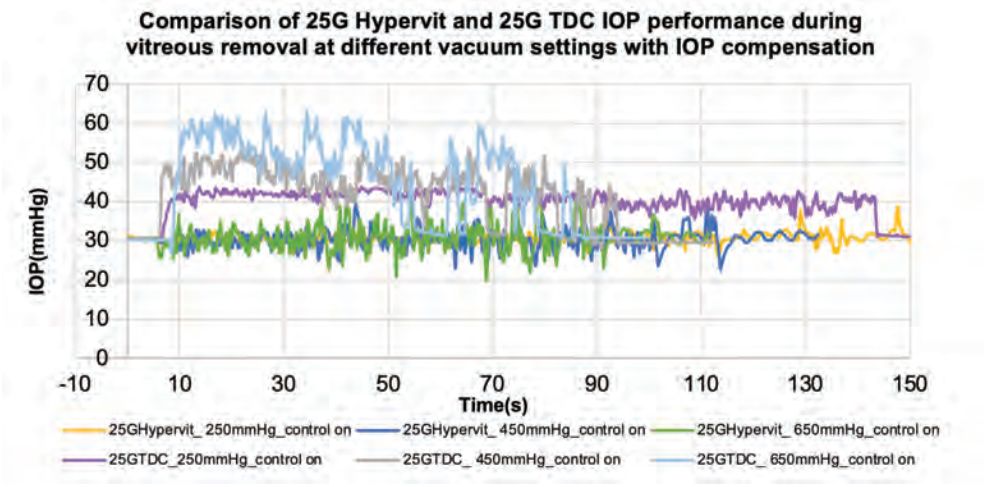


Figure 2. IOP performance (25G) during vitrectomy for the CONSTELLATION IOP Control and EVA AIC[14]

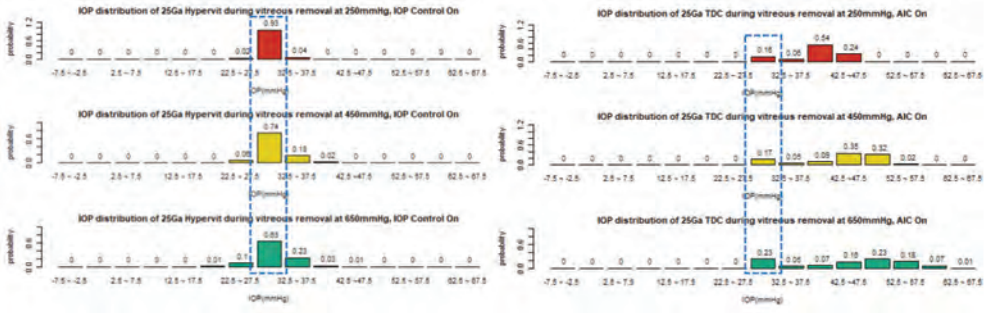


Figure 3. Comparison of the IOP distributions during 25-gauge vitrectomy using CONSTELLATION IOP Control (left) versus the EVA AIC (right). Blue rectangle demarcates the desired IOP range.[14]

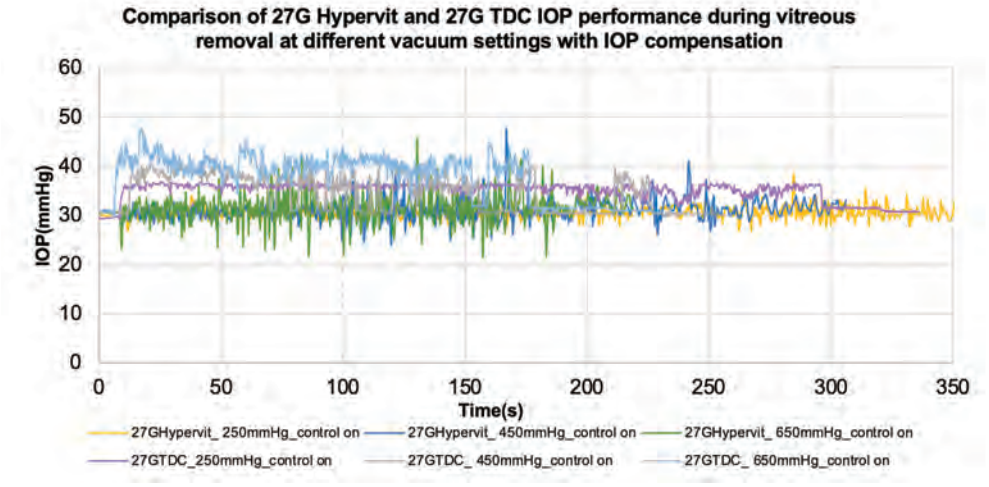


Figure 4. IOP performance (27G) during vitrectomy for the CONSTELLATION IOP Control and EVA AIC[14]

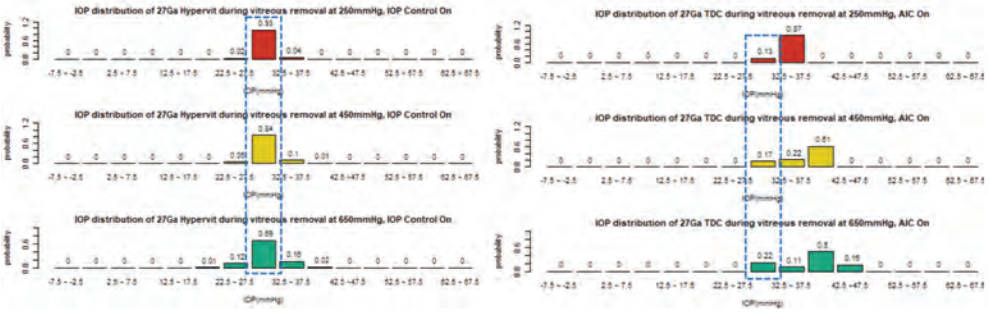


Figure 5. Comparison of the IOP distributions during 27-gauge vitrectomy using the CONSTELLATION IOP Control (left) versus the EVA AIC (right). Blue rectangle demarcates the desired IOP range.[14]

CLINICAL EXPERIENCE

When retinal surgeons perform a vitrectomy, it is paramount that the IOP remain steady and consistent. Large fluctuations in IOP can cause retinal incarceration in the mouth of the cutter while performing a close vitreous shave with mobile retina in retinal detachment cases. Large fluctuations in IOP can also cause decreased vascular perfusion to the optic nerve, most notably when injecting a stain, such as tissue blue, triamcinolone acetonide or ICG during chemovitrectomy prior to a membrane peel. Finally, large fluctuations in IOP can cause a rare, but detrimental suprachoroidal hemorrhage if low pressure ensues while converting from BSS to air in an Air-Fluid exchange maneuver. Regardless of where the anomalous pressure originates (anterior or posterior segment), the retina will be subjected to the consequences of IOP instability. Having confidence that the IOP is continuously monitored and adjusted with CONSTELLATION IOP Control, regardless of the operative conditions, instills confidence that this important intraoperative parameter will not need my attention during the case.

SUMMARY

Evidence regarding the extremes of low or high IOP indicates that visual loss can occur, especially in those with compromised retinal circulation. Not all IOP control systems operate equally; the closed-loop technology of IOP Control that has existed on the CONSTELLATION Vision System since 2008 rapidly adapts to changing intraoperative conditions and can provide confidence to the surgeon regarding IOP maintenance within a tight desired range regardless of probe gauge size or aspiration vacuum — this allows the surgeon to focus completely on the surgical procedure at hand. ■

CONSTELLATION® System with PUREPOINT® Laser Brief Statement
Caution: Federal law restricts this device to sale by, or on the order of, a physician.

Indications for Use: The CONSTELLATION® Vision System is an ophthalmic microsurgical system that is indicated for both anterior segment (i.e., phacoemulsification and removal of cataracts) and posterior segment (i.e., vitreoretinal) ophthalmic surgery.

The ULTRAVIT® Vitrectomy Probe is indicated for vitreous cutting and aspiration, membrane cutting and aspiration, dissection of tissue and lens removal. The valved entry system is indicated for scleral incision, canulae for posterior instrument access and venting of valved cannulae. The infusion cannula is indicated for posterior segment infusion of liquid or gas.

The PUREPOINT® Laser is indicated for use in photocoagulation of both anterior and posterior segments of the eye including:
- Retinal photocoagulation, panretinal photocoagulation and intravitreal endophotocoagulation of vascular and structural abnormalities of the retina and choroid including: Proliferative and nonproliferative retinopathy (including diabetic); choroidal neovascularization secondary to age-related macular degeneration; retinal tears and detachments; macular edema, retinopathy of prematurity; choroidal neovascularization; leaking microaneurysms.
- Iridotomy/Iridectomy for treatment of chronic/primary open angle glaucoma, acute angle closure glaucoma and refractory glaucoma.
- Trabeculoplasty for treatment of chronic/primary open angle glaucoma and refractory glaucoma.
- And other laser treatments including: internal sclerostomy; lattice degeneration; central and branch retinal vein occlusion; suturelysis; vascular and pigment skin lesions.

The FlexTip* laser probe is intended to be used with ALCON® 532nm laser systems.

Contraindications:
- Patients with a condition that prevents visualization of target tissue (cloudy cornea, or extreme haze of the aqueous humor of the anterior chamber of vitreous humor) are poor candidates for LIO delivered laser treatments.
- The infusion cannula is contraindicated for use of oil infusion.

Complications:
Corneal burns, inflammation, loss of best-corrected visual acuity, loss of visual field and transient elevations in intraocular pressure can occur as a result of ophthalmic laser treatment. Unintentional retinal burns can occur if excessive treatment beam power or duration is used.

Warnings and Precautions:
- The disposables used in conjunction with ALCON® instrument products constitute a complete surgical system.
- Use of disposables and handpieces other than those manufactured by Alcon may affect system performance and create potential hazards.
- Attach only Alcon supplied consumables to console and cassette luer fittings. Do not connect consumables to the patient's intravenous connections.
- Mismatch of consumable components and use of settings not specifically adjusted for a particular combination of consumable components may create a patient hazard.
- Vitreous traction has been known to create retinal tears and retinal detachments.
- The closed loop system of the CONSTELLATION® Vision System that adjusts IOP cannot replace the standard of care in judging IOP intraoperatively. If the surgeon believes that the IOP is not responding to the system settings and is dangerously high or low, this may represent a system failure. Note: To ensure proper IOP
- Compensation calibration, place infusion tubing and infusion cannula on a sterile draped tray at mid-cassette level during the priming cycle.
- Leaking sclerotomy may lead to post-operative hypotony.
- Back scattered radiation is of low intensity and is not harmful when viewed through a protective filter. All personnel in the treatment room must wear protective eyewear, OD4 or above at 532nm, when the system is in Standby/Ready mode as well as during treatment. The doctor protection filter is an OD greater than 4 at 532nm.

Attention: Please refer to the CONSTELLATION® Vision System Operators Manual for a complete listing of indications, warnings, and precautions.

*Trademarks are property of their respective owners.

References
1. Moran DS, Mendal L. Core temperature measurement: methods and current insights. *Sports Med*. 2002;32(14):879-85.
2. Tabandeh H, Flynn HW Jr. Suprachoroidal hemorrhage during pars plana vitrectomy. *Curr Opin Ophthalmol*. 2001 Jun;12(3):179-85.
3. Hayreh SS. Anterior ischemic optic neuropathy. IV. Occurrence after cataract extraction. *Arch Ophthalmol*. 1980 Aug;98(8):1410-6.
4. Fontes BM, Jung LS, Soriano ES, Chicani CF. Nonarteritic anterior ischemic optic neuropathy after uneventful phacoemulsification: case report. *Arq Bras Oftalmol*. 2007 May-Jun;70(3):544-6.
5. McCulley TJ, Lam BL, Feuer WJ. Nonarteritic anterior ischemic optic neuropathy and surgery of the anterior segment: temporal relationship analysis. *Am J Ophthalmol*. 2003 Dec;136(6):1171-2.
6. Findl O, Strenn K, Wolzt M, Menapace R, Vass C, Eichler HG, Schmetterer L. Effects of changes in intraocular pressure on human ocular haemodynamics. *Curr Eye Res*. 1997 Oct;16(10):1024-9.
7. Charles S. Fluidics and cutter dynamics. *Dev Ophthalmol*. 2014;54:31-37.
8. Stalmans P. Enhancing visual acuity. *Dev Ophthalmol*. 2014;54:23-30.
9. Moorhead LC, Gardner TW, Lambert HM, O'Malley RE, Willis AW, Meharg LS, Moorhead WD. Dynamic intraocular pressure measurements during vitrectomy. *Arch Ophthalmol*. 2005 Nov;123(11):1514-23.
10. Riemann CD, Buboltz DC. Prevention of Intraoperative Hypotony During Vitreoretinal Surgery: An Instrumental Comparison. Poster, American Society of Retina Specialists, 2010; Vancouver.
11. Comaratta M, Hariprasad SM, Reddy R. The Evolution of Vitreoretinal Surgery Platforms. *Ophthalmic Surg Lasers Imaging Retina*. 2017 Jul 1;48(7):532-538.
12. Sugiura Y, Okamoto F, Okamoto Y, Hiraoka T, Oshika T. Intraocular pressure fluctuation during microincision vitrectomy with CONSTELLATION vision system. *Am J Ophthalmol*. 2013 Nov;156(5):941-947.
13. Shinkai Y, Yoneda K, Sotozono C. Ex vivo Comparison of Intraocular Pressure Fluctuation during Pars Plana Vitrectomy Performed Using 25- and 27-Gauge Systems. *Ophthalmic Res*. 2020 (Online).
14. Charles, M. et al. "Intraocular Pressure (IOP) control in Vitreoretinal surgical systems", Film presented at American Society of Retina Specialists (ASRS) Annual Meeting; Seattle, WA, USA. July 31, 2023.

COGAN-REESE SYNDROME: AN IRIS MELANOMA MASQUERADER

This case highlights the overlap in presentation and distinguishing signs to look for.

BY MALLORY E. BOWERS, PHD; SARA E. LALLY, MD; AND CAROL L. SHIELDS, MD

Iris melanoma and Cogan-Reese syndrome (CRS), while pathologically distinct, share several clinical features that could lead to misdiagnosis. Each condition tends to present in middle-aged patients with structural changes to the iris, accompanied by obstruction of the iridocorneal angle and subsequent elevated IOP. Characteristics unique to CRS, a variant of iridocorneal endothelial (ICE) syndrome, include corneal endothelial "beaten metal" appearance, corneal edema, and broad peripheral anterior synechiae (PAS). Conversely, features particular to iris melanoma include a solid iris mass with additional iris stromal and angle seeding, as well as evidence of mass growth.[1]

The following case demonstrates the significant overlap in presentation between CRS and iris melanoma and outlines an approach to differentiate these diagnoses.

CASE REPORT

During a routine eye examination, a 60-year-old White man was discovered to have a thickened iris with an irregular pupil in his left eye, which is concerning for iris melanoma. The patient had an ocular history of glaucoma in his left eye that was controlled with topical medication. On examination, his BCVA was 20/30 OU with IOP of 12 mm Hg OD and 15 mm Hg OS. On slit-lamp and fundoscopic examination, the right eye was unremarkable. Dilated fundus examination of the left eye was also unremarkable.

The anterior segment of the left eye revealed a distorted pupillary margin dragged superotemporally with prominent ectropion irides, corectopia, and flattened iris appearance without crypts. The iris surface demonstrated multiple small, uniform nodules that were 300 µm in diameter (Figure 1). In the 2:30 meridian, there was an adhesion of the iris to the corneal endothelium with broad PAS. Close biomicroscopic inspection confirmed a corneal endothelium with a "beaten metal" appearance.

Imaging with ultrasound biomicroscopy and anterior segment OCT (AS-OCT) confirmed the presence of iris nodules and PAS (Figure 2). These features of regularly spaced iris nodules, broad PAS, and endothelial abnormalities were consistent with CRS masquerading as iris melanoma. Observation and continued treatment with IOP-lowering medications were recommended.

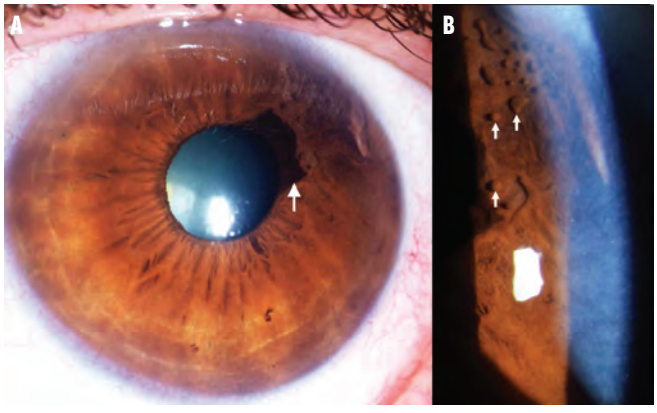


Figure 1. Slit-lamp photography showed ectropion uveae (A, white arrow) and multiple pedunculated nodules in the superotemporal quadrant of the left eye (B, white arrows).

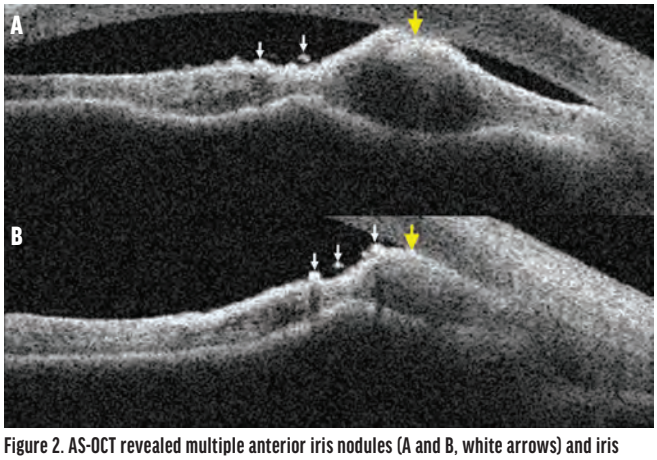


Figure 2. AS-OCT revealed multiple anterior iris nodules (A and B, white arrows) and iris adhesion to the corneal endothelium (yellow arrows) that was obstructing the iridocorneal angle outflow.

ABOUT CRS

ICE syndrome, an ophthalmic disorder characterized by abnormal corneal endothelial cells, is categorized into three variants: Chandler syndrome (CS), essential/progressive iris atrophy (EIA), and CRS.[2-4] In ICE syndrome, pathologic endothelial cells (perhaps triggered by Epstein-Barr virus or herpes simplex virus infection) proliferate and migrate onto the iridocorneal angle and the iris surface, subsequently manifesting features such as PAS, corectopia, ectropion uveae, and secondary angle-closure glaucoma.[5,6]

CRS is unique compared with CS and EIA in that patients present with fine, pigmented iris nodules between a smooth, matted anterior iris stroma lacking crypts.[3,7] The disrupted iris architecture seen in CRS is thought to result from the presence of epithelialization of the corneal endothelial cell layer, migrating onto the iris and causing it to flatten, with the nodules representing pinched-off portions of iris stroma.[7]

Although PAS is present in each of the three ICE variants, studies show that patients with CRS have more advanced glaucoma with higher IOP, worse glaucomatous optic atrophy, and greater visual field loss compared with that of CS and EIA.[8-10] However, one study examining Indian patients found that the frequency of glaucoma and surgical intervention is not significantly different between the ICE variants.[10] Corneal edema appears to be milder in CRS compared with CS.[8,10-12]

CRS typically affects adult women, as is typical of other ICE syndrome variants.[8] Studies across different ethnicities/races, however, suggest that CRS may be the most common variant in East Asian countries compared with North America.[8-10,12]

Helpful Imaging

Two recent case reports suggest that AS-OCT is useful in detecting iris alterations characteristic of CRS for a definitive diagnosis.[13,14] Serial AS-OCT may be useful in monitoring CRS progression by documenting increased iris folding and thickening, as well as nodule formation and PAS, as we found on AS-OCT in our patient.

Treatment Approaches

Antiglaucoma medications, including beta blockers, alpha agonists, and carbonic anhydrase inhibitors, are considered first-line therapies for elevated IOP secondary to PAS in patients with ICE syndrome.[15] However, data show that many patients with ICE do not respond to medical therapy and require repeat surgical interventions, such as trabeculectomy with adjunctive antifibrotic agents or aqueous shunt surgery, to control their IOP.[15-21] Patients with CRS, in particular, have been noted to require more frequent surgery compared with those with other ICE variants.[8,12]

Although corneal edema is less pronounced in CRS compared with CS, penetrating keratoplasty, Descemet stripping with endothelial keratoplasty, Descemet membrane endothelial keratoplasty, and deep lamellar endothelial keratoplasty have been successfully performed in patients with significantly diminished visual acuity due to ICE.[22-25]

PATIENTS WITH CRS, IN PARTICULAR, HAVE BEEN NOTED TO REQUIRE MORE FREQUENT SURGERY COMPARED WITH THOSE WITH OTHER ICE VARIENTS.

SIGNS OF IRIS MELANOMA

Suspicion for melanoma may increase when the iris nodule features are accompanied by corectopia and elevated IOP. Shields et al reviewed 71 consecutive cases of ICE syndrome referred to an Ocular Oncology Service for possible iris nevus or melanoma.[26] The data revealed that corneal guttata, corneal edema, multidirectional corectopia, iris atrophy, PAS, and elevated IOP from angle closure are features suggestive of ICE syndrome compared with circumscribed or diffuse iris melanoma.[26] Features more suggestive of iris melanoma, on the other hand, included episcleral sentinel vessels, extrascleral extension of tumor, extensive iris mass, iris tumor seeds, solid mass in angle, and angle seeding.[26] Tapioca melanoma, a rare type of diffuse iris melanoma, can also mimic CRS with multiple iris tumors, heterochromia, and elevated IOP.[27-29]

REMEMBER THESE CHARACTERISITC FINDINGS

Ectropion uveae and iris nodules seen in patients with CRS can mimic the appearance of an iris melanoma. Unique to CRS and other ICE variants, however, are PAS and corneal endothelial cell dysfunction with lack of anterior chamber seeding and episcleral sentinel vessels.

In our case, the patient's left iris exhibited ectropion uveae and multiple fine nodules superotemporally with corneal endothelial guttata-like changes and PAS, suggestive of CRS. ■

Support provided in part by the Eye Tumor Research Foundation, Philadelphia, PA (CLS). The funders had no role in the design and conduct of the study, in the collection, analysis and interpretation of the data, and in the preparation, review or approval of the manuscript. Carol L. Shields, MD, has had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

eyetube

THE LATEST FROM EYETUBE

CLINICAL MINUTE RETINA

Ramin Tadayoni, MD, PhD, and guests, discuss the latest research and clinical studies in retina.

LATEST VIDEO

ALOFT Study: Value of False Positive Alerts in Home Monitoring for Wet AMD Conversion

Ramin Tadayoni, MD, PhD, and Allen C. Ho, MD

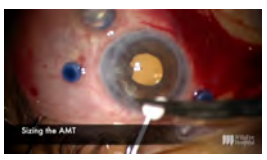
INSIDE THE WILLS OR

Watch as surgeons from Wills Eye Hospital review complex ophthalmic surgery cases.

LATEST VIDEO

Amniotic Membrane for Recalcitrant Macular Hole

Ajay E. Kuriyan, MD, MS



NEW RETINA RADIO

New Retina Radio is a place to hear stories about retina that are told nowhere else.

LATEST PODCAST EPISODE

New Retina Radio Journal Club: Wet AMD: Fluid-Free Visits' Association With Anatomic and Visual Outcomes

Katherine Talcott, MD; Kyle Kovacs, MD; and Rebecca Soares, MD, MPH

1. Shields CL, Kaliki S, Hutchinson A, et al. Iris nevus growth into melanoma: analysis of 1611 consecutive eyes: the ABCDEF guide. *Ophthalmology*. 2013;120(4):766-772.
2. Silva L, Najafi A, Suwan Y, Teekhasaenee C, Ritch R. The iridocorneal endothelial syndrome. *Surv Ophthalmol*. 2018;63(5):665-676.
3. Cogan DG, Reese AB. A syndrome of iris nodules, ectopic Descemet's membrane, and unilateral glaucoma. *Doc Ophthalmol*. 1969;26:424-433.
4. Eagle RC, Jr., Font RL, Yanoff M, Fine BS. Proliferative endotheliopathy with iris abnormalities. The iridocorneal endothelial syndrome. *Arch Ophthalmol*. 1979;97(11):2104-2111.
5. Alvarado JA, Underwood JL, Green WR, et al. Detection of herpes simplex viral DNA in the iridocorneal endothelial syndrome. *Arch Ophthalmol*. 1994;112(12):1601-1609.
6. Tsai CS, Ritch R, Straus SE, Perry HD, Hsieh FY. Antibodies to Epstein-Barr virus in iridocorneal endothelial syndrome. *Arch Ophthalmol*. 1990;108(11):1572-1576.
7. Eagle RC, Jr., Font RL, Yanoff M, Fine BS. The iris naevus (Cogan-Reese) syndrome: light and electron microscopic observations. *Br J Ophthalmol*. 1980;64(6):446-452.
8. Wilson MC, Shields MB. A comparison of the clinical variations of the iridocorneal endothelial syndrome. *Arch Ophthalmol*. 1989;107(10):1465-1468.
9. Feng B, Tang X, Chen H, Sun X, Wang N. Unique variations and characteristics of iridocorneal endothelial syndrome in China: a case series of 58 patients. *Int Ophthalmol*. 2018;38(5):2117-2126.
10. Chandran P, Rao HL, Mandal AK, Choudhari NS, Garudadri CS, Senthil S. Glaucoma associated with iridocorneal endothelial syndrome in 203 Indian subjects. *PLoS One*. 2017;12(3):e0171884.
11. Zhang M, Chen J, Liang L, Laties AM, Liu Z. Ultrasound biomicroscopy of Chinese eyes with iridocorneal endothelial syndrome. *Br J Ophthalmol*. 2006;90(1):64-69.
12. Teekhasaenee C, Ritch R. Iridocorneal endothelial syndrome in Thai patients: clinical variations. *Arch Ophthalmol*. 2000;118(2):187-192.
13. Hollo G, Naghizadeh F. Optical coherence tomography characteristics of the iris in Cogan-Reese syndrome. *Eur J Ophthalmol*. 2014;24(5):797-799.
14. Loya-Garcia D, Hernandez-Camarena JC, Valdez-Garcia JE, Rodriguez-Garcia A. Cogan-Reese syndrome: image analysis with specular microscopy, optical coherence tomography, and ultrasound biomicroscopy. *Digit J Ophthalmol*. 2019;25(2):26-29.
15. Laganowski HC, Kerr Muir MG, Hitchings RA. Glaucoma and the iridocorneal endothelial syndrome. *Arch Ophthalmol*. 1992;110(3):346-350.
16. Kidd M, Hetherington J, Magee S. Surgical results in iridocorneal endothelial syndrome. *Arch Ophthalmol*. 1988;106(2):199-201.
17. Chandran P, Rao HL, Mandal AK, Choudhari NS, Garudadri CS, Senthil S. Outcomes of primary trabeculectomy with mitomycin-C in glaucoma secondary to iridocorneal endothelial syndrome. *J Glaucoma*. 2016;25(7):e652-e656.
18. Shields MB, Campbell DG, Simmons RJ. The essential iris atrophies. *Am J Ophthalmol*. 1978;85(6):749-759.
19. Kim DK, Aslanides IM, Schmidt Jr CM, Spaeth GL, Wilson RP, Augsburger JJ. Long-term outcome of aqueous shunt surgery in ten patients with iridocorneal endothelial syndrome. *Ophthalmology*. 1999;106(5):1030-1034.
20. Doe EA, Budenz DL, Gedde SJ, Imami NR. Long-term surgical outcomes of patients with glaucoma secondary to the iridocorneal endothelial syndrome. *Ophthalmology*. 2001;108(10):1789-1795.
21. Mao Z, Guo X, Zhong Y, Liu X. Surgical outcomes of Ahmed glaucoma valve implantation in patients with glaucoma secondary to iridocorneal endothelial syndrome. *Eye (Lond)*. 2021;35(2):608-615.
22. Rotenberg M, Downward L, Curnow E, et al. Graft survival after penetrating and endothelial keratoplasty in iridocorneal endothelial syndrome. *Cornea*. 2020;39(1):18-22.
23. Ao M, Feng Y, Xiao G, Xu Y, Hong J. Clinical outcome of Descemet stripping automated endothelial keratoplasty in 18 cases with iridocorneal endothelial syndrome. *Eye (Lond)*. 2018;32(4):679-686.
24. Wu J, Dong X, Ouyang C, et al. Comparison of Descemet membrane endothelial keratoplasty for iridocorneal endothelial syndrome and Fuch endothelial dystrophy. *Am J Ophthalmol*. 2021;226:76-82.
25. Huang T, Wang Y, Ji J, Gao N, Chen J. Deep lamellar endothelial keratoplasty for iridocorneal endothelial syndrome in phakic eyes. *Arch Ophthalmol*. 2009;127(1):33-36.
26. Shields CL, Shields MV, Viloria V, Pearlstein H, Say EA, Shields JA. Iridocorneal endothelial syndrome masquerading as iris melanoma in 71 cases. *Arch Ophthalmol*. 2011;129(8):1023-1029.
27. Shields CL, Kaliki S, Shah SU, Luo W, Furuta M, Shields JA. Iris melanoma: features and prognosis in 317 children and adults. *J AAPOS*. 2012;16(1):10-16.
28. Reese AB, Mund ML, Iwamoto T. Tapioca melanoma of the iris. 1. Clinical and light microscopy studies. *Am J Ophthalmol*. 1972;74(5):840-850.
29. Iwamoto T, Reese AB, Mund ML. Tapioca melanoma of the iris. 2. Electron microscopy of the melanoma cells compared with normal iris melanocytes. *Am J Ophthalmol*. 1972;74(5):851-861.

MALLORY E. BOWERS, PHD
- Medical Student, Ocular Oncology Service, Wills Eye Hospital, Thomas Jefferson University, Philadelphia
- mallory.bowers@students.jefferson.edu
- Financial disclosure: None

SARA E. LALLY, MD
- Ocular Oncologist, Ocular Oncology Service, Wills Eye Hospital, Thomas Jefferson University, Philadelphia
- sara@shields.md
- Financial disclosure: None

CAROL L. SHIELDS, MD
- Director, Ocular Oncology Service, Wills Eye Hospital, Thomas Jefferson University, Philadelphia
- Editorial Advisory Board Member, *Retina Today*
- carolshields@gmail.com
- Financial disclosure: None

INDEX OF ADVERTISERS

This advertiser index is published as a convenience and not as part of the advertising contract. Although great care will be taken to index correctly, no allowances will be made for errors due to spelling, incorrect page number, or failure to insert.

JOIN US ON INSTAGRAM

Follow us for the latest clinical pearls and meeting insights straight from your peers.

@retina_today

RISING STARS IN RETINA

Get to know outstanding retina fellows from the class of 2023.

Hong-Uyen Hua, MD

Retina Today: When did you first know that you wanted to become a retina specialist?

I first discovered retina at the University of Miami as a medical student applying into ophthalmology with Audina Berrocal, MD, as my mentor. I have always known that I wanted to work with kids, and seeing her incredible work as a pediatric retina specialist further inspired me to pursue pediatric retina. During my first year of residency at the University of Southern California (USC), the amazing patients and pathology I saw sealed the deal. The diversity and surgical creativity in retina, long-lasting relationships with patients, and the renaissance of new retinal therapies continue to inspire me daily.

_RT:_ Who do you look to as mentors in the field?

Selfless and dedicated mentorship has been the cornerstone of my education and training. Dr. Berrocal continues to support me closely to this day. During my fellowship at the Cleveland Clinic Cole Eye Institute, Sunil K. Srivastava, MD; Aleksandra Rachitskaya, MD; Peter Kaiser, MD; Katherine Talcott, MD; and Jonathan Sears, MD, along with each of the retina faculty members have shown me incredible support and mentorship. They inspire me to pursue excellence in all dimensions of my career, from clinical care to surgery, research, and leadership.

I could write several paragraphs about my many mentors, from Bascom Palmer, USC, and the Cole Eye Institute!

_RT:_ What has been one of the most memorable experiences of your fellowship thus far?

During my fellowship, Dr. Srivastava and Prithvi Mruthyunjaya, MD, created the Cole Eye Institute and Byers Eye Institute surgical retina rounds (COBRA) to share and discuss surgical education, particularly for retina fellows. During the 2022 AAO annual meeting, COBRA hosted its first live surgical rounds in Chicago. It was a highlight of my fellowship. All the fellows, myself included, had so much fun presenting cases with the dynamic and engaging faculty.

FIRST CAREER MILESTONE

Dr. Hua is joining Bascom Palmer Eye Institute, University of Miami, Miller School of Medicine, as an assistant professor of Ophthalmology in adult and pediatric retina.

_RT:_ What are you hoping to accomplish once you are in practice?

In 5 to 10 years, I see myself as a faculty member at an academic center practicing adult and pediatric retina care. I plan to work with trainees to shape the future of ophthalmology and retina. In addition, I will continue research in retinopathy of prematurity, pediatric retinal imaging, clinical trials, and gender and racial disparities in retina. I also plan on continuing leadership and advocacy at the society level, including with the Vit-Buckle Society, Women in Ophthalmology, American Society of Retina Specialists, and AAO.

_RT:_ What advice can you offer to residents who are considering retina?

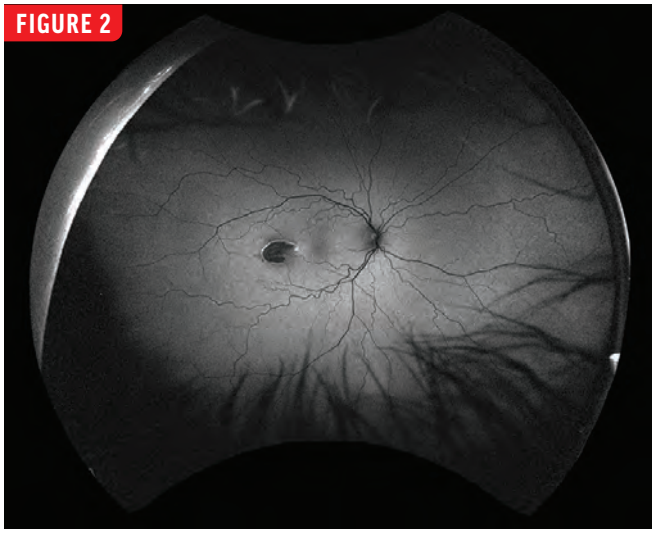
If you have any inkling of pursuing a retina fellowship, start with a strong clinical foundation and develop comfort and skill with retina procedures. Identify mentors early, and start research: the earlier, the better! ■

HONG-UYEN HUA, MD

- Former Vitreoretinal Surgery Fellow, Cole Eye Institute, Cleveland Clinic, Cleveland
- honguyenhua@gmail.com
- Financial disclosure: Personal Fees (Alimera Sciences, Allergan/AbbVie, Genentech/Roche)

(Continued from page 66)

FIGURE 2



retinal structures without outer retinal cavitation. Type 2 shows attenuation of the outer retinal structures with outer retinal cavitation, causing mild to moderate visual field defect.[3] A type 3 lesion is defined by excavated inner layers, retinal thinning, inner retinal hyperreflective spaces, and no subretinal cleft. Patient education must be performed when TM is suspected, as this condition, although benign, may progress into other pathologies, especially type 2 lesions.[2]

The etiology of TM is unclear but is thought to derive from the fetal temporal bulge at approximately 4 to 6 months of gestation. In type 2 TM, fluorescein angiography can be performed if choroidal neovascular membrane formation is suspected.

The differential diagnosis of TM includes other types of scars, both acquired and congenital, such as:

1) toxoplasmosis scars, which can be differentiated from TM based on the presence of full-thickness chorioretinal atrophy and non-uniform location, shape, and size, along with a known history of toxoplasmosis[2];

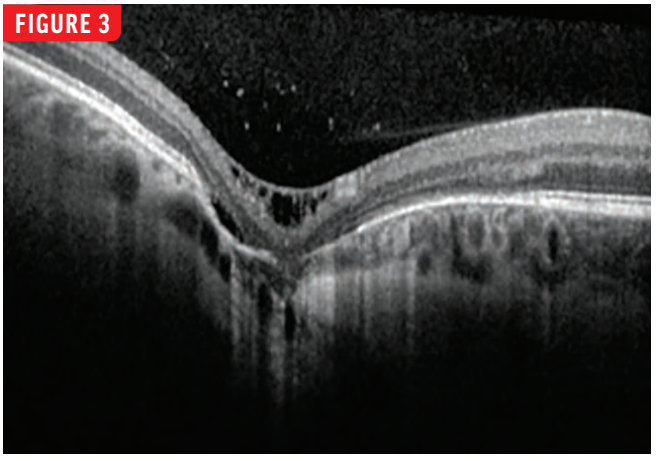
2) congenital hypertrophy of the RPE, which presents with pigmented lesions with well-defined borders typically found in the periphery of the retina and rarely near the macula, a differentiating factor from TM[2];

3) histoplasmosis, which typically presents with numerous scars, along with peripapillary scarring with choroidal neovascular membrane[2];

4) chorioretinal scars caused by blunt trauma to the orbit, which present with varying degrees of hyper- and hypopigmentation, are concentric to the optic nerve head, and are shaped in an elongated manner with a pattern in the choroidal rupture; and

5) amelanotic nevi, which are round and hypopigmented retinal lesions that typically lack the outer retinal attenuation and excavation seen in TM.[2]

FIGURE 3



KEEP AN EYE ON IT

TM should be monitored as part of a patient's annual eye examination, as there is risk of choroidal neovascularization growing through the scar. An at-home Amsler grid can also be used to supplement the in-office examination.[4] ■

1. Shirley K. Torpedo maculopathy: spectrum and associated choroidal neovascularization in a pediatric population. *Eye (Lond)*. 2018;32(8):1315-1320.
2. Reilly J. Torpedo Maculopathy: A teaching case. *Optom Ed*. 2021;47(1).
3. Raval V, Rao S, Sudana P, Das T. *J Ophthalmic Vis Res*. 2020;15(1):113-115.
4. Roseman RL, Gass JD. Solitary hypopigmented nevus of the retinal pigment epithelium in the macula. *Arch Ophthalmol*. 1992;110(10):1358-1359.

VIKTORIYA GONCHAROV, COA, OSC, BSC
- Regulatory and EHR Specialist, Colorado Retina Associates, Denver Colorado
- vgoncharov@retinacolorado.com
- Financial disclosure: None

AARON JODEH, MD
- Internal Medicine, Brookdale Hospital, Brooklyn, New York
- ajodeh@retinacolorado.com
- Financial disclosure: None

BRIAN JOONDEPH, MD
- Retina Specialist, Colorado Retina Associates, Denver, Colorado
- bjoondeph@retinacolorado.com
- Financial disclosure: None

MANISH NAGPAL | SECTION EDITOR
- Senior Consultant, Retina and Vitreous Services, The Retina Foundation, Ahmedabad, India
- dr.manishnagpal@yahoo.com
- Financial disclosure: Consultant (Nidek)

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

FIGURE 1

TORPEDO MACULOPATHY

Watch for choroidal neovascularization associated with this generally benign condition.

BY AARON JODEH, MD; VIKTORIYA GONCHAROV, COA, OSC, BSC; AND BRIAN JOONDEPH, MD

A 24-year-old man was referred by his optometrist because of a fundus lesion found in his right eye on routine examination. The patient was asymptomatic and had an otherwise normal examination. His medical and family history was negative.

Based on our clinical and imaging findings (Figures 1-3), we made a diagnosis of torpedo maculopathy (TM), a rare, asymptomatic congenital deformity of the retinal pigment epithelium (RPE) that is considered to be an incidental finding.[1] TM characteristically presents as a hypopigmented lesion temporal to the fovea with a narrow point directed toward the fovea, as seen in our case.

ABOUT TORPEDO MACULOPATHY

TM is typically unilateral but may rarely develop bilaterally. TM has a prevalence of two in 100,000 patients and is considered to be nonprogressive. Although most TM lesions are solitary in nature, satellite lesions can also exist in the same eye as the parent lesion. TM is underreported in the literature because of the asymptomatic nature of the condition. However, when found, it is important to differentiate TM from other pathologies that may require treatment. TM is classified into types based on subtle differences that can be detected on OCT[2]: Type 1 shows attenuation of the outer

(Continued on page 65)

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 from baseline to week 100 was 5% (64 out of 1,262) in patients treated with VABYSMO compared with 5% (32 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=1,262	AMD N=662	DME N=625
Cataract	3%	15%	2%	12%
Conjunctival hemorrhage	7%	8%	8%	7%
Vitreous floaters	3%	4%	2%	3%
Retinal pigment epithelial tear[a]	3%		1%	
Intraocular pressure increased	3%	4%	2%	3%
Eye pain	3%	3%	3%	3%
Intraocular inflammation[b]	2%	1%	1%	1%
Eye irritation	1%	< 1%	< 1%	1%
Lacrimation increased	1%	1%	1%	< 1%
Ocular discomfort	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, ocular hyperemia, blurred vision, sensation of foreign body, endophthalmitis, conjunctival hyperaemia, visual acuity reduced, visual acuity reduced transiently, vitreous hemorrhage, 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(v2.0) 2/23

START NOW | WITH DUAL-PATHWAY VABYSMO

VABYSMO™
faricimab-svoa injection 6 mg

THE POWER 2 OPEN THEIR WORLD

VABYSMO® (faricimab-svoa) is the first and only treatment that delivers **powerful efficacy** with **1–4 month dosing**[1–5*†]

Discover more at vabysmo-hcp.com/start

***nAMD:** VABYSMO met its primary endpoint of non-inferior mean change from baseline in BCVA vs aflibercept 2 mg at year 1 (avg. of weeks 40, 44, and 48) using a margin of 4 letters. Differences in LS means for VABYSMO were +0.7 letters (CI: [95%] -1.1, +2.5) in TENAYA; and 0.0 letters (CI: [95%] -1.7, +1.8) in LUCERNE. DME: VABYSMO met its primary endpoint of non-inferior mean change from baseline in BCVA vs aflibercept 2 mg at year 1 (avg. of weeks 48, 52, and 56) using a margin of 4 letters. Differences in LS means in YOSEMITE were +0.7 letters (CI: [97.5%] -1.1, +2.5) for VABYSMO Q4W-Q16W and -0.2 letters (CI: [97.5%] -2.0, +1.6) for VABYSMO Q8W. Differences in LS means in RHINE were +0.5 letters (CI: [97.5%] -1.1, +2.1) for VABYSMO Q4W-Q16W and +1.5 letters (CI: [97.5%] -0.1, +3.2) for VABYSMO Q8W. A non-inferiority margin was not available for year 2.[1]

†nAMD: 4 monthly loading doses followed by OCT and visual acuity evaluations 8 and 12 weeks later to inform Q16W (weeks 28 and 44), Q12W (weeks 24, 36, and 48), Q8W (weeks 20, 28, 36, and 44), or Q4W (no added benefit) dosing. **DME:** at least 4 monthly loading doses followed by extensions ≤4 weeks or reductions ≤8 weeks based on OCT and visual acuity evaluations OR 6 monthly loading doses followed by Q8W. Q4W dosing may be needed (no added benefit).[1]

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 infection, in patients with active intraocular inflammation, and 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.

Warnings and Precautions
Endophthalmitis and Retinal Detachments
Intravitreal injections have been associated with endophthalmitis and retinal detachments. 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.

Increase in Intraocular Pressure
Transient increases in intraocular pressure (IOP) have been seen within 60 minutes of intravitreal injection, including with VABYSMO. IOP and the perfusion of the optic nerve head should be monitored and managed appropriately.

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.

The incidence of reported ATEs in the DME studies from baseline to week 100 was 5% (64 out of 1,262) in patients treated with VABYSMO compared with 5% (32 out of 625) in patients treated with aflibercept.

Adverse Reactions
The most common adverse reactions (≥5%) reported in patients receiving VABYSMO were cataract (15%) and conjunctival hemorrhage (8%).

Pregnancy, Lactation, Females and Males of Reproductive Potential
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. 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. 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.

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 additional Important Safety Information in the full VABYSMO Prescribing Information.

References: 1. VABYSMO [package insert]. South San Francisco, CA: Genentech, Inc; 2023. **2.** Beovu® (brolucizumab-dbll) [package insert]. East Hanover, NJ: Novartis; 2022. **3.** Eylea® (aflibercept) [package insert]. Tarrytown, NY: Regeneron Pharmaceuticals, Inc; 2023. **4.** LUCENTIS® (ranibizumab) [package insert]. South San Francisco, CA: Genentech, Inc; 2018. **5.** SUSVIMO™ (ranibizumab injection) [package insert]. South San Francisco, CA: Genentech, Inc; 2022.

BCVA=best corrected visual acuity; CI=confidence interval; LS=least squares; OCT=optical coherence tomography; Q4W=every 4 weeks; Q8W=every 8 weeks; Q12W=every 12 weeks; Q16W=every 16 weeks.

M-US-00020375(v1.0) 06/23

Genentech
A Member of the Roche Group