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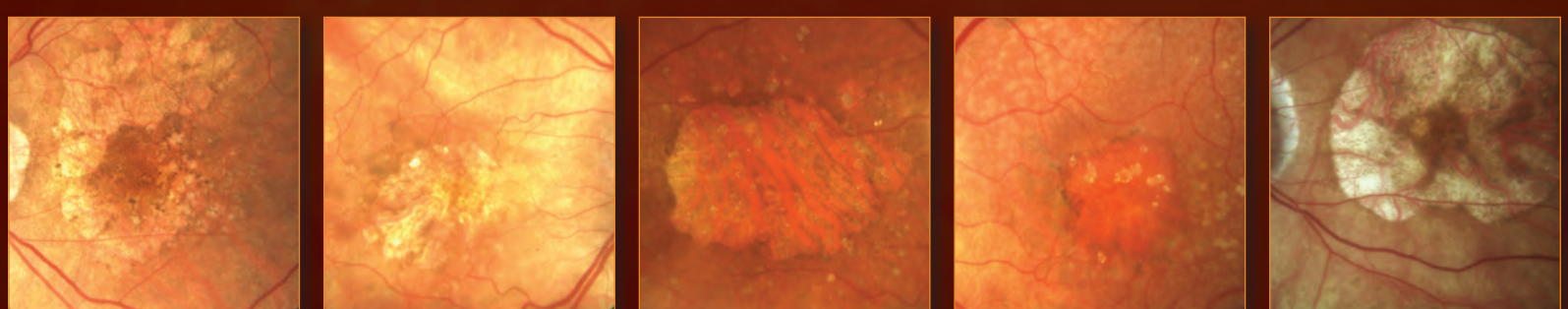
eyetube

GEOGRAPHIC ATROPHY

A LOOK AT BIOMARKERS, THERAPIES, AND MORE.



GEOGRAPHIC ATROPHY TREATMENT PEARLS | NOVEL GEOGRAPHIC ATROPHY BIOMARKERS | QUANTIFYING FLUID IN AMD

NOW APPROVED: the first and only FDA-approved treatment for GA secondary to AMD[1]

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

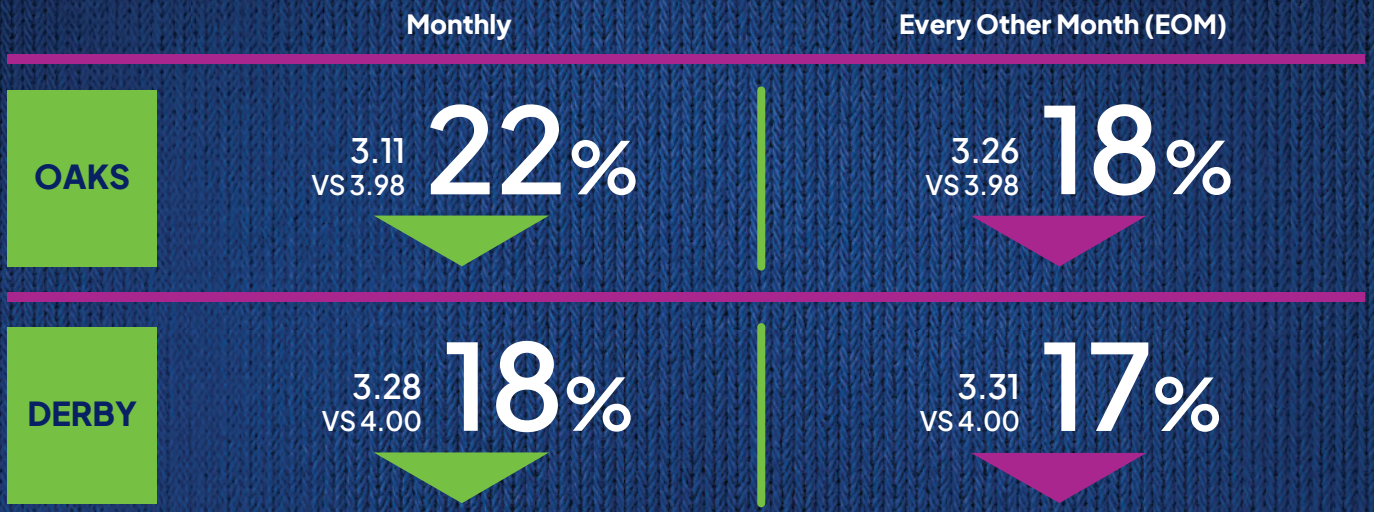
CONTRAINDICATIONS

- 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]
AMD=age-related macular degeneration; GA=geographic atrophy; SE=standard error.

Explore more at SyfovreECP.com

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)
15 mg / 0.1 mL

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

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2/23 US-PEGGA-2200163 v2.0

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THE END OF THE BEGINNING


Back in 2006, we said that it was "an exciting time to be a retina specialist," noting that, for Eugene de Juan, MD, the approval of ranibizumab (Lucentis, Genentech/Roche) "stands out as one of the most important medical developments in ophthalmology during my 25 years in the field."[1]

Some of us remember the days when we had little to offer wet AMD patients because photodynamic therapy provided only modest benefits. Anti-VEGF therapy ushered in an era of reassurance when discussing the long-term visual outcomes with our wet AMD patients.

That sentiment voiced by Dr. de Juan didn't resurface for the next 15 years, as we integrated anti-VEGF therapy into practice and forged ahead with clinical research. Sure, we had drug approvals, imaging advances, and improved surgical tools, but nothing topped that 2006 feeling.

Since the fall of 2021, however, "it is an exciting time to be a retina specialist," has been rolling off our tongues almost daily with the recent approvals of longer-duration anti-VEGF agents and approaches.

Not only that, the historic FDA approval of the first therapy to treat geographic atrophy (GA) secondary to AMD, pegcetacoplan (Syfovre, Apellis Pharmaceuticals), brought a feeling reminiscent of 2006. The approval finally provides us with a treatment option for an entire patient population that once had no options. As if that relief isn't palpable enough, a second therapy, avacincaptad pegol (Zimura, Iveric Bio), is also awaiting approval.

As with our initial discussions with wet AMD patients about photodynamic therapy, we will have to manage expectations—a new experience for some, and an old skill some of us must dust off. Both these therapies slow, but do not stop, GA progression. While it's a definite step in the right direction, it's not the magic bullet that anti-VEGF agents felt like, considering we aren't improving vision.

We also have much in the pipeline to look forward to, and we are particularly interested in the gene and cell therapies under investigation. Researchers are working toward stopping GA progression and reversing vision loss—and perhaps one day, all with a longer duration of effect.

This is one editorial we have been waiting to write for quite some time. We rarely have an opportunity to quote Winston Churchill, but Eleonora Lad, MD, was spot on when she said, "It's the end of the beginning for GA therapy." She, along with Jeffrey S. Heier, MD, and Dilsher Dhoot, MD, shared with us their pearls regarding the new therapeutics that will shape the early days of GA therapy.

We have many questions about how the era of GA therapy will unfold. Hopefully the articles in this issue help answer a few of them, or at least get the conversation started. Still, only time and clinical experience will garner the answers for most of these unknowns. We can't wait to get started. ■


ALLEN C. HO, MD
CHIEF MEDICAL EDITOR

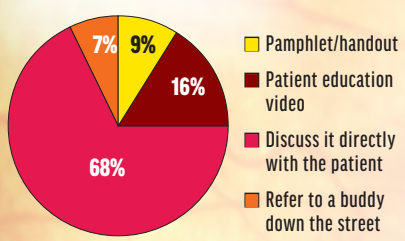
ROBERT L. AVERY, MD
ASSOCIATE MEDICAL EDITOR

1. Breaking ground in the treatment of retinal diseases. *Retina Today*. September 2006. Accessed May 5, 2023. retinatoday.com/articles/2006-sept/0906_01.html

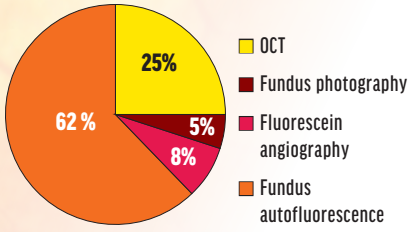
WE ASKED, YOU ANSWERED

We took to social media to see how your peers feel about incorporating the new geographic atrophy (GA) therapy into clinical practice. Here's what they had to say:

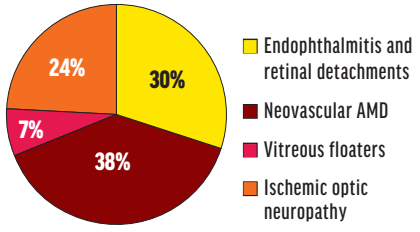
How are you planning to educate your patients about the new GA therapy?



What imaging modality do you plan to use when following GA patients treated with a complement inhibitor?

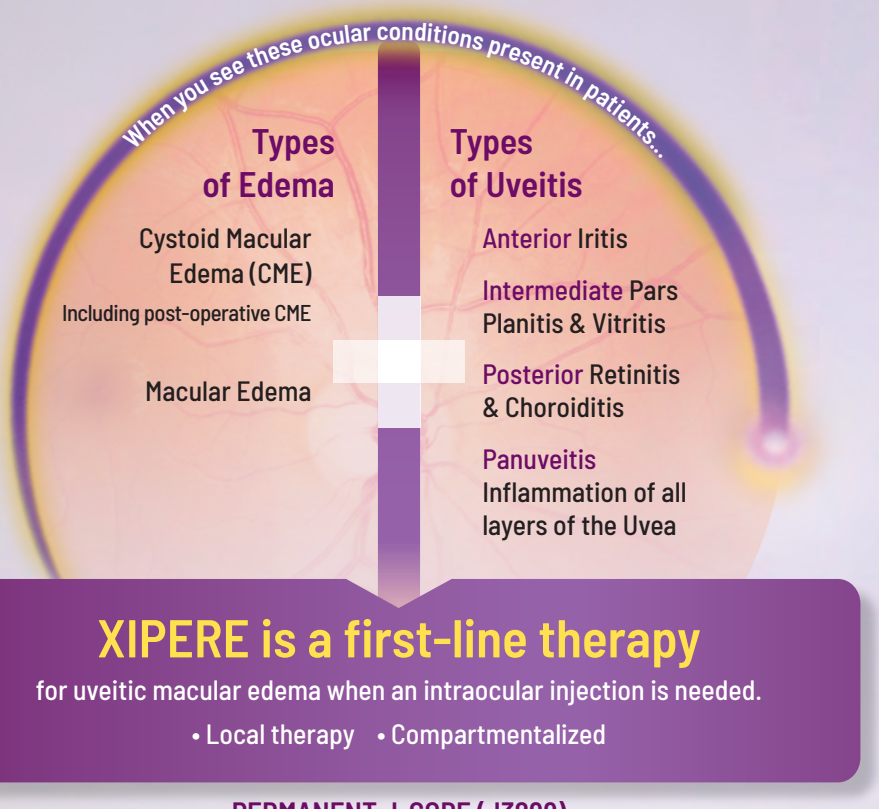


What potential adverse reaction worries you the most with the new GA therapy?



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

MAY/JUNE 2023
VOL. 18, NO. 4 | RETINATODAY.COM

ADVANCES IN THE RETINITIS PIGMENTOSA THERAPEUTIC PIPELINE

Recent advances in retinitis pigmentosa (RP) research have shown promising results for improving vision and the quality of life for affected individuals.

Preliminary results from Kiora Pharmaceuticals' phase 1b clinical trial of KIO-301 show the potential to restore light perception in patients with ultra-low vision or blindness due to RP.[1] The light-sensing small molecule is designed to reactivate visual function in response to light. One of six patients evaluated reported improvements in their ability to perceive light/dark contrast at days 7, 14, and 29 after treatment, and MRI showed increased brain activity in the visual cortex 3 and 15 days post-injection compared with baseline.[1]

Ocugen announced preliminary data from its phase 1/2 trial of OCU400 for RP associated with *NR2E3* and *rhodopsin* gene mutations and Leber congenital amaurosis with mutations in the *CEP290* gene. The positive findings from 18 patients suggest a favorable safety profile, and all eyes showed a stable or improved multi-luminance mobility testing score. Three of the seven treated eyes included in the initial reporting showed a BCVA improvement of 8 to 11 letters compared with none of the untreated eyes.[2]

Nanoscope Therapeutics announced positive results from its phase 2b RESTORE trial of MCO-010, an optogenetic therapy for vision restoration in patients with advanced RP.[3] The trial demonstrated visual function improvements and a favorable safety profile, with all 18 patients in the treatment arm showing vision improvement in the multi-luminance Y-mobility test, multi-luminance shape discrimination test, or BCVA at 12 months.

Endogena Therapeutics successfully completed the dose-escalation stage of its phase 1/2a study of EA-2353 in RP, with no clinically relevant or dose-limiting adverse events identified.[4] The study is enrolling patients into the expansion cohort using the highest dose evaluated to explore efficacy.

At Michigan State University, a gene therapy that treats RP associated with the *CNGB1* gene was successfully trialed in dogs with an inherited eye disease and is now ready for development in humans with RP.[5]

1. Kiora: Investigational drug KIO-301 has potential to restore light perception in patients with retinitis pigmentosa. EyeWire+. April 27, 2023. Accessed May 9, 2023. bit.ly/41HUKnq
2. Ocugen announces positive preliminary safety and efficacy results from the phase 1/2 trial of gene therapy OCU400, for the treatment of RP and LCA. EyeWire+. April 14, 2023. Accessed May 9, 2023. bit.ly/3BumyB5
3. Nanoscope Therapeutics presents key results from phase 2b RESTORE Trial of MCO-010 for the treatment of RP at ARVO. EyeWire+. May 1, 2023. Accessed May 9, 2023. bit.ly/3Wbm5x6
4. Endogena Therapeutics completes dose escalation in the phase 1/2a clinical trial of EA-2353 for the treatment of RP. EyeWire+. April 5, 2023. Accessed May 9, 2023. bit.ly/430dzn3
5. Precision eye therapy for dogs ready for human clinical development. EyeWire+. April 28, 2023. Accessed May 9, 2023. bit.ly/42YYFxb

GEOGRAPHIC ATROPHY LESION GROWTH IS CORRELATED WITH VISION LOSS IN POST-HOC ANALYSIS

A combined post-hoc analysis of the phase 3 GATHER1 and GATHER2 trials of avacincaptad pegol (Zimura, Iveric Bio) showed that worsening vision is correlated with geographic atrophy (GA) lesion growth.[1] The results of this analysis were presented at the 2023 Association for Research in Vision and Ophthalmology (ARVO) meeting.

In the analysis, GA lesion growth was compared with the degree of vision loss in patients treated with 2 mg avacincaptad pegol or sham from baseline to 12 months. In each group, greater BVCA loss was seen in patients who experienced greater GA lesion growth. In addition, the data demonstrated a 56% risk reduction in the rate of persistent vision loss in patients with GA who received treatment with 2 mg avacincaptad pegol compared with sham up to month 12.[1]

The company's new drug application was granted priority review, with a Prescription Drug User Fee Act date of August.

Iveric Bio also made headlines when Astellas Pharma announced that it has entered into a definite agreement to acquire the company.[2] Under the terms of the agreement, Berry Merger Sub, a subsidiary of Astellas Pharma, will acquire 100% of the outstanding shares of Iveric Bio for a total of $5.9 billion. The acquisition is expected to be complete in the third quarter of 2023.

1. Iveric Bio announces new functional vision loss reduction data from avacincaptad pegol GATHER trials. Eyewire+. April 24, 2023. Accessed May 4, 2023. bit.ly/42HaWqn
2. Japanese drugmaker Astellas Pharma acquires Iveric Bio for $5.9 billion. Eyewire+. May 1, 2023. Accessed May 4, 2023. eyewire.news/news/japanese-drugmaker-astellas-pharma-acquires-iveric-bio-for-59-billion-1

POST-HOC ANALYSIS SHOWS BENEFITS OF PEGCETACOPLAN IN PATIENTS WITH EXTRAFOVEAL GA LESIONS

A post-hoc analysis of 24-month data from the OAKS and DERBY trials of pegcetacoplan intravitreal injection (Syfovre, Apellis Pharmaceuticals) for the treatment of GA showed positive effects on visual function and quality-of-life in patients who have extrafoveal lesions (ie, located ≥ 0.25 mm from the foveal center).

The data showed that, compared with sham, patients treated with pegcetacoplan experienced preservation of 5.6 letters or 1 line of vision on ETDRS, as well as a 4.1-point benefit on the National Eye Institute Visual Function Questionaire-25.[1]

In addition, treatment with monthly and every-other-month pegcetacoplan led to a significant reduction in the loss of photoreceptors ($P = .0001$ for each trial/treatment regimen) and retinal pigment epithelium cells (every-other-month: OAKS [$P = .0002$] and DERBY [$P = .0005$]; monthly: OAKS [$P = .0002$] and DERBY [$P < .0001$]). Data were also consistent when pegcetacoplan-treated eyes were compared with untreated fellow eyes.[1]

1. Apellis presents phase 3 functional analyses of Syfovre for geographic atrophy. Eyewire+. April 24, 2023. Accessed May 4, 2023. eyewire.news/news/apellis-presents-phase-3-functional-analyses-of-syfovre-for-geographic-atrophy

PROMISING PHASE 1/2A RESULTS FOR RG6501 IN TREATING PATIENTS WITH GEOGRAPHIC ATROPHY

Lineage Cell Therapeutics announced positive results from its phase 1/2a trial of RG6501 (OpRegen), an allogeneic retinal pigment epithelial cell therapy for the treatment of patients with GA.[1]

The data, presented at the 2023 ARVO meeting, show that patients in cohort 4 had an average gain in VA of 7.6 letters at 12 months in the study eye; three patients within that cohort had a 15-letter or greater gain. In addition, the researchers noted that the outer retinal structure improvement seen in treated eyes persisted for up to 4 years of follow-up.

The analysis suggests that extensive bleb coverage led to the maintenance or improvement in the outer retina structure in treated eyes compared with worsening in fellow eyes.

A phase 2a study is enrolling patients to further evaluate the treatment's success.

1. RG6501 (OpRegen) phase 1/2a clinical results support the potential for OpRegen to slow, stop or reverse disease progression in GA. EyeWire+. April 27, 2023. Accessed May 9, 2023. eyewire.news/news/rg6501-opregen-phase-12a-clinical-results-support-the-potential-for-opregen-to-slow-stop-or-reverse-disease-progression-in-ga

Pharma Updates From Eyewire+

- The FDA granted investigational new drug (IND) clearance for AVD-104 (Aviceda Therapeutics), an intravitreal nanoparticle molecule drug candidate that modulates critical inflammatory pathways via inhibition of retinal macrophages and repolarizing activated macrophages to their resolution state.
- Allegro Ophthalmics received FDA approval for the design of its phase 2b/3 study of risuteganib for the treatment of intermediate dry AMD under special protocol assessment. The study evaluates the efficacy of the drug at 52 weeks and safety through 96 weeks with an endpoint of change in BVCA compared with sham.
- The FDA granted clearance to Atsena Therapeutics' IND application for a phase 1/2 clinical trial of ATSN-201, a gene therapy candidate for the treatment of X-linked retinoschisis. The company also announced positive 6-month safety and efficacy data of ATSN-101, another investigational gene therapy for treatment of *GUCY2D*-associated Leber congenital amaurosis.
- The first patient has been dosed with OLX10212 (OliX Pharmaceuticals) in a phase 1 clinical trial of this investigational RNAi therapeutic for the treatment of AMD. The trial evaluates the safety and efficacy of OLX10212 administered via intravitreal injection in up to 60 patients with wet AMD.
- New 56-week data from the phase 3 trial of SB15 (Samsung Bioepis), a proposed biosimilar to aflibercept (Eylea, Regeneron), showed that the biosimilar's efficacy, safety, immunogenicity, and pharmacokinetics were comparable with the reference drug.
- The FDA accepted the supplement biologics license application for 6 mg faricimab-svoa (Vabysmo, Genentech/Roche) for the treatment of retinal vein occlusion.

Want more retina news from ***Eyewire+***?

RESEARCHERS FIND FASTER FLUID RESOLUTION WITH FARICIMAB

Genentech/Roche announced that post-hoc data revealed faricimab-svoa (Vabysmo) showed more effective and faster retinal fluid drying with fewer injections compared with aflibercept (Lucentis, Regeneron) in patients with wet AMD and diabetic macular edema.[1]

The data revealed that, for patients with wet AMD, central subfield thickness reductions were 145 µm in the faricimab-svoa arm and 133 µm in the aflibercept arm at 12 weeks. For the group with diabetic macular edema, 75% of study patients achieved a central subfield thickness less than 325 µm, which occurred at 20 weeks with faricimab-svoa versus 36 weeks with aflibercept.[1] ■

1. Genentech: New Vabysmo data suggest greater retinal drying vs. aflibercept in wet AMD and DME. EyeWire+. April 25, 2023. Accessed May 9, 2023. eyewire.news/news/genentech-new-vabysmo-data-suggest-greater-retinal-drying-vs-aflibercept-in-wet-amd-and-dme

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WHERE IT ALL BEGAN

Durga S. Borkar, MD, MMCi, was born and raised in the Chicagoland area. Her parents are engineers who immigrated from India, and they emphasized the value of education for her and her younger sister. She completed her undergraduate degree in mathematics and financial economics at Northwestern University and attended medical school there.

HER PATH TO RETINA

While a resident at Massachusetts Eye and Ear, Dr. Borkar spent almost all of her time planning to be a cornea specialist. Later in residency, however, she participated in the retina OR and was hooked. She still remembers being in complete awe the first time she performed a core vitrectomy. Additionally, the fast-paced and high-volume nature of clinic was exciting. The opportunity to handle complex and varied pathology and the idea that retina surgeons are often the "last stop" for many patients appealed to her. She found the retina community to be an incredibly dynamic and fun group that she wanted to be a part of.

SUPPORT ALONG THE WAY

She has been fortunate to have many wonderful mentors in retina. Dr. Borkar's mentors at Northwestern University inspired her to become an ophthalmologist and encouraged her to pursue a variety of training opportunities. Her mentors at Massachusetts Eye and Ear introduced her to the wonders of vitreoretinal surgery, as well as the importance of prioritizing teaching and mentoring others. She would not be the surgeon she is today without the training she received as a vitreoretinal surgery fellow at Wills Eye Hospital. Lastly, mentorship does not end once training is complete, and she is grateful for the ongoing mentorship from her senior vitreoretinal colleagues at Duke. They are true role models as surgeons and people.

Two of her longtime ophthalmology mentors who are not retina specialists, but have had a lasting effect, are Nisha Acharya, MD, MS, and Kathryn Colby, MD, PhD, who she met in medical school and residency, respectively. Both inspired her to pursue a career in academic medicine, be persistent in achieving her goals, and always advocate for patients.

Dr. Borkar's Advice:
Although it is important to have a vision for your early career, some of the best professional successes can come from keeping an open mind, being flexible, and seizing unexpected opportunities.

AN EXPERIENCE TO REMEMBER

Some of Dr. Borkar's most meaningful experiences have involved taking care of young patients with diabetic tractional retinal detachments. Operating on this population and improving their quality of life is rewarding and humbling. It has also opened her eyes to the complex interplay between the medical factors and social determinants of health that drive advanced complications from diabetes. ■

Durga S. Borkar, MD, MMCi, is an assistant professor of Ophthalmology and a vitreoretinal surgeon at the Duke Eye Center in Durham, North Carolina. As an academic retina specialist, she enjoys a dynamic role that includes performing complex surgery, teaching fellows in the OR, and conducting clinical outcomes and informatics research. She also has a masters degree in clinical informatics, which has allowed her to expand her research through industry partnerships, in particular working with Verana Health, AAO's technology partner, for the IRIS Registry. Dr. Borkar is a consultant for Allergan/Abbvie, Genentech/Roche, Glaukos, and Iveric Bio. She can be reached at durgaborkarmd@gmail.com.

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Angiogenesis 2023: Quick Hits

Retina Today would like to thank Sheila Donahey from Retina Vitreous Associates of Florida for supplying this issue's cover images.

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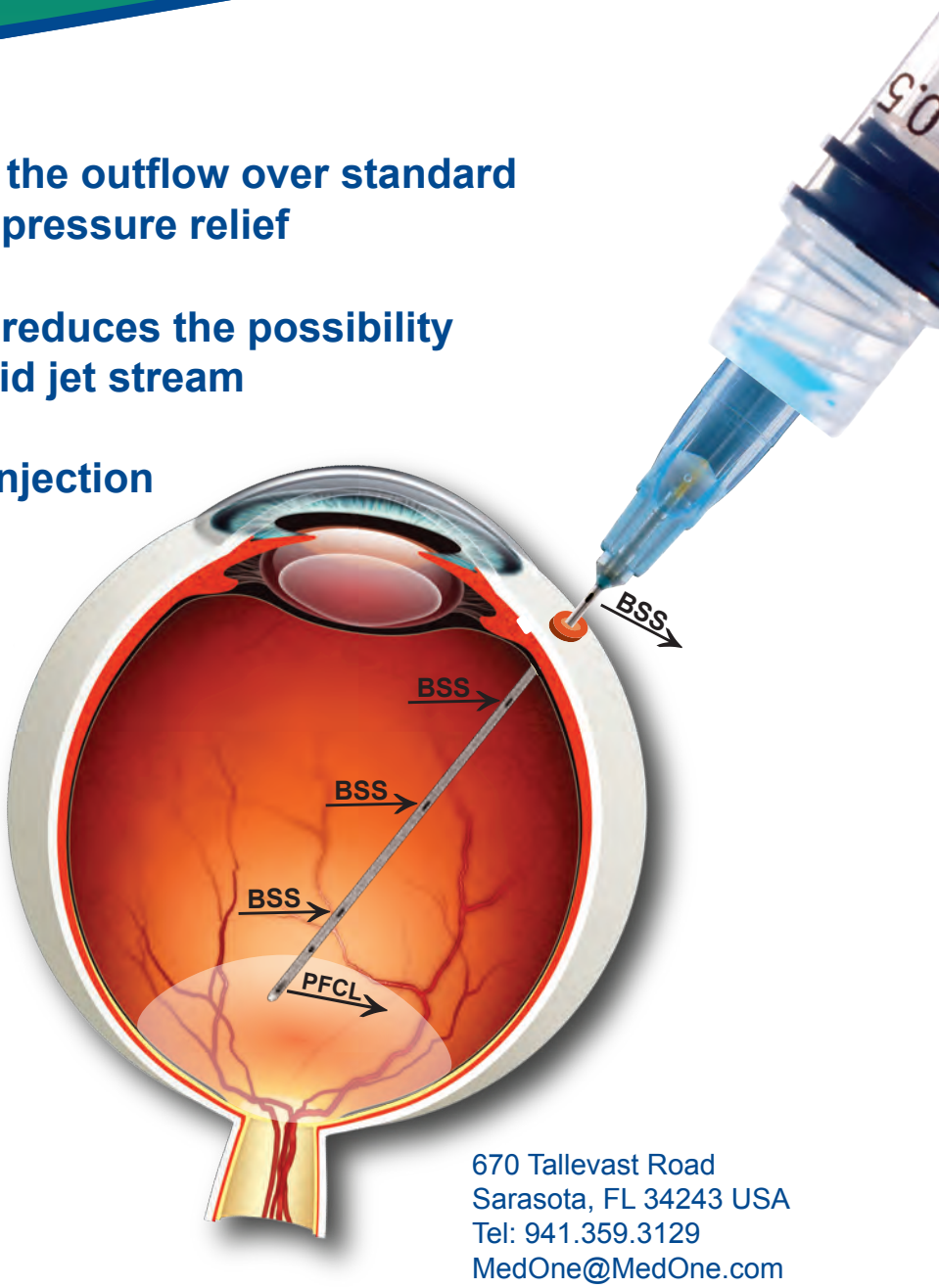

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BEWARE OF AMN WITH COVID-19 INFECTION

A potential ocular complication that can lead to a reduction in visual acuity.

BY EVGENIIA PEREVOZNIKOVA, MD; VLATKA BRZOVIĆ ŠARIĆ, MD, PHD; AND NENAD VUKOJEVIĆ, MD, PHD

Acute macular neuroretinopathy (AMN) is a rare retinal disease, the etiology of which is not entirely understood. It is most commonly diagnosed in young, otherwise healthy women.[1] Risk factors associated with AMN may include use of contraceptives, caffeine or cocaine intake, trauma, viral illness, and vaccination.[2]

Studies report different ophthalmological manifestations of COVID-19, conjunctivitis being the most common.[3-6] We present a case of COVID-19-associated bilateral AMN in a previously healthy man. Clinical manifestation typically involves sudden onset of single or multiple unilateral or bilateral paracentral scotomas with unaffected visual acuity.

THE CASE

A 43-year-old man presented with an acute onset of visual field defects in each eye, located in the upper outer quadrant in the right and more centrally in the left eye. He tested positive for COVID-19 infection via a PCR test and experienced mild respiratory symptoms and fever, for which no specific medication was required. The visual field defects started 3 days after the beginning of COVID-19 infection, following a high fever. His medical history was otherwise unremarkable. He reported no prior eye injury, medication usage, or sungazing.

His BCVA was unremarkable in his right eye (6/60 OD), but significantly decreased in his left eye (6/95 OS). His IOP and anterior segment findings were unremarkable. The fundoscopic examination revealed reddish-brown petaloid perifoveal lesions, with the tips pointing toward the center of the fovea (Figure 1). Findings on the optic nerve head were unremarkable. OCT imaging showed subtle disruption of the ellipsoid zone (Figure 2), while OCT angiography (OCTA) showed inner choroidal flow void that corresponded to the abnormal regions on OCT (Figure 3).

Visual field testing revealed a perifoveal scotoma in the right eye and a central foveal scotoma in the left eye, which were causing his reduced visual acuity (Figure 4). Multifocal electroretinography was also performed, showing reduced amplitudes corresponding to the retinal lesions (Figure 5).

The patient's subjective complaints and the diagnostic testing suggested bilateral AMN associated with COVID-19.

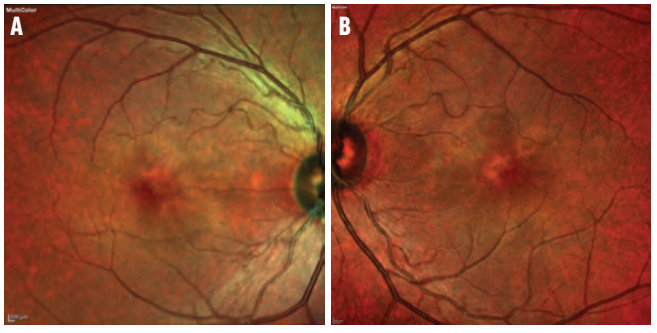

Figure 1. Fundoscopic examination revealed reddish-brown petaloid perifoveal lesions in the right (A) and left (B) eyes.

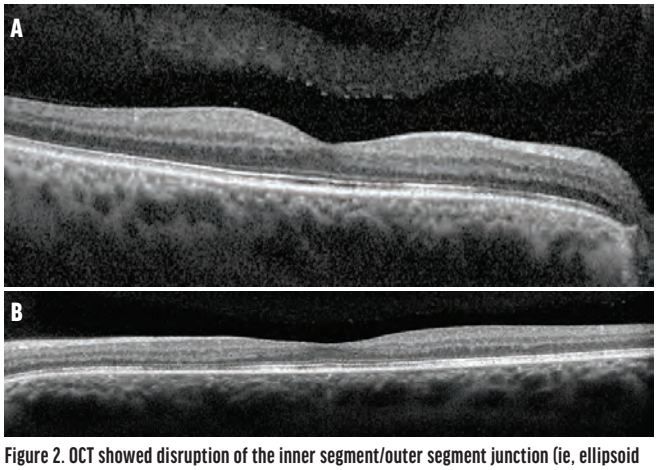

Figure 2. OCT showed disruption of the inner segment/outer segment junction (ie, ellipsoid zone) in the right (A) and left (B) eyes.

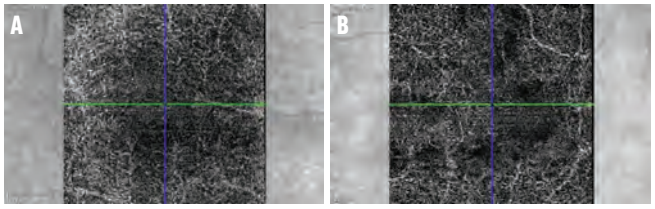

Figure 3. OCTA showed an inner choroidal flow void in the right (A) and left (B) eyes.

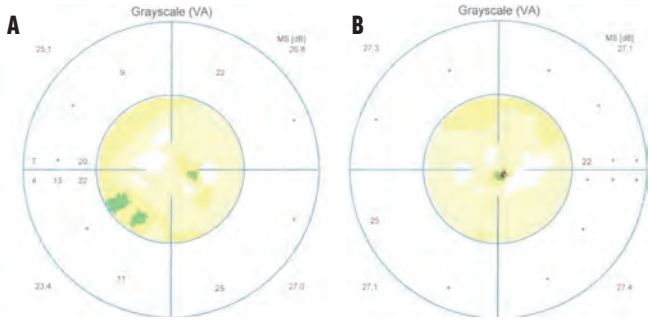

Figure 4. Visual field testing showed a perifoveal scotoma on the right eye (A) and a central foveal scotoma in the left eye (B).

Because this disease is considered to be self-limiting, no treatment was required. The patient reported subjective improvement 5 months following the initial examination with BCVA of 6/60 OD and 6/48 OS, along with improvements on OCTA (Figure 6). He still reported the presence of a visual field scotoma in each eye, however.

ETIOLOGY AND MANAGEMENT

Although the etiology of AMN is unclear, it is proposed that deep retinal vascular ischemia found in AMN can result from COVID-19 infection because the angiotensin-converting enzyme 2 (ACE-2) is the main receptor for coronavirus, causing multi-organ complications.[2] ACE-2 is present in the retina, making it a target for COVID-19 and a possible cause of deep vascular ischemia in AMN.

Different mechanisms can cause retinal hypoperfusion and ischemia, including vasoconstriction due to an increase in catecholamine release; lack of choriocapillaris autoregulation and decreased flow; hyperviscosity; endothelial dysfunction; coagulopathy; immune complex deposition; or acquired hypercoagulable state, each of which many occur in the inflammatory phase of COVID-19.[1] Cytokine storm and overactivation of immunological response, typical events during COVID-19 infection, may also cause systemic vascular injuries, including to the retina.[7]

One case report used treatment with systemic corticosteroids, which led to the improvement of scotomas.[8] Other cases report gradual resolution of the lesions over a few months, often with persistent visual field scotomas. Although this case showed improvement in OCTA findings, another reported persistence of choroidal flow void with improvement in retinal hyperreflectance on OCT.[9]

One ophthalmological disease with an ischemic event similar to that seen in AMN is paracentral acute middle maculopathy, which also presents with paracentral macular

(Continued on page 18)

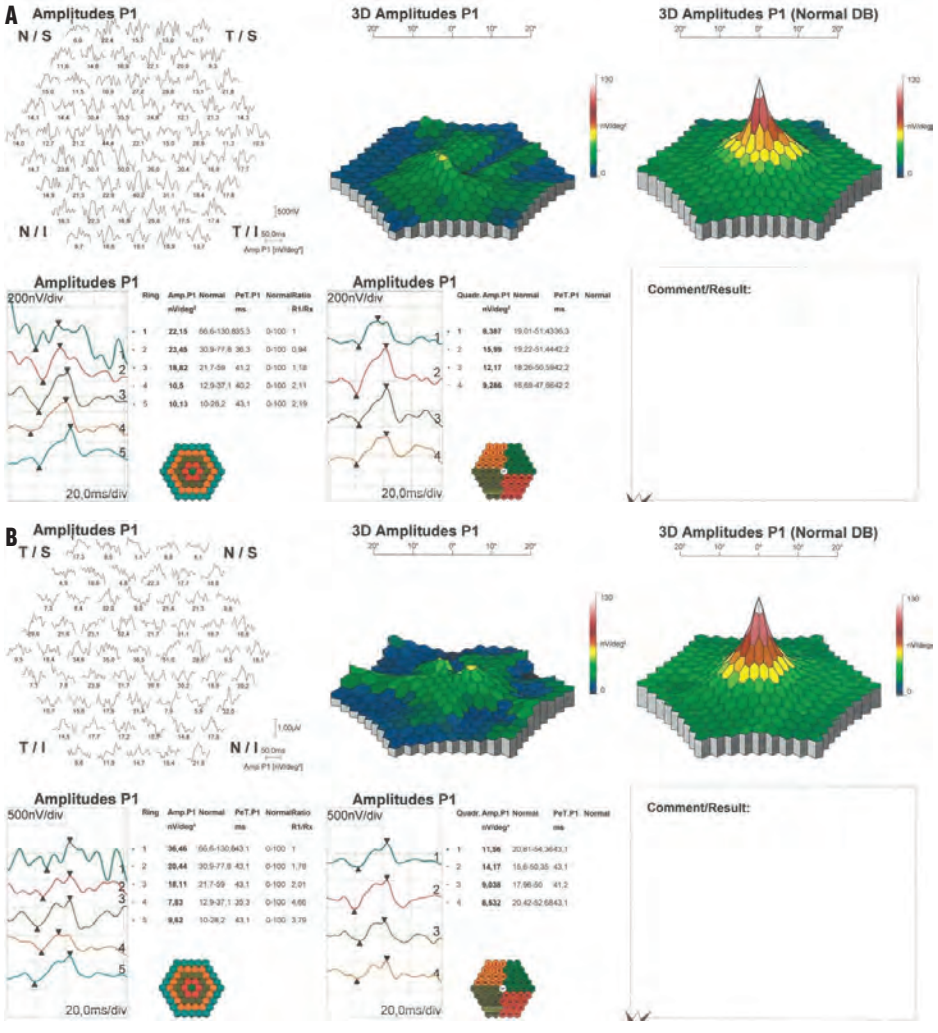

Figure 5. Multifocal electroretinography showed reduced amplitudes in the right (A) and left (B) eyes.

NO MORE FORCEPS: A CUTTER-BASED APPROACH TO ILM PEELING


This technique could reduce surgical time, improve patient satisfaction, and save on instrument costs.

BY SCOTT D. WALTER, MD, MSC, AND SIMON D. ARCHAMBAULT, MD, MSC

Vitrectomy with internal limiting membrane (ILM) peeling has become the standard procedure for full-thickness macular holes (FTMHs) and epiretinal membranes (ERMs). ILM peeling can improve success rates for FTMH closure and reduce postoperative ERM recurrence.[1,2] The traditional technique involves initiating an ILM rhexis using ILM forceps ("pinch and peel") or a secondary instrument, such as a membrane scraper. The surgeon then completes the ILM peel using ILM forceps. As the ILM is peeled, the surgeon must manually remove each fragment from the eye using the forceps.

However, some surgeons have described techniques for ILM peeling and removal without the use of forceps. Timothy Murray, MD, MBA, reported a case of ILM peeling with the vitrectomy probe, and Carl Awh, MD, reported a series of 24 patients who underwent ILM peeling with an aspirating pick (Awh MVP Micro Vacuum Pick, Katalyst Surgical).[3,4]

At our institution, we historically peeled ILM using a flexible loop scraper (Finesse Flex Loop, Alcon) to create the ILM rhexis before switching to an ILM forceps to peel and remove the remaining ILM tissue. Currently, after initiating the ILM rhexis with a Flex Loop (Figure 1A), we use only the aspiration function of the vitrectomy handpiece to complete the ILM peeling (Figure 1B). A key advantage of this technique is the ability to peel and remove ILM tissue without removing instruments from the eye. By reducing the number of instrument exchanges, this technique has the potential to reduce surgical time and the risk of intraoperative complications.

We sought to better understand the feasibility, efficiency, safety, and effectiveness of cutter-based membrane peeling compared with conventional forceps-based peeling. In this article, we review the findings, their significance, and how to apply the new technique.

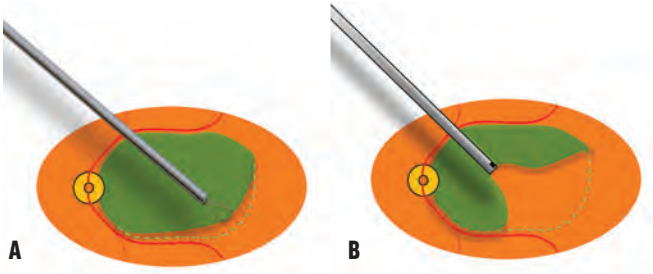

Figure 1. There is a two-step technique for ILM peeling without forceps. A 180° ILM rhexis is created along the arcades with a flexible loop scraper (A). Using the vitrectomy probe on aspiration mode, the ILM flap is then peeled to release all traction on the fovea, the ILM rhexis is completed, and the amputated ILM flap is aspirated into the port (B).

WHAT WE FOUND

Between April 2020 and December 2021, we performed 92 consecutive vitrectomies with ILM peeling for ERMs (n = 62, 68%) and FTMHs (n = 30, 32%) at a single ambulatory surgery center. Most of the aspects of the surgical procedure were consistent: a 25-gauge vitrectomy, the use of "heavy" ICG for ILM staining, and the initiation of the ILM rhexis using a flex loop. The one surgical variable was whether the ILM peeling was performed using a 25-gauge ILM forceps (n = 12) or a 25-gauge vitrectomy probe, or "cutter" (n = 80). The baseline demographics, visual acuities, macular volumes, and central subfield thicknesses (CST) were similar between the two groups. The patients were followed for a minimum of 3 months postoperatively.

The primary outcome of this study was total surgical time. Cutter-based membrane peeling significantly reduced the total operative time by an average of 10 minutes (P = .001). Patients in both groups had significant improvements in visual acuity (P = .001), macular volume (P = .001), and CST (P = .001) 3 months postoperatively compared with preoperative values.

CUTTER-BASED MEMBRANE PEELING HAS NOW BECOME OUR STANDARD METHOD FOR ILM PEELING, INCLUDING CASES REQUIRING ADVANCED ILM MANEUVERS.

There were no intraoperative complications encountered in either group, including iatrogenic macular holes, retinal breaks, retinal detachments (RDs), or choroidal detachments. There was only one case (1.2%) of postoperative RD seen in the cutter-based group after 3 months—which is less than the expected cumulative incidence of RD (2% to 3%) observed in large claims-based studies of vitrectomy with ILM peeling.[5]

WHAT THIS MEANS

This study suggests the feasibility, efficiency, safety, and efficacy of cutter-based membrane peeling as an alternative to forceps-based peeling for routine indications, such as FTMHs and ERMs. When the cutter-based approach was implemented, patients had high rates of single-operation anatomic success (> 96%) and significant postoperative improvements in visual acuity, macular volume, and CST. All outcomes were comparable with traditional forceps-based ILM peeling. More importantly, the safety profile of cutter-based membrane peeling appears comparable with conventional techniques. There were no iatrogenic complications, and the rate of postoperative RD was comparable with the national average.[5]

Based on our findings, a cutter-based approach can reduce operative time by increasing surgical efficiency and ergonomics. The surgeon can simultaneously peel and remove membrane tissue—thereby reducing the number of intraoperative instrument exchanges. The port geometry of the 25-gauge cutter allows for efficient engagement and release of ILM tissue, thereby eliminating the need for multiple fine grasping maneuvers with the ILM forceps.

Effective peeling and manipulation of ILM tissue with the cutter require some skill and finesse, but these maneuvers should come naturally to most vitreoretinal surgeons.

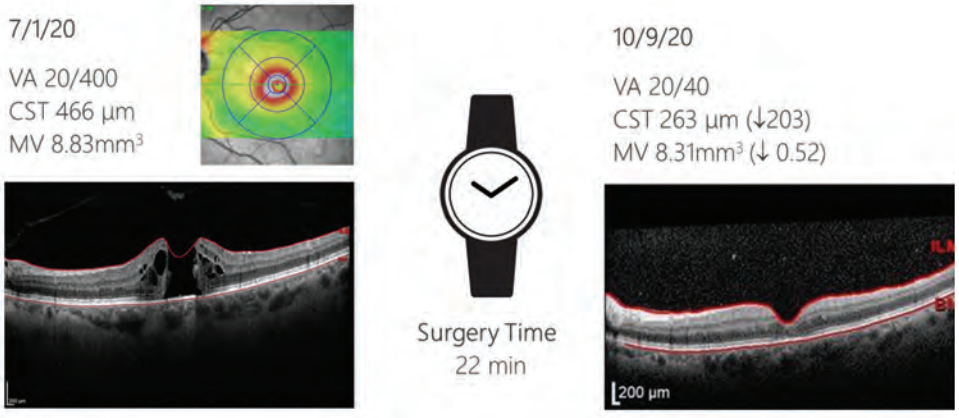

Figure 2. The first patient in this consecutive case series of cutter-based membrane peeling showed a successful closure of a large FTMH with clinically significant improvements in visual acuity, macular volume, and CST at postoperative month 1 versus baseline.

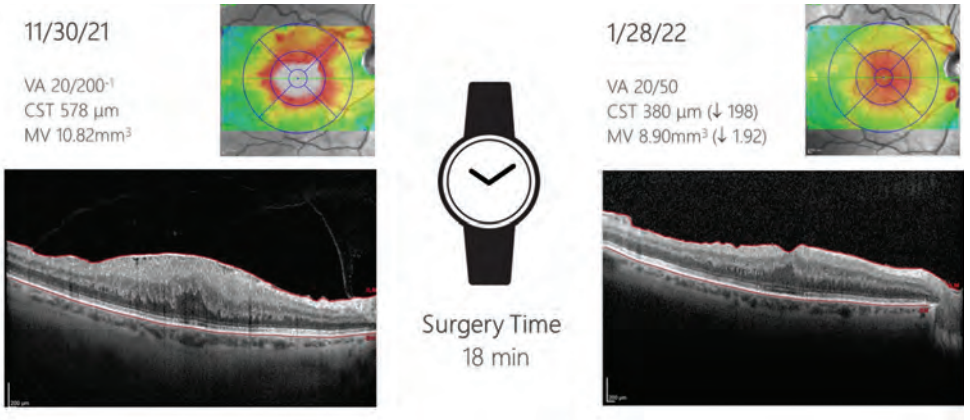

Figure 3. The last patient treated in this consecutive case series of cutter-based membrane peeling showed successful removal of an ERM with improvements in visual acuity, macular volume, and CST at postoperative month 1 versus baseline.

TIPS FOR NEW USERS

Start by creating a large ILM rhexis. Typically, we use the flex loop to create a 180° rhexis along the inferotemporal arcade, extending all the way into the temporal macula.

Next, engage the ILM flap with the cutter and increase proportional vacuum aspiration with the foot pedal until the port is occluded by ERM/ILM tissue.

Then, maintain a low level

of vacuum so the port remains occluded. The cutter now functions as if the surgeon were grasping the tissue with forceps. The tissue is then peeled by moving the cutter, rotating the port, increasing the vacuum, or a combination of these maneuvers.

At any point, the tissue can be released—either passively (by reducing vacuum to release tissue from the port) or actively (by increasing the vacuum to complete the rhexis and aspirate the tissue into the port). We find that it's best to work on releasing all traction from the fovea before amputating the ILM/ERM flap. In some cases, a second peel may be required to remove residual ILM tissue after ERM peeling.

GETTING STARTED

Cutter-based membrane peeling has now become our standard method for ILM peeling, including cases requiring advanced ILM maneuvers. It is feasible in most cases, and we can count on one hand the number of times we have had to open a pair of ILM forceps in the last 2 years. Our study showed that patients achieved excellent anatomic and visual outcomes without sacrificing safety (Figures 2 and 3).

This technique has saved time and reduced our ambulatory surgery center instrument costs. By reducing instrument exchanges and other inefficiencies, our average incisional time for macular surgeries has decreased to approximately 18 minutes. Decreased operative time contributes to increased patient satisfaction. Patients are often amazed by how quickly their procedure was performed. ■

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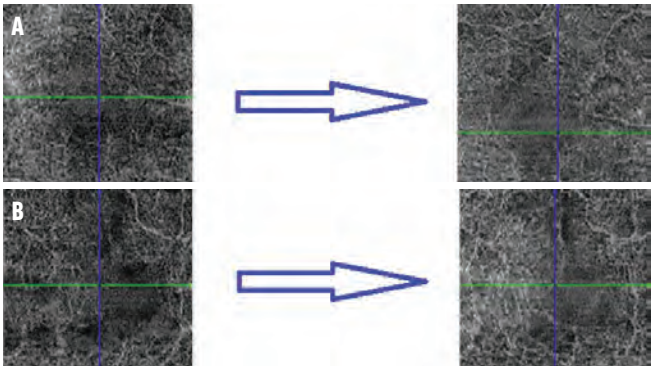

Figure 6. OCTA imaging 5 months after initial presentation of the right (A) and left (B) eyes.

lesions, hyperintense OCT lesions, and subjective paracentral scotomas.[1] Fluorescein angiography can be used to differentiate these conditions, since it is unremarkable in AMN.

BEWARE OF OCULAR COMPLICATIONS WITH COVID-19

This case raises awareness of possible retinal vascular injuries and ischemia caused by COVID-19 acute infections, although further research is needed to completely understand the etiology of this disease. ■

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NO supplemental treatment needed to maintain anesthesia*†[1]

NO serious adverse events with an established safety profile[2]

NO patients reported experiencing pain[2]

*In the clinical trial, no patient undergoing routine cataract surgery receiving IHEEZO required supplemental treatment to maintain anesthesia; this was not the case for patients receiving tetracaine. Supplemental treatment was defined as general anesthesia, intraoperative systemic analgesia, or local anesthesia. Though supplemental administration was not required by any patient in the clinical trial, IHEEZO may be reapplied as needed to maintain anesthesia.[1,2]

†Sufficient anesthesia with IHEEZO lasted an average of 21.5 minutes in the clinical trial, while mean total surgical time was 13.9 minutes.[2]

APPROVED USE

IHEEZO is indicated for ocular surface anesthesia.

IMPORTANT SAFETY INFORMATION

IHEEZO is contraindicated in patients with a history of hypersensitivity to any component of this preparation.

IHEEZO should not be injected or intraocularly administered.

Patients should not touch the eye for at least 10 to 20 minutes after using anesthetic as accidental injuries can occur due to insensitivity of the eye.

Prolonged use of a topical ocular anesthetic may produce permanent corneal opacification and ulceration with accompanying visual loss.

Do not touch the dropper tip to any surface as this may contaminate the gel.

IHEEZO is indicated for administration under the direct supervision of a healthcare provider. IHEEZO is not intended for patient self-administration.

The most common adverse reactions in studies following IHEEZO administration (incidence greater than or equal to 5%) were mydriasis, conjunctival hyperemia, and eye irritation.

You are encouraged to report suspected adverse reactions to the FDA. Visit **www.fda.gov/medwatch**, or call **1-800-FDA-1088**.

Please see Brief Summary of Full Prescribing Information for IHEEZO on adjacent page.

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IZO-00047 03/23

References: 1. Iheezo. Prescribing information. Harrow IP, LLC; 2022. **2.** Data on File. Harrow IP, LLC; 2023.

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BRIEF SUMMARY OF PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

IHEEZO™ (chloroprocaine hydrochloride ophthalmic gel) 3% is a preservative-free ester anesthetic indicated for ocular surface anesthesia.

4 CONTRAINDICATIONS

IHEEZO is contraindicated in patients with a history of hypersensitivity to any component of this preparation.

5 WARNINGS AND PRECAUTIONS

5.1 Not for Injection or Intraocular Administration

IHEEZO should not be injected or intraocularly administered.

5.2 Corneal Injury Due to Insensitivity

Patients should not touch the eye for at least 10 to 20 minutes after using anesthetic as accidental injuries can occur due to insensitivity of the eye.

5.3 Corneal Opacification

Prolonged use of a topical ocular anesthetic may produce permanent corneal opacification and ulceration with accompanying visual loss.

5.4 Risk of Contamination

Do not touch the dropper tip to any surface as this may contaminate the gel.

5.5 For Administration by Healthcare Provider

IHEEZO is indicated for administration under the direct supervision of a healthcare provider. IHEEZO is not intended for patient self-administration.

6 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.

The data described below reflect 201 patients undergoing various surgical ocular procedures in two placebo-controlled trials (Study 1 and Study 2). Patients in Study 1 were randomized to receive a single instillation of 3 drops of IHEEZO or placebo. Patients in Study 2 were randomized to receive a single or multiple instillations of 1, 3, or 3+3 drops of IHEEZO or placebo.

The most common adverse reactions in these studies (incidence greater than or equal to 5%) following IHEEZO administration were mydriasis, conjunctival hyperemia, and eye irritation.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate and well-controlled studies of IHEEZO use in pregnant women to inform a drug-associated risk. There are no animal reproduction studies for chloroprocaine.

8.2 Lactation

Risk Summary

There are no data on the presence of chloroprocaine in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for IHEEZO and any potential adverse effects on the breastfed infant from IHEEZO.

8.4 Pediatric Use

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

8.5 Geriatric Use

No overall differences in safety or effectiveness of IHEEZO have been observed between elderly and younger patients.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Chloroprocaine, like other local anesthetics, blocks the generation and the conduction of nerve impulses, presumably by increasing the threshold for electrical excitation in the nerve, slowing the propagation of the nerve impulse, and reducing the rate of rise of the action potential. In general, the progression of anesthesia is related to the diameter, myelination, and conduction velocity of affected nerve fibers. Clinically, the order of loss of nerve function is as follows: (1) pain, (2) temperature, (3) touch, (4) proprioception, and (5) skeletal muscle tone.

12.3 Pharmacokinetics

The systemic exposure to chloroprocaine following topical ocular administration of IHEEZO has not been studied.

Elimination

Metabolism

Chloroprocaine is metabolized by plasma pseudocholinesterases and nonspecific esterases in ocular tissues. Chloroprocaine is rapidly metabolized in plasma by hydrolysis of the ester linkage by pseudocholinesterase. The hydrolysis of chloroprocaine results in the production of ß-diethylaminoethanol and 2-chloro-4-aminobenzoic acid, which inhibits the action of the sulfonamides.

Excretion

Chloroprocaine plasma half-life in vitro is approximately 25 seconds in adults and approximately 43 seconds in neonates. The kidney is the main excretory organ for most local anesthetics and their metabolites. Urinary excretion is affected by urinary perfusion and factors affecting urinary pH.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long-term studies in animals to evaluate carcinogenic potential of chloroprocaine have not been conducted.

Mutagenesis

2-chloroprocaine and the main metabolite, ACBA, were negative in the in vitro bacterial reverse mutation test (Ames assay) and the in vitro chromosome aberrations assay.

Impairment of Fertility

Studies in animals to evaluate the impairment of fertility have not been conducted with chloroprocaine.

14 CLINICAL STUDIES

14.1 Study 1 and Study 2

Study 1 (NCT04779606) and Study 2 (NCT04753710) were randomized, double-blinded, placebo-controlled studies conducted to evaluate the efficacy, safety, and local tolerability of IHEEZO in 145 healthy volunteers.

In Study 1, 85 healthy males and females were randomized in a 4:1 ratio to receive a single ocular instillation of IHEEZO (n=68) or placebo (n=17). The double-blinded treatment included an IHEEZO or a placebo dose of 3 drops instilled at 1-minute (±15 seconds) intervals in the right eye of each volunteer. The median age was 39 years (range 19 to 55 years); 59% female and 41% male.

In Study 2, 60 healthy males and females were randomized (40:20) to receive single or multiple ocular instillations of an IHEEZO dose of 3 drops in the right eye. The median age was 25 years (range 18 to 59 years); 54% female and 46% male.

The efficacy in Study 1 and Study 2 was determined by proportion of patients achieving full conjunctival anesthesia evaluated by conjunctival pinching 5 minutes after administration.

Efficacy results of Study 1

The proportion of subjects with successful anesthesia was 90% in the IHEEZO group and 12% in the placebo group (P<0.01). The median time for the IHEEZO group achieving anesthesia was 0.67 minutes. The median duration of anesthesia was 14.3 minutes.

Efficacy results of Study 2

The proportion of subjects with successful anesthesia was 95% in the IHEEZO group and 20% in the placebo group (P<0.01). The median time for the IHEEZO group achieving anesthesia was 0.67 minutes. The median duration of anesthesia was 19.3 minutes.

14.2 Study 3

Study 3 (NCT04685538) was a randomized, prospective, multicenter, active-controlled, observer-masked study conducted to evaluate the efficacy and safety of IHEEZO (n=166) versus tetracaine ophthalmic solution 0.5% (n=172) in patients undergoing cataract surgery.

The primary endpoint was defined as the proportion of patients in each treatment group gaining successful anesthesia without any supplementation. On average, patients needed 1 to 1.5 minutes to obtain sufficient anesthesia to successfully perform the surgical procedure, which lasted on average 22 minutes.

No patient treated with IHEEZO required supplemental treatment to complete the intended surgical procedure.

17 PATIENT COUNSELING INFORMATION

Eye Care Precaution

Do not touch the dropper tip to any surface as this may contaminate the gel. Advise patients that their eyes will be insensitive for up to 20 minutes due to the effect of the anesthetic, and that care should be taken to avoid accidental injuries.

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SURGICAL TECHNIQUE FOR SCLERAL-FIXATED IOLS

A challenging but beneficial approach for cases with poor capsular support.

BY ALEJANDRO LONDOÑO, MD; DANIEL FRANCISCO LOPEZ, MD; NATALIA TRUJILLO ÁNGEL, MD; AND ANDRÉS AMAYA ESPINOSA, MD

The main treatment for aphakia is the implantation of an IOL; however, therapeutic challenges may arise in the of absence of capsular support. The absence of capsular support is often secondary to trauma or congenital or metabolic conditions (eg, Marfan syndrome, homocystinuria, pseudoexfoliation syndrome).

Surgical alternatives in cases of absent capsular support include use of anterior chamber IOLs (ACIOLs), iris-fixated IOLs (IFIOLs), or scleral-fixated IOLs (SFIOLs).[1-5] There are advantages and disadvantages to each of these lens types, and the decision depends on the individual patient.[1,2]Implanting an ACIOL tends to be easier compared with the implantation of other IOLs,[3] and implantation of either an ACIOL or IFIOL increases the risk of glaucoma, hyphema, intraocular inflammation, cystoid macular edema, and corneal decompensation, as they are implanted closer to the iridocorneal angle and the corneal endothelium.[2,4-6] For this reason, use of an SFIOL may often be the most appropriate for certain patients.

Herein, we describe our study of 20 patients (20 eyes) who underwent SFIOL implantation, including an overview of the technique, complications, and visual outcomes.

REVIEW OF SFIOLS

SFIOLs are the most widely used option globally for IOL implantation in the absence of capsular support, especially in young patients with a history of trauma or those with diabetes, guttate cornea, narrow anterior chamber, or post-penetrating keratoplasty.[4-6] SFIOLs are also more often considered in patients whose life expectancy is more than 10 years.[5]

However, SFIOL implantation can be challenging and can lead to postoperative complications, such as exposure of the suture and knot, lens decentration, high IOP, secondary open-angle glaucoma, endophthalmitis, vitreous hemorrhage, retinal detachment (RD), choroidal effusion, and hemorrhage.[1,5,7,8-10]

An SFIOL may be idea for patients with a subluxed or dislocated IOL that can be repositioned, patients with an IOL that must be exchanged, or an aphakic patient who requires secondary IOL placement.[3]

OUR SURGICAL TECHNIQUE

In our study, complete 25-gauge vitrectomy was performed. Some patients with a history of RD or trauma had already undergone this procedure. The 10 steps we used were as follows:

STEP 1. Perform a superior and inferior conjunctival peritomy, and use a caliper to measure a 7.5 mm superior scleral incision (Figure 1A).

STEP 2. Use a No. 15 scalpel blade to create a 7.5 mm superior scleral tunnel (Figure 1B).

STEP 3. Use a 2.75 mm diamond blade to enter the anterior chamber at the 12 clock hour through the scleral tunnel and extend to all principal wounds (Figure 1C). Temporarily close the scleral wound with a 10-0 nylon suture.

STEP 4. Load a 27-gauge straight needle with a 10-0 nylon suture (Figure 1D) and pass it through the inferior scleral 2.5 mm posterior to the limbus (Figure 1E and 1F).

STEP 5. Using an ab externo technique, visualize through the pupil and capture the suture with end-gripping forceps through the superior scleral wound (Figure 1G).

STEP 6. Repeat steps 4 and 5 (Figure 1H, 1I, and 1J).

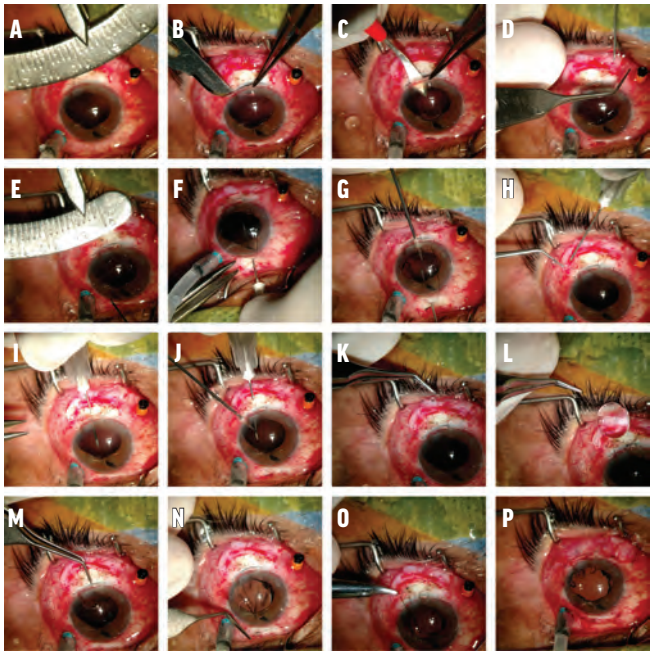


Figure 1. This patient had a history of RD that required management with vitrectomy, endolaser photocoagulation, and silicone oil tamponade. Afterward, the patient underwent silicone oil removal and SFIOL implantation with a two-point fixation technique.

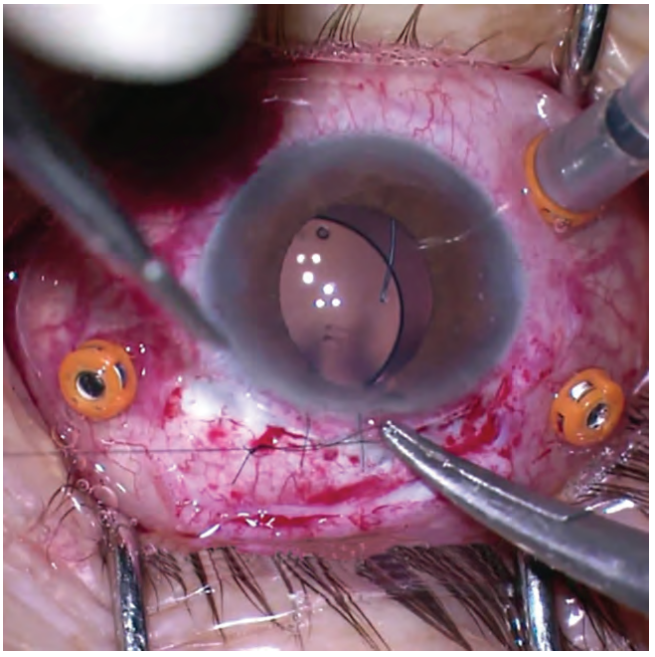


Figure 2. After cataract surgery and IOL implantation, this patient experienced inferior subluxation secondary to zonular dialysis. The lens was repositioned with a one-point fixation technique because of partial capsular support.

STEP 7. Using the CZ70BD IOL (Alcon), the haptic of which contains a single eyelet, insert the two segments of 10-0 nylon through the superior and inferior eyelet separately (Figure 1K and 1L).

STEP 8. Insert the lens into the eye posterior to the pupil (Figure 1M).

STEP 9. Tie the superior and inferior knots to the sclera (Figure 1N and 1O).

STEP 10. Close the upper incision with 10-0 nylon, and close the incisions from Tenon's and conjunctiva peritomy with 6-0 vicryl to cover the scleral knots (Figure 1P).

If there are remnants of the posterior capsule, they can be used as partial lens support, and the secondary IOL only requires one point of fixation to the sclera (Figure 2).

TABLE 1. PREOPERATIVE LENS STATUS AND INDICATION FOR SFIOL

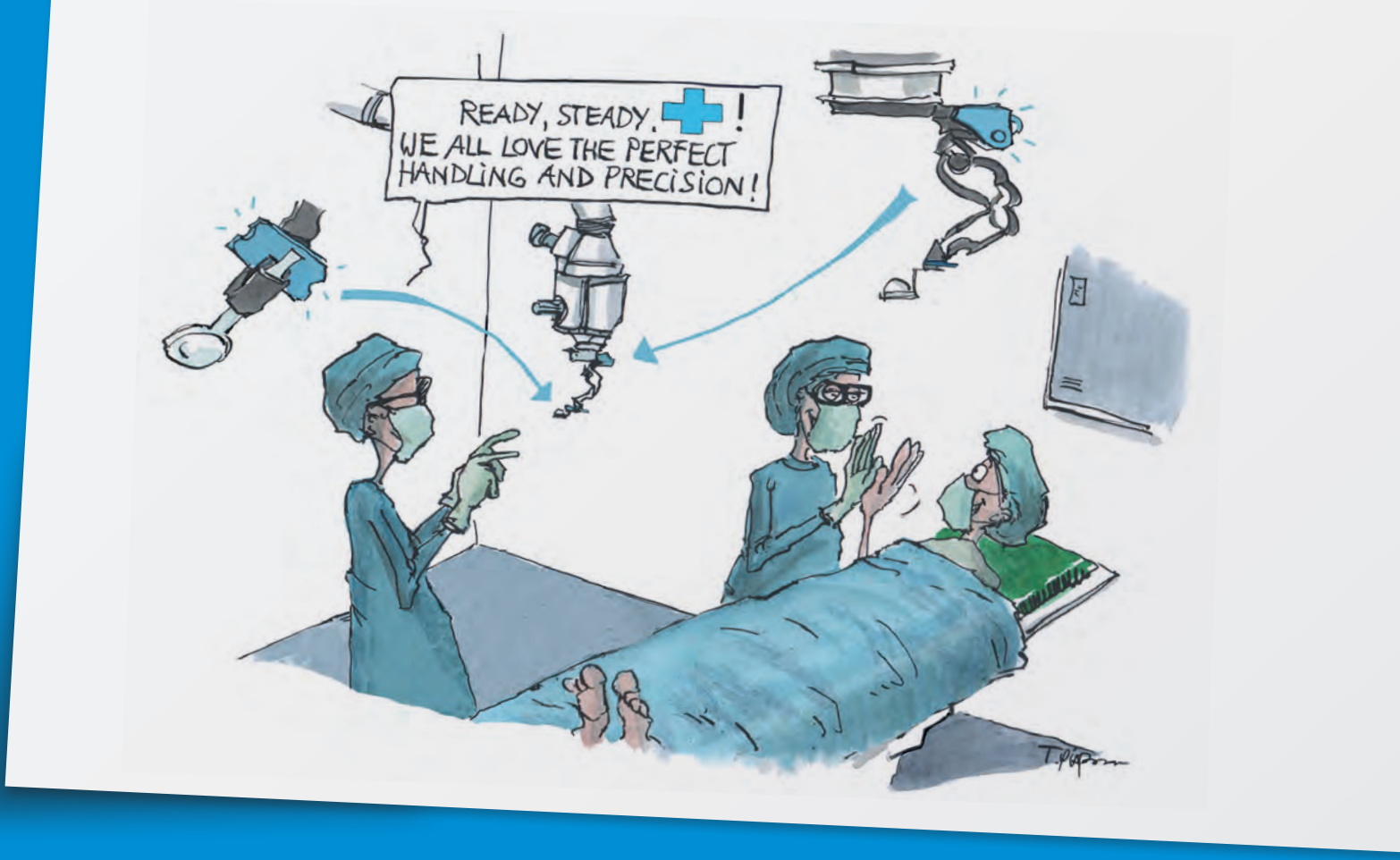
	Eyes, n (%)
Aphakic • Post complicated cataract removal • Post cataract removal due to trauma	15 (75%) 11 (55%) 4 (20%)
Pseudophakic • Dislocated posterior chamber IOL	5 (25%) 5 (25%)

RESULTS

Our study included 20 eyes of 20 patients with an average age of 60.75 years (range 3–85 years). The median follow-up after surgery was 6 months (range 1–65 months). The preoperative BCVA ranged from 20/100 to light perception. Preoperative ocular history of the patients included RD, trauma, leukoma, iridodonesis, vitreous hemorrhage, choroidal detachment, pterygium, corectopia/dyscoria, posterior synechiae, aniridia, AMD, vitreous prolapse, intraocular foreign body, iris

TABLE 2. POSTOPERATIVE COMPLICATIONS

	Eyes, n (%)
None	9 (45%)
Ocular hypertension	6 (30%)
Retinal redetachment	2 (10%)
Pseudophakic bullous keratopathy	2 (10%)
Knot exposure	1 (5%)
Decentration	1 (5%)
Subluxation	1 (5%)
Posterior luxation	1 (5%)



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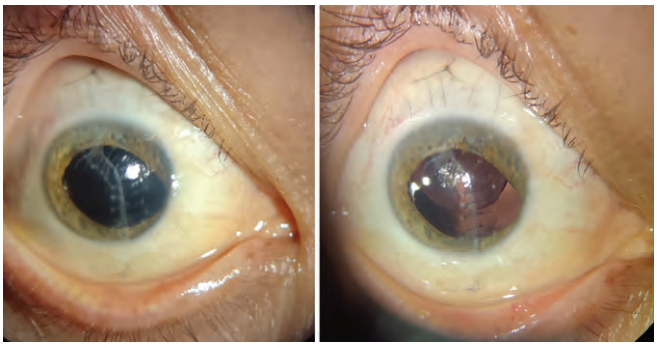

Figure 3. A patient with a history of open-globe trauma and RD underwent a secondary SFIOL implantation. The lens is seen decentered postoperatively with the superior and inferior fixation points in position. Postoperative BCVA was 20/100.

atrophy, pigment dispersion syndrome, and corneal decompensation.

Of the 15 aphakic patients (75%), 11 had a previous complicated cataract surgery and four underwent cataract removal due to trauma. Each of the five pseudophakic patients had been previously implanted with a posterior chamber IOL that had become dislocated (Table 1).

Mean BCVA at follow-up was 20/160; 20% (four eyes) had a follow-up BCVA of 20/40 or better; 55% (11 eyes) had VA < 20/40 ≥ 20/400; and 25% (five eyes) had a VA of counting fingers or light perception.

Five patients had their lenses reposition, and 15 underwent a secondary SFIOL implantation.

Nine eyes (45%) did not experience any complications following the SFIOL technique. Postoperative complications are summarized in Table 2. Of note, posterior dislocation occurred in one eye (Figure 3), and another eye experienced decentration. Other authors have found similar decentration rates.[7,11]

DISCUSSION

SFIOLs continue to be a challenge for ophthalmologists in the management of patients with postsurgical aphakia and IOL dislocation.[5] The prevalence of poor capsular support is higher than may be supposed, especially in patients with traumatic open-globe injuries because of damage to the lens capsule or iris.[3]

Varying haptic designs facilitate the suture of the lens to the sclera, including holes or eyelets that allow the passage of a suture through it, thus reducing its movement.[1]

There has been controversy around the stability of 10-0 polypropylene, as the incidence of suture breakage in the literature is variable—from as low as 0.5% to as high as 27.9% after 6 years of follow-up.[4,8,10,12] With our technique, 10-0 nylon sutures were used with no breakage reported.

Higher risk of RD has been associated with SFIOLs, ranging in the literature from as low as 3.2% to as high as 8.2%.[5,7,8,11] In our study, none of the patients developed a primary RD, although two eyes (10%) developed retinal redetachment in the postoperative term.

LONG-TERM STUDIES ARE NEEDED

This SFIOL technique may be of benefit for select aphakic and pseudophakic patients. It is important to consider that most of the patients included in this study had a history of ocular pathology that could compromise their visual outcomes.

Limitations of this study include a short period of follow-up and a small sample size. For this reason, larger studies with a longer follow-up will be necessary to determine the benefits of this surgical technique. ■

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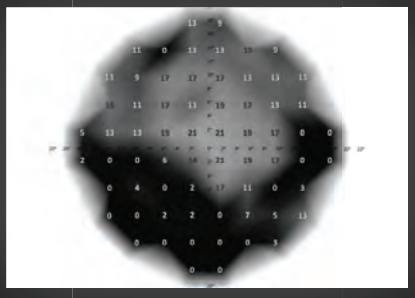

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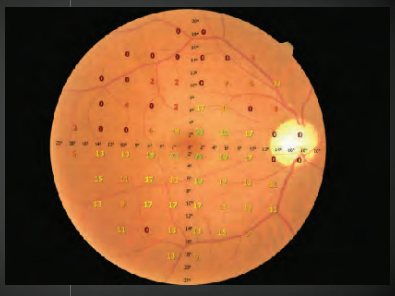

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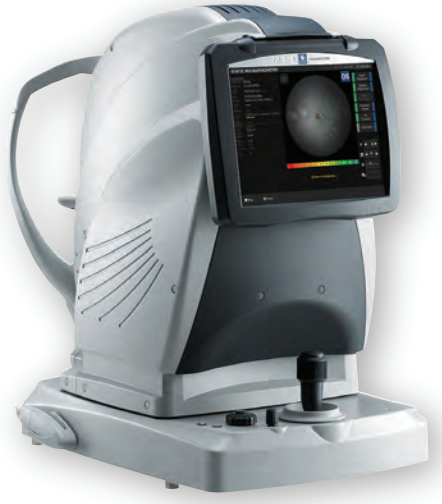

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April 19, 2021
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GEOGRAPHIC ATROPHY TREATMENT PEARLS

Experts share their insights on caring for a whole new patient population with newly approved therapeutics.

A CONVERSATION WITH ELEONORA M. LAD, MD, PHD; JEFFREY S. HEIER, MD; AND DILSHER S. DHOOT, MD

MODERATED BY ALLEN C. HO, MD, AND ROBERT L. AVERY, MD

The FDA approval of pegcetacoplan (Syfovre, Apellis Pharmaceuticals) for the treatment of geographic atrophy (GA) secondary to AMD is a milestone. We've had clinical trials for GA that have failed with complement modulation, and it wasn't clear whether modifying the complement pathway was going to work. Now we know that it does work, and it's providing significant hope to patients losing vision from GA. Now that the new drug is in our clinics, we have a very different patient education opportunity on our hands, considering that the treatment slows, but does not stop, progression. We asked experts in our field to share their thoughts on how they are approaching their care for a previously untreatable patient population and what pitfalls we must avoid.

– Allen C. Ho, MD, and Robert L. Avery, MD

DR. HO: HOW ARE YOU DISCUSSING THIS NEW THERAPEUTIC WITH YOUR PATIENTS?

Jeffrey S. Heier, MD: When patients with wet AMD presented 15 or 20 years ago, we did not have a treatment—then we had an explosion of anti-VEGF agents, and we were able to offer nothing short of a remarkable treatment that could control the disease and, in many patients, improve vision. But we also realized that dry AMD was a debilitating and unremitting disease that was continuing to affect patients' central vision. Thus, the development and approval of pegcetacoplan is an important step in our ability to control this disease.

I tell patients that we now have an FDA-approved therapy that has a modest benefit. It's a first step to slow the rate of GA progression. I make sure they understand that it doesn't stop it or reverse it; even with treatment, they will lose vision, just at a slower rate than if they did nothing.

For many patients, the earlier in the disease process that we diagnose their GA, before it involves the fovea, the more likely we can have a noticeable effect on their outcome.

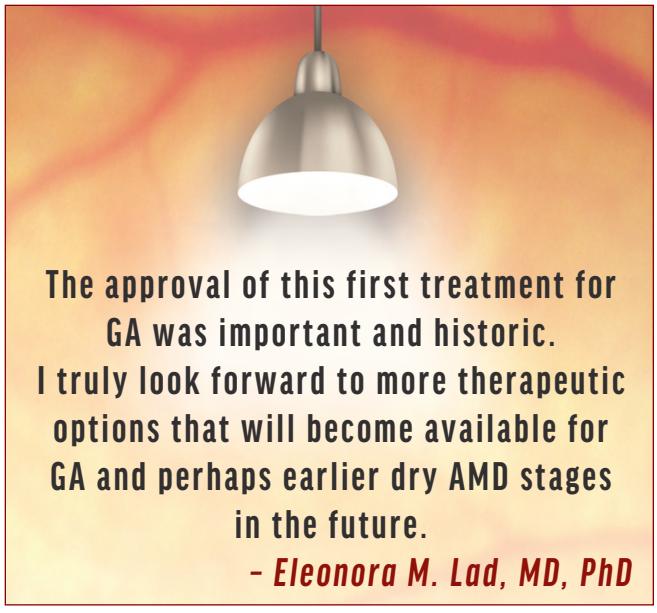
DR. AVERY: WHAT ABOUT PATIENT SELECTION? FOR THIS DRUG, WILL WE BE APPLYING THE ART OF MEDICINE BECAUSE THE LABEL IS QUITE BROAD?

Eleonora M. Lad, MD, PhD: Although pegcetacoplan does not stop or reverse the disease, the effect is very meaningful because it preserves the cells in the retina that are responsible for vision for longer. In addition, we know that the protective effect of the drug increases with treatment duration. When recommending treatment for patients, I remember that it works best when treatment is initiated earlier in the disease process before the fovea is involved. I consider the visual status of the fellow eye, but I keep in mind that extrafoveal lesions benefit the most.

I have a full conversation with each patient about how nearly all medicines have side effects if they work. I also

AT A GLANCE

- The FDA approval of pegcetacoplan (Syfovre, Apellis Pharmaceuticals) for the treatment of geographic atrophy secondary to AMD provides patients with an option to slow the rate of progression.
- When recommending treatment, remember that pegcetacoplan works best when it is initiated earlier in the disease process before the fovea is involved.
- The authors are favoring every-other-month treatment for three reasons: efficacy (the difference between monthly and every-other-month dosing was only 3% at 24 months), treatment burden, and safety.



explain that one of the side effects is the potential conversion to wet AMD, for which we have excellent treatments. Otherwise, the drug was shown to be safe and well tolerated.

Patient selection will be a significant part of the art of medicine, and we must consider each patient's comorbidities, their ability to come in for frequent injections (whether monthly or every other month), and the status of the fellow eye.

Dr. Ho: The label is surprisingly broad with no restrictions for lesion size or location or whether the patient has concomitant wet AMD in an eye with GA. That may be a sweet spot for me—patients who have had chronic anti-VEGF injections to control wet AMD but are starting to decline from GA.

Dilsher Dhoot, MD: I applaud the FDA's decision to make this label broad. The studies were large and enrolled a very heterogeneous population. In fact, most patients in the OAKS and DERBY trials had foveal-involving lesions. The therapy isn't right for every patient, so it's important to have an informed discussion with patients. It's remarkable how many patients are aware of this drug already, and I've already had many asking if they are candidates for treatment.

When it comes to the decision to treat, the trials suggest patients who are treated early may have the greatest benefit. Patients who already have poor vision may not benefit from treatment, but I will still offer it to a wide variety of patients, similar to the inclusion and exclusion criteria used in the trials. In particular, I find that patients who have documented GA growth are great candidates for this drug.

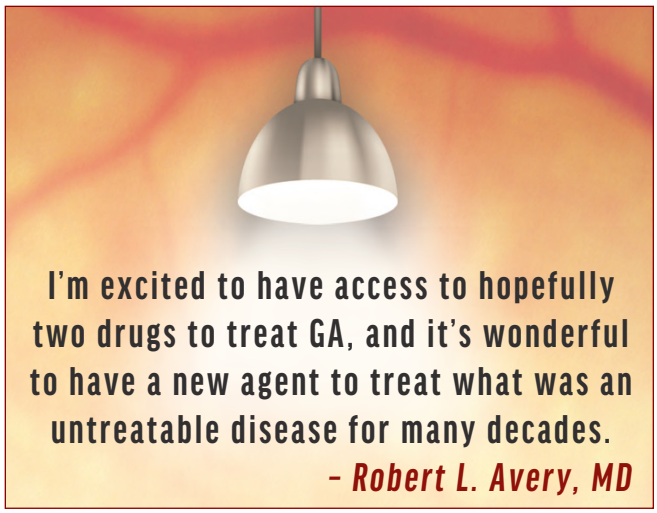
Dr. Heier: I also plan to recommend treatment for patients with foveal-sparing GA. Still, I had a patient with center-involving GA come in today who asked why I didn't think he was a good candidate. He was aware that the drug slowed the progression of the disease, and he said it was important to have as small of a central lesion as possible. The patient brings up a good point. We've certainly seen patients with bilateral disease with 20/400 lesions, but one is two disc areas and one is six disc areas, and the patient with two disc areas is noticeably better.

DR. HO: THE LABEL ALLOWS US TO TREAT EVERY 25 TO 60 DAYS. HOW ARE YOU DECIDING ON THE RIGHT TREATMENT INTERVAL?

Dr. Dhoot: With time, we'll have a better means of risk stratifying these patients, possibly with the help of artificial intelligence. But for now, I am favoring every-other-month dosing for three reasons. The first is efficacy. The difference between monthly and every-other-month dosing in the combined data set was only 3% at 24 months—a 17% reduction in lesion growth in the every-other-month group versus a 20% reduction in the monthly group.

The second is the treatment burden. The loss to follow-up was less in the every-other-month group—21% to 22% in the every-other-month versus 29% to 31% in the monthly group at 24 months. This is likely going to be greater in the real-world population, and offering a more palatable dosing scheme from the start is prudent.

The third reason is safety. The rates of key adverse events, such as choroidal neovascularization (CNV) or ischemic optic neuropathy, were lower in the every-other-month dosing groups.



That said, patients who are high risk with documented rapid GA growth that is parafoveal may opt for monthly or even every 6-week dosing. But most of my patients will likely begin with every-other-month treatment.

Dr. Lad: In the end, most of these decisions will be patient driven, and we must have thorough conversations about all these issues. We must also remember that these GA injections will add to our already large clinic volumes, and if a patient converts to wet AMD, we must decide how, and even if, we should give the two injections. Are we going to give the injections on the same day 30 minutes apart as in the trials, or should we give them on separate days depending on clinic flow and patient-physician preference? Patient preference will be a key factor in all these decisions.

There will be patients who will be very motivated to slow their disease progression, especially if they lost the other eye or if they really feel that the disease is encroaching on their central vision or impairing their peripheral vision. We will have a lot of chair time upfront to discuss these considerations and make a joint decision.

Dr. Heier: The main component that will drive my decision is safety because the efficacy is relatively close. There are clear benefits seen in the monthly over the every-other-month dosing, but the safety was also clearly better in the every-other-month group compared with the monthly group. The rate of CNV was roughly 12%, 7%, and 3% at 24 months for the monthly, every-other-month, and sham groups, respectively. The rates of ischemic optic neuropathy were clearly more prevalent in the monthly versus the every-other-month dosing groups. For most patients, the safety is going to drive that decision. Still, there are certainly some patients who will be extremely motivated to have as big an effect as possible and will want monthly dosing.

Dr. Avery: I completely agree, and in reference to safety, I have been focused on ischemic optic neuropathy; that was seen in seven patients in the monthly group, one patient in the every-other-month group, and no patients in the sham group. Only three of the eight cases were severe, and these numbers may not hold as we progress to real-world experience. Still, this risk is pushing me to recommend every-other-month dosing, given that the efficacy is not that dissimilar.

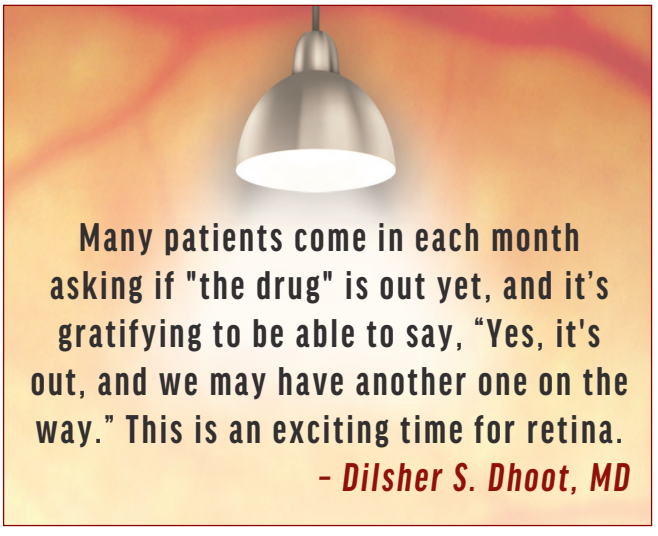
Safety is paramount, particularly because the ideal patients are often monocular. The most motivated patients have lost central vision in one eye from GA, and they are seeing well in the other eye. I want to protect the seeing eye, but minimize the risk of any sight-threatening complications.

Dr. Heier: It does appear as if those who developed ischemic optic neuropathy were largely patients with discs at risk, as well as other vasculopathic concerns. While there may be characteristics that you can look out for when treating these patients, the safety of the every-other-month dosing reduces this risk.

DR. AVERY: HOW ARE YOU GOING TO HANDLE WET AMD PATIENTS WHO ALSO HAVE GA? ARE YOU CONCERNED ABOUT BILLING TWO INJECTION CODES FOR THE SAME EYE WITHIN A 28-DAY WINDOW?

Dr. Dhoot: I'm quite concerned. There's a high chance that we will have rejected claims in the beginning, and we must be cautious. Unfortunately, many patients require treatment for both GA and CNV, and in the absence of anticipated payer issues, I would be comfortable injecting them on the same day. I would consider starting with the anti-VEGF injection because the volume is less, waiting 15 to 30 minutes between the injections, and then proceeding with the GA drug. Receiving reimbursement for two injection codes on the same day or within 28 days of one another may also be an issue. I'm hoping there will be guidance, and I'm optimistic that the billing will work itself out so that we can code and be paid for both the medications and the injection codes on the same day or within a 28-day window.

Dr. Ho: We have a data set that includes 12,000 injections, which is a large number of injections but not a large number



ARVO 2023 UPDATES

While OAKS and DERBY were not designed to evaluate visual function, Apellis released new post-hoc data at ARVO 2023 suggesting a modest visual benefit with pegcetacoplan (Syfovre) therapy: preservation of 5.6 letters at 24 months compared with sham. Results from patients' visual function questionnaire-25 showed a 4.1-point benefit in vision-related quality-of-life outcomes.[1]

Iveric Bio also presented visual function findings from post-hoc analyses of the GATHER trial data. The researchers found that the reduced rate of vision loss in patients receiving therapy correlated with reduced geographic atrophy (GA) growth—linking disease progression and worsening visual acuity. The company previously announced data suggesting a 56% risk reduction in the rate of persistent vision loss in patients with GA who were treated with 2 mg avacincaptad pegol compared with sham at 12 months.[2]

1. Apellis presents phase 3 functional analyses of SYFOVRE (pegcetacoplan injection) for geographic atrophy [press release]. Apellis Pharmaceuticals. April 23, 2023. Accessed April 26, 2023. bit.ly/3APgMcR
2. Iveric Bio announces new functional vision loss reduction data from avacincaptad pegol GATHER trials presented at ARVO annual meeting [press release]. Iveric Bio. April 23, 2023. Accessed April 26, 2023. bit.ly/3HtcuMg

of patients. It will be important for our community to be vigilant in monitoring for the safety issues that we may see when new products are introduced to the market.

We have not seen ischemic optic neuropathy with our anti-VEGF agents, which gave me pause, especially considering that these might be the vulnerable patients with only one good eye. We must monitor patients for safety issues and report our findings to organizations that provide systematic reporting, such as the American Society of Retina Specialists Research and Safety in Therapeutics Committee. We owe that to our patients.

But just like with anti-VEGF agents, which started with version 1.0, then moved to 2.0, and is now maybe at 3.0 with combination therapy, GA therapy will evolve. I'm happy that this is approved, and I hope that others will be as well. This allows the ecosystem to continue to invest in new treatments for this condition.

Dr. Avery: We've had major failures with prior agents, and I've been promising something to my patients for quite a long time. It's great to finally have something in the clinic that can help them. In the days of photodynamic therapy (PDT), we were just delaying the visual loss for patients with wet AMD. Innovation doesn't usually happen all at once, and PDT was just a steppingstone until we eventually discovered the anti-VEGF agents, which we have continued to improve over time. I believe that we'll make progress from this steppingstone for GA as well.

Dr. Dhoot: There's been some criticism regarding the vision benefit of this drug. In the trials, most patients had large foveal-involving lesions, approximately 8 mm in diameter on average. If we look at subsets of patients, I expect that it's easier to show vision benefit in smaller nonfoveal lesions. In these trials, they did show some vision benefit in terms of microperimetry data with a reduced number of scotomatous points in the 18- to 24-month period in the junctional zone of lesions. A second analysis presented at ARVO reports on vision benefit in patients with extrafoveal lesions (see *ARVO 2023 Updates*). I suspect over time we may see more benefit, but the size and location of the lesions may have blunted the vision benefit in the overall population in these trials.

Dr. Lad: In addition, it is difficult to measure visual function in these elderly individuals; these are very noisy tests, microperimetry and BCVA included. These studies were not designed to evaluate function as a primary endpoint. To do that, Usha Chakravarthy, MD, PhD, CBE, and others have shown that you need to have a large dataset that includes small subfoveal lesions so that you have some area next to the fovea that you can monitor for treatment effect. This study was too short to pick up a functional change, although we might see it in the GALE extension study.

Still, we have a mixed population with more than 60% with large lesions—not the small lesions you need to measure function—and the rest are extrafoveal at different distances from the fovea. This type of study would require a different design where functional outcomes are primary.

DR. AVERY: WHAT ARE YOUR THOUGHTS ON IVERIC BIO'S DRUG, AVACINCAPTAD PEGOL, AND ITS STUDY THAT REPORTS LESS VISUAL LOSS OF THREE LINES OR GREATER WITH TREATMENT?

Dr. Heier: It's encouraging to see potential functional benefits from these agents. They are different studies, and it's hard to make cross study comparisons, although the Apellis study does have more than 400 patients that are nonfoveal as well. It's important to look at the safety and efficacy of each agent. All these opportunities to help discern which patients may benefit the most from these treatments will be important. Both Apellis and Iveric Bio are working to understand those outcomes and figure out how to use these agents best.

Dr. Ho: It's an incredibly important time for us and our patients. In addition to Iveric Bio, there are oral medications and gene and cell therapies under investigation for GA. We have a lot of shots on goal, but we need to start looking earlier in the course of dry AMD. ■

Editor's note: This manuscript has been edited from the original transcipt for clarity and space purposes.

(Continued on page 44)

A LOOK AT NOVEL GEOGRAPHIC ATROPHY BIOMARKERS

Multimodal imaging is now the standard for diagnosing dry AMD–here's what you need to know.

BY FARHAN E. HIYA, MD; ABRAHIM AHMED, BS; AND DAVID A. EICHENBAUM, MD



AMD is a multifactorial disease that involves an ill-defined interaction between aging, genetics, and environmental factors that are associated with oxidative stress, inflammation, and impaired extracellular matrix functioning within the retina, predominantly at the macula. AMD classification—traditionally tied to the presence and size of drusen and the presence of pigmentary changes or other signs of atrophy—provides prognostic estimates of disease progression. Unlike early AMD, intermediate AMD (iAMD) has a higher progression rate to late AMD, defined as either the development of geographic atrophy (GA) or subfoveal macular neovascularization (MNV).[1] One study found that the 5-year risk of progression to advanced AMD was 0.4% for eyes without large drusen or pigmentary abnormalities and 47% for eyes with bilateral large drusen and pigmentary abnormalities.[2]

GA now has a treatment option with the approval of pegcetacoplan (Syfovre, Apellis Pharmaceuticals). Significant research is underway to better understand the potential treatment paradigm for patients with iAMD, especially selecting those with high-risk imaging features for progression to late AMD.[3] As such, clinicians must be able to identify patients with iAMD who are at a high risk for progression.

A NEW STANDARD FOR AMD IMAGING

While ophthalmoscopy and color fundus photography (CFP) have been the standard for the examination and staging in AMD, the adoption of other imaging modalities—such as fundus autofluorescence (FAF), near-infrared imaging (NIR), and OCT—led the Classification of Atrophy Meeting (CAM) group to update the definition of the stages of AMD and progression. Now, multimodal imaging should be routine for proper diagnosis and prognostication of AMD.

OCT was particularly highlighted for its ability to[4]:

- provide greater accuracy in the evaluation of the retina in a volumetric fashion, given the high axial resolution;
- allow clinicians to independently evaluate each retinal layer and detect early signs of pathology;
- produce an en face image, which can be used to demarcate the borders of atrophy and directly correlate with other imaging modalities;
- calculate related enlargement rates over time; and
- provide as many scans as needed in a single visit.

Drusen and Hyper-Reflective Foci

Various OCT imaging studies have assessed the classical risk factors of AMD progression rates, such as drusen burden and pigmentary changes (visualized on OCT as hyper-reflective foci [HRF]). They found an increased risk of progression with increased baseline drusen area and volume measurements, as well as the presence of HRF.[2,5,6]

Abdelfattah et al found that eyes with a drusen volume of at least 0.03 mm^3 had a four-fold increased risk of developing MNV or GA within 2 years, while Christenbury et al found a five-fold increased risk of developing GA within 2 years in eyes with HRF compared with eyes without baseline HRF.[7,8]

Reticular Pseudodrusen and Calcified Drusen

Reticular pseudodrusen (RPD), also known as subretinal drusenoid deposits, are commonly found in the superior

AT A GLANCE

- The adoption of multimodal imaging led to an updated definition of AMD stages and progression.
- The new nomenclature to classify AMD-related atrophy on OCT includes incomplete retinal pigment epithelium (RPE) and outer retinal atrophy and complete RPE and outer retinal atrophy.
- Visual function is decreasing before foveal involvement is diagnosed, and there is a large variation in visual acuity.

regions of the macula and represent an increased risk of AMD progression.[9-12] Chan et al found that the prevalence of RPD (best imaged with NIR imaging) varied with AMD staging, with the highest prevalence in eyes with iAMD (62.6%).[11] Furthermore, Zweifel et al showed that the presence of RPD was associated with a nearly three-fold increased risk of progression to late AMD.[12]

Calcified drusen (CaD) are prevalent in iAMD and are of high prognostic value for the development of late AMD.[13-16] Tan et al found that heterogeneous internal reflectivity within drusen (caused by multilobular nodules of crystalline calcium phosphate) was present in 45% of eyes with iAMD and was associated with the development of late AMD within 1 year (odds ratio: 6.36).[16] Liu et al found that 42.7% of eyes with iAMD had CaD, and the majority of CaD develop into areas of GA, regardless of the exact B-scan appearance.[13] Thus, CaD should be accounted for in AMD risk assessment.

Defining Atrophy on OCT

Because GA was originally defined on CFP, the CAM group developed new nomenclature to classify AMD-related atrophy on OCT: incomplete retinal pigment epithelium (RPE) and outer retinal atrophy (iRORA) and complete RPE and outer retinal atrophy (cRORA, Figure 1). cRORA corresponds to an area of at least 250 µm on a single horizontal B-scan showing the following:

1. attenuation or complete loss of the RPE, alongside
2. a corresponding hyper-transmission defect (hyperTD) through the area of RPE change, and
3. signs of photoreceptor degeneration, such as subsidence of the inner nuclear layer (INL) or the outer plexiform layer; thinning of the outer nuclear layer; presence of a hyporeflective wedge in the Henle fiber layer; or disruption of the external limiting membrane (ELM) or ellipsoid zone (EZ), all in the absence of an RPE tear.

iRORA refers to a horizontal B-scan area that has some, but not all, of the features of cRORA (Figures 2 and 3).[4,17]

Researchers are working to determine the utility of identifying iRORA lesions and assessing their risk of progression to cRORA on OCT and/or GA on CFP.

Although there is some variability in stratifying the risk of progression, iRORA features imply an enhanced risk of progression to cRORA. For example, Corradetti et al found that approximately 93% of iRORA lesions converted to cRORA within 24 months, while Wu et al found that iRORA lesions convert to GA on CFP at a rate of about 3% by 24 months and 10% by 30 months.[18,19]

Another OCT precursor to GA is nascent GA (nGA), which is defined as having a hyporeflective wedge in the Henle fiber layer and/or subsidence of the INL and outer plexiform layer with or without RPE or hyperTDs; Wu et al found that nGA had a much higher conversion rate to GA on CFP than iRORA within 24 months (38% vs 3%).[19,20]

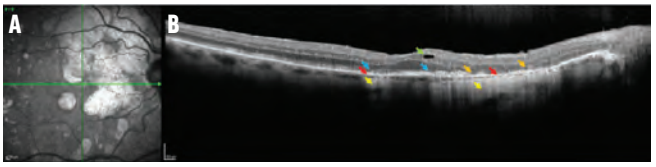


Figure 1. NIR imaging (A) and an OCT B-scan of a cRORA lesion (B) show disruption of the ELM and EZ (blue arrows) and regions of RPE attenuation (red arrows) with associated hyperTDs into the choroid (yellow arrows). There are areas of photoreceptor degeneration (orange arrows) and an incidental degenerative cyst (green arrow).

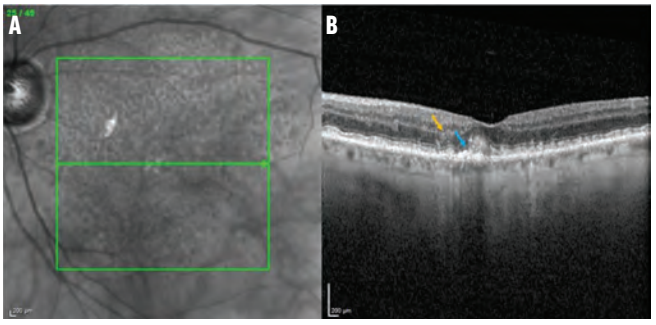


Figure 2. NIR imaging (A) and an OCT B-scan of an iRORA lesion (B) show disruption of the ELM and EZ (blue arrow) and subsidence of the INL (orange arrow).

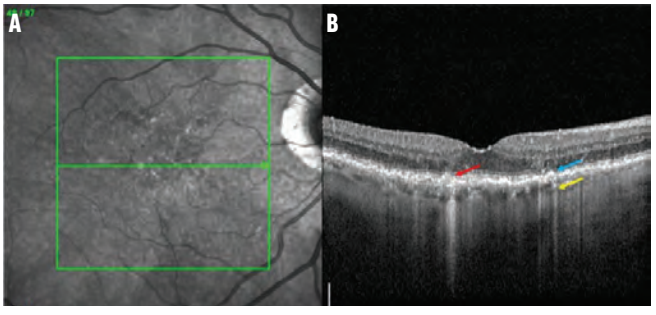


Figure 3. NIR imaging (A) and an OCT B-scan of an iRORA lesion (B) show disruption of the ELM and EZ (blue arrow) and focal attenuation of the RPE (red arrow) with associated hyperTDs into the choroid (yellow arrow).

Atrophy can be seen much earlier on OCT than on CFP, and nGA has more specific criteria than iRORA. Therefore, these findings show that iRORA will convert to cRORA (ie, true irreversible retinal atrophy) in a relatively short time but may remain undetected on CFP until much later.

In addition, iRORA may signify that irreversible functional damage has already occurred (ie, iRORA and related visual changes may be clinically similar to cRORA and related visual changes). Trivizki et al showed that many cRORA lesions are miscategorized as iRORA because the iRORA diagnostic criteria fail to incorporate all dimensions of atrophic lesions; the atrophic area would meet cRORA criteria if vertical and diagonal B-scans were evaluated with the horizontal B-scans.[21]

En Face HyperTD

As an alternative to OCT-mediated iRORA/cRORA, hyperTDs into the choroidal layer—seen as bright areas on en face OCT images positioned in the sub-RPE segmentation

with borders from 64 µm to 400 µm under Bruch membrane—provide a reliable, reproducible, and independent feature and risk factor for GA.[22-24] Compared with iRORA/cRORA grading criteria, the grading of hyperTDs via en face images allows for: a lesion's greatest linear dimension (GLD) to be measured in any vector (not only horizontally); direct visual comparison with other AMD imaging modalities, such as CFP, NIR, and FAF; and a rapid assessment of the entire scan region. Studies show that hyperTDs with a GLD of at least 250 µm will likely persist for at least 3 years, correlate strongly with nGA (79%), and signify an 80-fold risk of the formation of cRORA within 3 years. While hyperTDs of smaller sizes were found to be transient and not as highly correlated to developing atrophy, they may still signify areas of at-risk RPE, as the areas may qualify as iRORA.[23,24]

RISK ASSESSMENT AFTER GA

Once iRORA/cRORA, nGA, or hyperTDs form in an eye, more lesions are likely to develop in the same eye and the fellow eye. Additionally, once GA develops on OCT and/or CFP, certain characteristics (ie, larger lesions, multifocality, and an extrafoveal location) are associated with increased growth rates.[25-30] Notably, although sub-foveal GA lesions can correlate with large drops in visual acuity, visual function is decreasing before foveal involvement is diagnosed, and there is a large variation in visual acuity even when imaging suggests highly affected visual acuity. Therefore, visual acuity is not a reliable tracker of disease severity.[30,31]

Finally, as the CAM group recommended, multimodal imaging such as FAF can provide additional risk-assessment information. While GA corresponds to hypoautofluorescence, GA growth rates differ depending on the extent and pattern of hyperautofluorescence. Absence of hyperautofluoresence or focal patterns of hyperautofluorescence relate to slow GA growth rates (0.38 to 0.81 mm^2/year), diffuse and banded patterns have greater than double the growth rates (1.77 to 1.81 mm^2/year), and the "diffuse-trickling" subtype pattern has the highest growth rate (3.02 mm^2/year).[32] Additionally, the extent of hyperautofluorescence surrounding GA lesions, representing at-risk RPE, positively correlates with GA growth rates on a per lesion basis.[33]

Our understanding of the presence and characteristics of drusen, CaD, HRF, RPD, iRORA/cRORA, nGA, and hyperTDs and the risks associated with these imaging findings are clinically relevant in determining which patients will benefit the most from early treatment. ■

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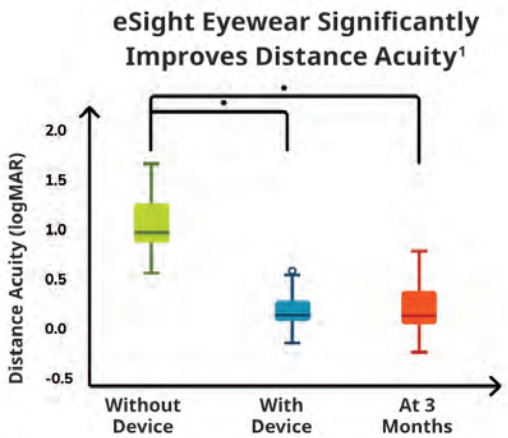

Figure 1. Distance acuity equivalent of print size correctly read on the ETDRS chart at baseline without the device, at fitting with the device, and after 3 months of device use. Mean baseline acuity without device was 20/177 (mean logMAR, 0.95 [SD, 0.25]), which improved to 20/32 (mean, 0.20 [SD, 0.31]) with the device but stayed unchanged after 3 months of device use and training (mean, 0.19 [SD, 0.30]). *Statistically significant differences. ETDRS = Early Treatment Diabetic Retinopathy Study.

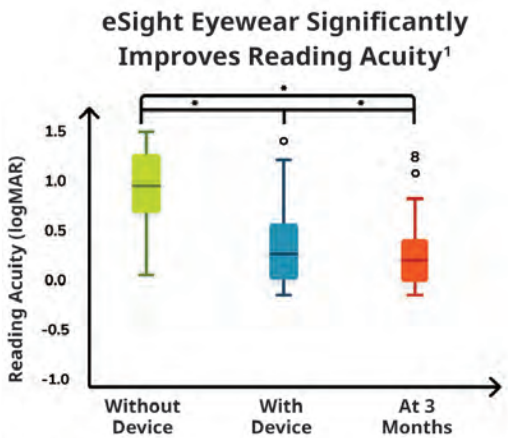

Figure 2. Reading acuity equivalent of print size read on the MNREAD chart at baseline without the device, at fitting with the device, and after 3 months of device use. Mean baseline reading acuity without device was 20/159 (mean logMAR, 0.90 [SD, 0.34]), which improved to 20/43 (mean, 0.33 [SD, 0.39]) with the device but stayed unchanged after 3 months of device use and training (mean, 0.24 [SD, 0.36]). *Statistically significant

Device training is fully supported by the patient program **eSight TeleHealth**.[2,3]

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THE COMPLEMENT SYSTEM: A NEW THERAPEUTIC TARGET

A deeper understanding of the innate immune system is opening new avenues for the treatment of geographic atrophy.

BY AUMER SHUGHOURY, MD, AND THOMAS A. CIULLA, MD, MBA


The complement system is strongly implicated in the development and progression of geographic atrophy (GA) and has emerged as an attractive therapeutic target. In February, pegcetacoplan intravitreal injection (Syfovre, Apellis Pharmaceuticals), a complement inhibitor, gained FDA approval for the treatment of GA secondary to AMD, marking a significant milestone in the progress of therapeutics for AMD. This article reviews our understanding of the complement system, its role in GA, and current investigational therapies that target this system.

THE COMPLEMENT SYSTEM AND GA

The complement system serves as the first line of defense against invading pathogens by inducing cell lysis and enhancing the activity of the antibody-driven adaptive immune system (Figure 1). The three complement pathways (classical, alternative, and lectin) converge upon a shared terminal series of reactions that lead to the formation of the membrane attack complex (MAC) on target cell surfaces.[1] MAC causes cell lysis, the major endpoint of the complement system. Byproducts of this enzyme cascade recruit leukocytes and tag pathogens for phagocytic destruction, while MAC itself can induce several localized inflammatory reactions.[1] The potency of the complement system requires tight regulation to prevent local host tissue damage.

Chronic, low-grade inflammation is a primary driver of AMD and GA pathogenesis, and overactivity of the complement system has been specifically implicated.[2,3] For example, several complement-related gene mutations are strongly associated with increased AMD risk, likely due to complement dysregulation within the retina.[4] Accordingly, high concentrations of complement byproducts have been found in the plasma of patients with AMD, as well as within the retinal pigment epithelium (RPE) and photoreceptor outer segments in areas of GA.[5] Complement byproducts have also been found in high concentrations within drusen,[3] raising the possibility that drusen may represent biomarkers of a localized, complement-mediated inflammatory process driving GA pathogenesis at the RPE-Bruch membrane junction.[6]

Therefore, the complement system is an attractive target for GA therapy (Figure 2) with the most promising strategy involving the inhibition of C3 and C5 activation.[7,8]

THERAPEUTIC TARGETS

Common Pathway Target: C3

Pegcetacoplan is a C3 inhibitor that binds and prevents activation of C3 by C3 convertase, blocking activation of downstream effectors and halting the cascade's progression.

The phase 3 OAKS and DERBY trials enrolled patients with BCVA ≥ 24 ETDRS letters (approximately 20/320 Snellen equivalent) and total GA area between 2.5 mm^2 and 17.5 mm^2.[9] In the OAKS trial, both monthly and every-other-month treatment arms showed statistically significant reductions in GA growth (22% and 18%, respectively) at 24 months when compared with sham.[10] DERBY data followed a similar trend with reductions in GA growth of 19% and 16%, respectively.[10] A phase 3 extension study evaluating the long-term safety of pegcetacoplan for up to 36 months is underway.[11]

Another C3 inhibitor, NGM621 (NGM Biopharmaceuticals),

AT A GLANCE

- Chronic, low-grade inflammation is thought to be a primary driver of AMD and geographic atrophy (GA) pathogenesis, and overactivity of the complement system has been specifically implicated.
- The most promising interventions for GA currently involve inhibiting the activation of C3 and C5.
- There is some concern for increased risk of exudative transformation with complement inhibition for GA.

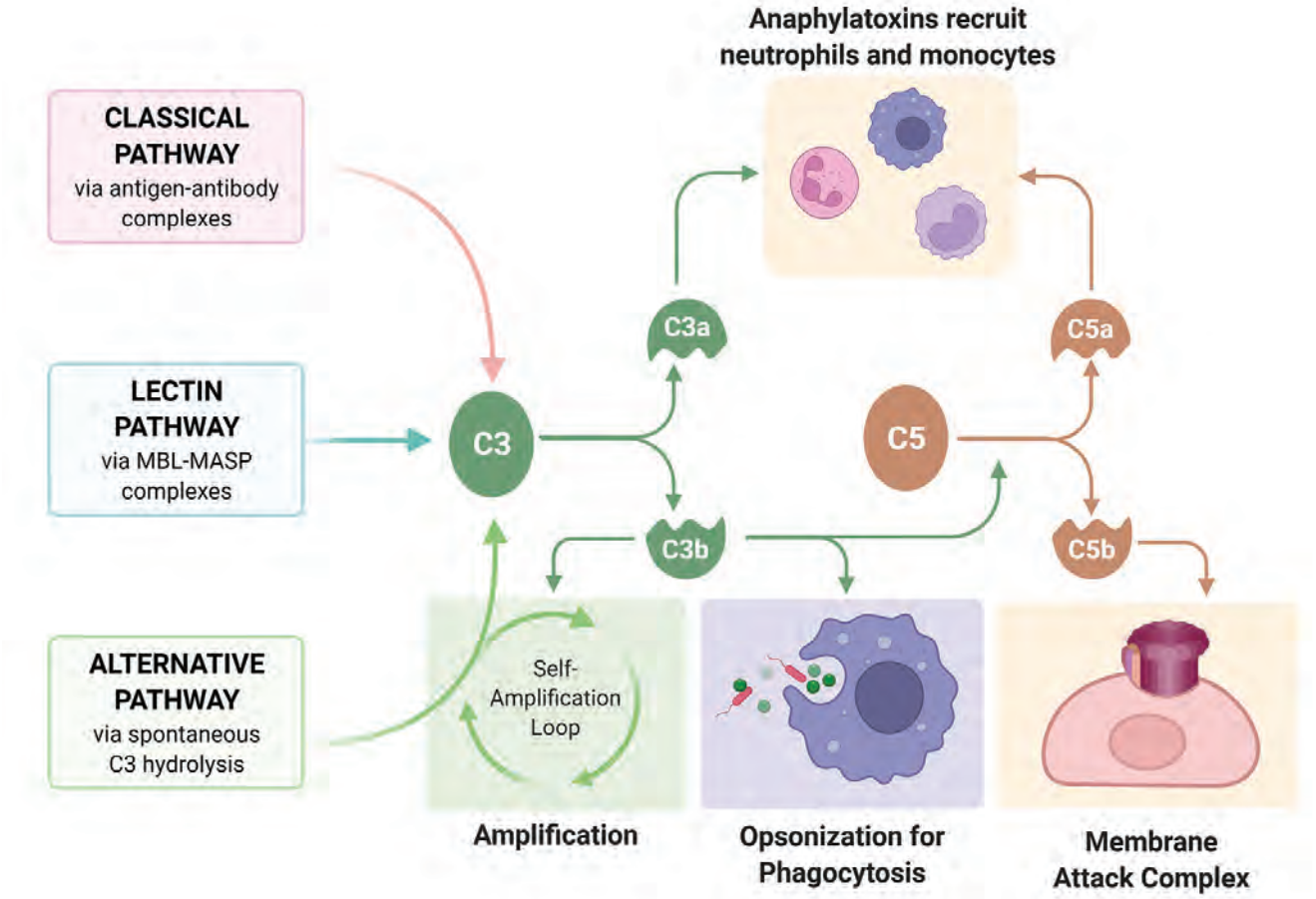

Figure 1. The complement system consists of three distinct pathways. The classical pathway is triggered by IgG or IgM antibody-antigen complexes. The alternative pathway is continuously activated through slow, spontaneous hydrolysis of C3, requiring constant inhibition by endogenous regulatory proteins that pathogens do not possess. The lectin pathway is triggered by recognition of specific carbohydrates on microbial surfaces. Image reproduced from Kislev S. Complement Overview. Wikimedia Commons. 2022. bit.ly/40nW7HI.

is a monoclonal antibody that was recently evaluated in the phase 2 CATALINA trial.[12] Although the study failed to reach its primary endpoint,[12] a post-hoc analysis suggests a statistically significant reduction in GA growth rate (21.9% and 16.8% with every 4- and 8-week injections, respectively) among a subgroup of eyes exhibiting a narrower range of baseline GA area than the trial inclusion criteria.[13]

Other C3 inhibitors in development include CB 2782-PEG (Catalyst Biosciences) and KNP-301 (Kanaph Therapeutics), both of which are currently in preclinical testing.[14,15]

Terminal Pathway Targets: C5 and MAC

C5 is another attractive therapeutic target due to its key role in initiating the formation of MAC.[8] The C5 inhibitor avacincaptad pegol (Zimura, Iveric Bio) is a pegylated RNA aptamer that binds and prevents activation of C5. The phase 2/3 GATHER1 trial found a statistically significant decrease in mean rate of GA area growth with monthly injections of 2 mg and 4 mg avacincaptad pegol at 12 months compared with sham (27.4% and 27.8% reduction in rate of square root of GA area growth, respectively).[16] The ongoing GATHER2 trial is evaluating monthly injections of 2 mg avacincaptad pegol for 12 months, followed by monthly or every-other-month injections for 23 months. The trial met its primary endpoint, demonstrating a statistically significant 14.3% reduction in mean rate of GA area growth (square root transformed) with monthly treatment compared with sham.[17] The FDA has accepted the company's new drug application, granting priority review status with a Prescription Drug User Fee Act goal date in August.[18]

MAC inhibition is also a therapeutic strategy for GA. HMR59 (Hemera Biosciences) is a gene therapy that induces expression of the endogenous MAC-inhibitory protein CD59; the safety of its intravitreal administration in GA is the subject of an ongoing phase 1 trial.[19]

Alternative Pathway Targets

The alternative pathway accounts for more than 80% of terminal pathway activation and ultimate MAC formation, making it a prime therapeutic target.[20] The pathway is constitutively activated by spontaneous hydrolysis of C3 into soluble C3a and C3b fragments, which then participate

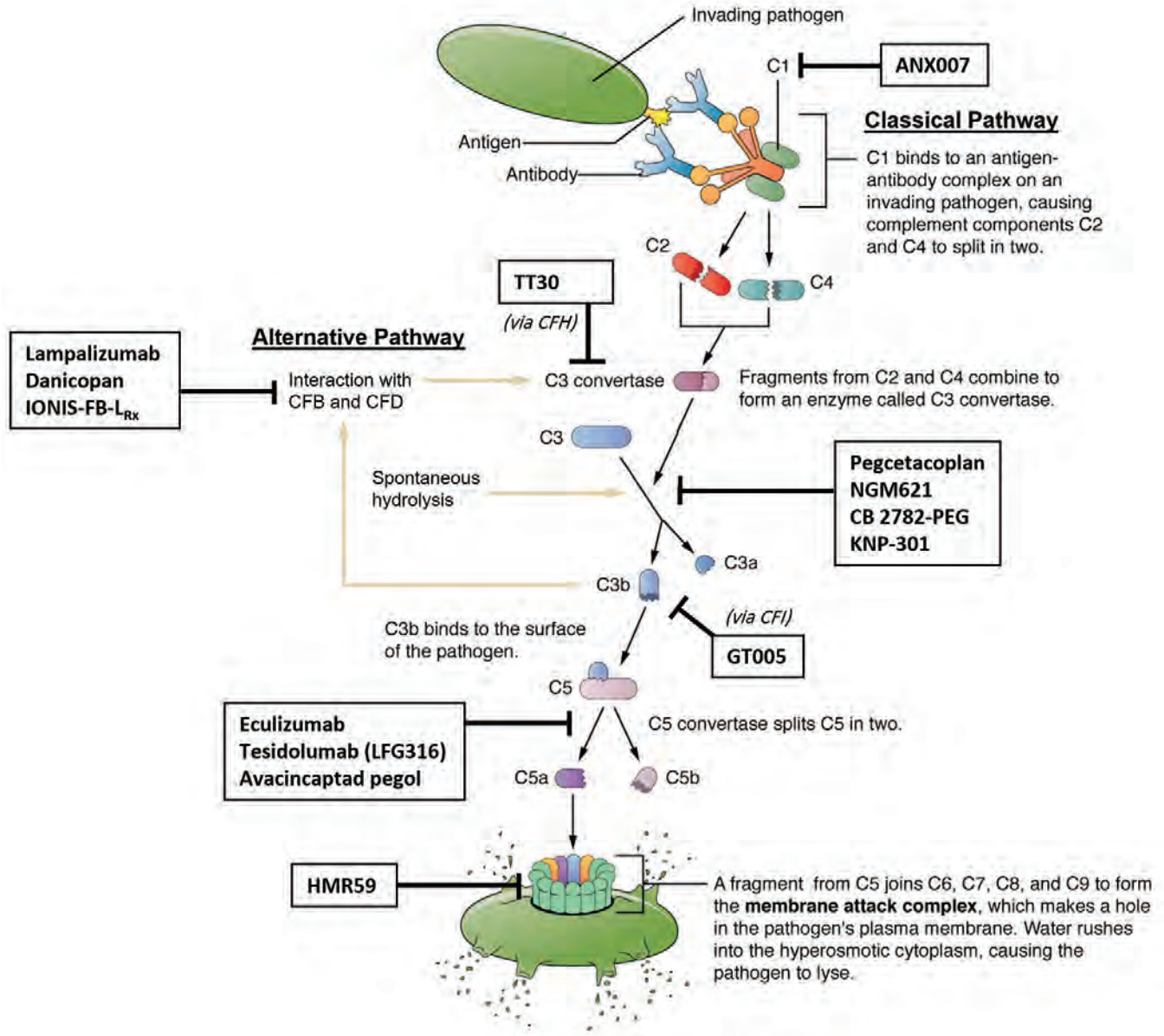

Figure 2. Investigational therapies for GA have largely focused on interfering with C5 and C3 activity. Other therapies have targeted MAC formation and specific components of the alternative and classical pathways. The lectin pathway has not been strongly implicated in AMD and does not currently represent a major therapeutic target. Image adapted from Betts JG, et al. Barrier defenses and the innate immune response. In: Anatomy and Physiology. OpenStax College. 2022. bit.ly/40rvcum.

in a positive feedback amplification loop by creating C3 convertase. The activity of this amplification loop is tightly regulated by several complement factors (CF), including CFH, CFI, CFD, and CFB. Selectively targeting these complement factors in the alternative pathway is theoretically advantageous due to the preservation of host defense via intact classical and lectin pathways.

CFH plays the most prominent role in downregulating alternative pathway activity, degrading C3b and inactivating C3 convertase. CFH deficiency has been strongly implicated in the development of GA, and genetic mutations reducing CFH expression represent the strongest genetic risk factors for AMD, increasing the risk by up to seven-fold.[21,22]

CFI, an important cofactor of CFH in the degradation of C3b, has been targeted with GT005 (Gyroscope Therapeutics/Novartis), a gene therapy designed to induce local overexpression of CFI following subretinal or suprachoroidal administration.[23] Interim data from the phase 1/2 FOCUS trial suggests that GT005 is well tolerated in GA, while two phase 2 trials are ongoing: HORIZON and EXPLORE.[24-26] An additional, observational, long-term follow-up cohort trial, ORACLE, is also in progress.[27]

The alternative pathway amplification loop may also be targeted directly by inhibiting CFB and CFD. A CFD inhibitor,

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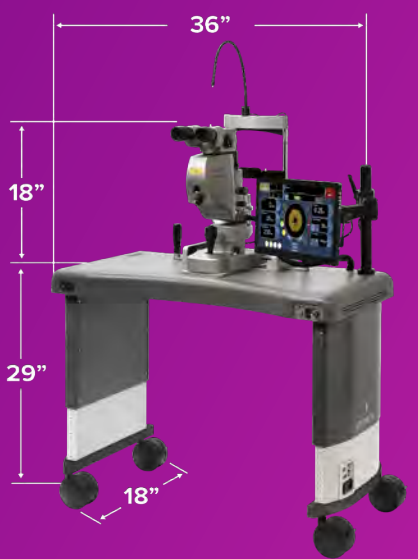

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ACH-4471 (Danicopan, Alexion Pharmaceuticals), is being studied as an oral therapy for GA in a phase 2 trial.[28] CFB is being targeted by subcutaneous administration of IONIS-FB-LRx (Ionis Pharmaceuticals), an antisense oligonucleotide that reduces CFB protein expression by degrading CFB messenger RNA[29]; the phase 2 GOLDEN trial is active.[30]

Classical Pathway Target: C1

The classical pathway has also been a therapeutic target of some interest. This pathway is initiated by antibody-antigen complexes binding and activating the C1 complex. ANX007 (Annexon) is an intravitreally-injected antigen-binding fragment designed to inhibit C1q, the functional component of C1.[31] The phase 2 ARCHER trial is assessing the safety of ANX007 in GA, with topline data expected this year.[32]

SAFETY CONSIDERATIONS

Complement inhibition for GA has generally been well tolerated in clinical trials. However, there is some concern for increased risk of exudative transformation with anti-complement therapy. In the combined phase 3 pegcetacoplan trial data, new-onset exudation was noted in 11.9% of the monthly groups, 6.7% in the every-other-month groups, and 3.1% in the sham groups at 24 months.[10] Patients at greatest risk were those with exudative AMD in the contralateral eye and those exhibiting the OCT double-layer sign—a potential marker of subclinical type 1 macular neovascularization.[33,34] The GATHER1 and GATHER2 trials also demonstrated a slightly increased risk of exudative transformation with avacincaptad pegol therapy.[16,17] The mechanism by which complement inhibition may increase the risk of exudation and neovascular disease remains uncertain, and further research is ongoing. Additional theoretical concerns have been raised regarding endophthalmitis risk with intravitreal injection of immunosuppressive complement inhibitors. However, endophthalmitis rates in the pegcetacoplan and avacincaptad pegol trials have reassuringly been similar to or lower than those reported with other intravitreal therapies.[10]

FUTURE PERSPECTIVES

Our approach to AMD is rapidly evolving with a growing array of promising treatment options. The development of sustained release technologies and novel drug delivery methods will hopefully increase the durability and lessen the burden on our patients. With ongoing research and innovation, we are confident that new treatments for AMD will continue to advance, helping preserve vision and improve the quality of life of countless individuals around the world. ■

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WHERE IT ALL BEGAN

Katherine E. Talcott, MD, was raised in Cleveland, Ohio, the middle of three girls, and attended Catholic school through high school. She studied history of science as an undergraduate at Harvard College and wrote her thesis on bloodletting.

During medical school at the University of California, San Francisco (UCSF), she was drawn to the care of underserved populations. She pursued her residency at Massachusetts Eye and Ear (MEE) and spent an extra year after residency doing a chief residency before completing her surgical retin fellowship at Wills Eye Hospital/Mid Atlantic Retina. After completing fellowship, she moved back to Cleveland with her husband and 3-year-old twins to start practice at the Cole Eye Institute at the Cleveland Clinic.

Dr. Talcott's Advice:
Pick a job that offers as much of what you are looking for as possible, and then show up interested and ready to work. It's surprising what opportunities arise that allow you to craft a career that gets you all the things you were looking for.

HER PATH TO RETINA

Dr. Talcott is myopic, and she saw a retina specialist as a teenager for concerns for a retinal tear. Thus, she thought it would be good to learn more about the retina and, as an undergraduate, worked at the Cole Eye Institute in the basic science lab of pediatric retinal specialist Jonathan Sears, MD. She found the retina to be fascinating. During medical school, she was exposed to the clinical side of ophthalmology and loved the mix of medicine and surgery. During her research year with Jacque L. Duncan, MD, at UCSF, she analyzed adaptive optic images in patients with retinitis pigmentosa, which furthered her interest in retina. During residency, she loved the excitement of retina, with new technologies and therapeutics always being developed.

SUPPORT ALONG THE WAY

Dr. Talcott has been fortunate to have great mentors, including Dr. Duncan; Joan W. Miller, MD; Dean Eliott, MD; Carl D. Regillo, MD; Allen C. Ho, MD; and Julia A. Haller, MD. They have been sounding boards for career decisions and have offered their advice on how to reach various career goals.

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AN EXPERIENCE TO REMEMBER

Working with trainees turned out to be the most memorable experience for Dr. Talcott so far. Whether it's watching a surgical fellow master a technique or push through a difficult case for the first time, meeting a resident who has decided to go into retina, or working on research with medical students, it's a privilege to be able to watch them grow and develop their interests. ■

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THE EFFECT OF BIOSIMILARS ON CLINICAL PRACTICE

A look at the true cost of the new drugs that are shaking up our therapeutic approaches.

BY MARGARET M. RUNNER, MD, AND GEORGE A. WILLIAMS, MD


There are two categories of prescription drugs: small molecules and biologics. Small molecules (conventional drugs) are simple and chemically synthesized; biologics are large, complex molecules manufactured via living organisms. The price of biologics is significantly higher than conventional drugs, and in 2021, biologics accounted for 46% of net drug spending, despite being only 3% of all prescription drugs by volume.[1,2]

In ophthalmology, biologics such as anti-VEGF agents account for the second largest Medicare Part B drug expenditure.[3] Aflibercept (Eylea, Regeneron) and ranibizumab (Lucentis, Genentch/Roche) continue to be ranked the 2nd and 6th highest drug cost, respectively–accounting for 12% of all Medicare Part B spending within the last 5 years.[3]

In this article, we discuss the introduction of biosimilars into our ecosystem to address this growing cost, and what it might mean for our day-to-day practice.

CUTTING COSTS

To curtail the rising cost of biologics, the FDA promotes the development of biosimilars via an abbreviated approval pathway. Biosimilars are highly analytically similar to or interchangeable with an FDA-approved biologic, a *reference product*. The FDA has approved 40 biosimilars, 22 of which are available to patients.[4] Biosimilar competition is driving prices down for both biosimilars and reference products, contributing to an estimated $7 billion in savings in 2021.[1]

The Centers for Medicare and Medicaid Services will incorporate approved biosimilars into the Average Sales Price (ASP) payment methodology. When a biosimilar is first introduced, Medicare's payment will be based on the Wholesale Acquisition Cost (WAC) listed by the manufacturer plus 3% while the ASP is being established. After two quarters, Medicare reimbursement is based on the ASP, which will factor in rebates and discounts reported by the drug manufacturer. Furthermore, under the Inflation Reduction Act, Medicare will pay the ASP plus 8% of the reference product's ASP, rather than the traditional 6%, for certain biosimilar products for a 5-year period.[6]

A review of biosimilars introduced over the past 5 years shows a trend for biosimilars to use a *high WAC, high rebate* strategy. A biosimilar manufacturer often lists the initial WAC at an approximate 30% reduction of the reference product's retail price, although that strategy is variable. Increased use of biosimilars, along with the high rebates and discounts, quickly drives the ASP and Medicare allowable down each quarter. Within 5 years of increasing market share, a biosimilar's ASP will have dropped by more than 50% of its initial WAC listed price and the reference product's ASP at the time the biosimilar was launched.[1] This reimbursement model incentivizes early use of biosimilars, and the net effect leads to a reduction in overall health care spending.

WHAT THIS MEANS FOR RETINA

In ophthalmology, there are two approved biosimilars: ranibizumab-nuna (Byooviz, Samsung Bioepis/Biogen) and ranibizumab-eqrn (Cimerli, Coherus). A review of the Medicare allowable for anti-VEGF injections over the last decade shows a steady decline in the price of anti-VEGF agents as the exclusivity end date of the drug nears.[6] If

AT A GLANCE

- The introduction of biosimilars may lower overall health care spending on biologics.
- Michigan insurers announced that new patient approval for aflibercept (Eylea, Regeneron) will first require a failure to both off-label bevacizumab (Avastin, Genentech/Roche) and ranibizumab-nuna (Byooviz, Samsung Bioepis/Biogen).
- Bevacizumab-vikg (Outlook Therapeutics), if approved, may not affect access to off-label bevacizumab.

ophthalmology follows the oncology market trends, the incorporation of biosimilars into practice could trigger a rapid decline in ASP for the biosimilar and reference drug.

Insurance companies, particularly Medicare Advantage plans, may accelerate the early use of biosimilars via step therapy requirements. Given that in 2023, a single beneficiary has an average of 43 available Medicare Advantage plans, incorporation of biosimilars into variable and constantly changing step therapy protocols will only add to the administrative burden for practices.[7]

Recently, Blue Cross Blue Shield of Michigan and Blue Care Network announced that new patient approval for aflibercept will first require a failure to both off-label bevacizumab and ranibizumab-nuna.[8] Interestingly, branded ranibizumab and faricimab-svoa (Vabysmo, Genentech/Roche) do not require ranibizumab-nuna failure per these insurers' updated guidelines.[9,10] Per a discussion with Regeneron representation, there are plans to counter the recent incorporation of biosimilars in step therapy for aflibercept in Michigan, but these changes confirm that the use of biosimilars in step therapy should be anticipated.

FINANCIAL RAMIFICATIONS

Unlike in oncology, the potential cost savings of biosimilars in ophthalmology is thought to be limited, as a less expensive alternative to branded anti-VEGF drugs already exists in off-label use of repackaged bevacizumab (Avastin, Genentech/Roche). The widespread use of repackaged bevacizumab has saved billions of dollars compared with brand-name drugs since 2006.[11] There is growing concern that the anticipated FDA approval of bevacizumab-vikg (Lytenava, Outlook Therapeutics) will threaten access to repackaged bevacizumab.[12] The Drug Quality Security Act regulates that 503B outsourcing facilities cannot compound a drug that is "essentially a copy of an approved drug."[13] The definition of "essentially a copy" has never been articulated, nor has it been argued in court to establish precedent. However, if bevacizumab-vikg obtains FDA approval, it will be designated as a new molecular entity, further labeling it as containing new active moieties that the FDA has not previously approved. Unlike simple molecule drugs, the complexity of biologics creates inherent variability, making it impossible to create an identical biologic. This suggests that, if bevacizumab-vikg is approved, it may not affect access to repackaged bevacizumab by compounding pharmacies, although this may be contested and further settled in court.

THE BOTTOM LINE

The introduction of ophthalmic biosimilars may lower overall health care spending with time and increasing market share. Insurers may force early use by incorporating biosimilars into step therapy protocols. With longer-acting anti-VEGF drugs on the horizon, there is growing concern that biosimilar step therapy may hinder advance treatment options for patients. Furthermore, bevacizumab biosimilars have the potential to threaten the availability of off-label bevacizumab. Although biosimilars will be an increasingly important aspect of anti-VEGF therapy, many questions remain. ■

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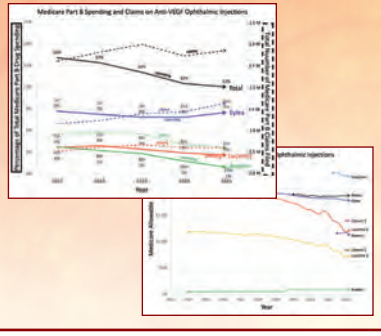
CRUNCHING THE NUMBERS

Follow the QR code or visit retinatoday.com to see how Medicare spending on ophthalmic injections has changes through the years.

Medicare Part B Spending and Claims on Anti-VEGF Ophthalmic Injections

Medicare Allowable of Anti-VEGF Ophthalmic Injections



QUANTIFYING FLUID IN AMD

Central subfoveal thickness isn't the only biomarker clinicians can use to track disease progression and treatment effect.

BY STELA VUJOSEVIC, MD, PHD, FARVO, FEBO

Wet AMD is a major cause of severe vision loss in eyes with AMD, representing a significant burden to health care systems in developed countries.[1] Given that wet AMD is a chronic condition, the assessment of disease activity for appropriate management is essential. Most therapeutic clinical trials define markers for wet AMD activity as reduced visual acuity (> 5 ETDR letters), new hemorrhages on fundus examination, and the presence of retinal fluid on OCT.[2-4] The presence of these markers usually prompts treatment with monthly intravitreal anti-VEGF agents.[5] Management strategies often include either PRN or treat and extend.[5]

OCT is the current standard of care for image-guided diagnosis and management of wet AMD. For example, central subfoveal thickness (CST) has been widely used as a surrogate OCT biomarker for wet AMD activity to assess the presence of fluid and inform retreatment decisions.[6,7] However, evidence now suggests that CST is not an ideal marker of exudative disease activity and may not properly guide management decisions. Limitations include inaccurate fluid representation, inability to segment fluid compartments, and moderate to poor correlation with BCVA.[8,9]

Therefore, researchers are working to identify other parameters more relevant to visual outcomes, disease activity, and prognosis to improve patient care.[9]

NEW APPROACHES

Advanced multimodal imaging techniques and OCT devices have provided new perspectives on the characterization of qualitative and quantitative features in acute and degenerative stages of wet AMD. OCT allows the precise identification and quantification of small anatomic changes within the retina and abnormal retinal fluids, which highlight the presence of pathological macular neovascularization (MNV) in wet AMD. Using OCT, clinicians and researchers can generally distinguish intraretinal fluid (IRF), subretinal fluid (SRF), and pigment epithelium detachment (PED).[9]

Post-hoc analyses of clinical trials and real-life studies have investigated these new OCT findings and suggest that the amount and location of fluid have a distinct effect on functional outcomes.[10-14] For example, eyes with IRF are likely to exhibit worse visual outcomes, regardless of location and severity, while eyes with SRF are associated with a comparably more benign disease course.[9,15] PED is often considered unresponsive to therapy and is associated with visual decline during PRN regimens.[9,15]

Therefore, OCT-based analysis that includes macular volumes instead of thicknesses, characterizes fluid subtypes, and differentiates fluid from neural tissue volumes can provide novel insights into how fluid affects visual outcomes in wet AMD.[9,16-18] Such an analysis can also reflect the fluid resolution during different treatment regimens and with varying drug molecules. IRF and SRF volumes at different time points should be considered for retreatment decisions in wet AMD, together with other OCT findings.

In the CATT and HARBOR trials, the OCT-based outcome measure was change in CST, while the fluid subtypes from MNV were included in binary terms of *present* or *absent* in the PRN retreatment regimen.[18-20] The HAWK and HARRIER trials evaluated the presence of IRF, SRF, and subretinal pigment epithelium fluid as qualitative parameters.[21]

However, treatment decisions do not always match reading center fluid determinations based on OCT scans,

AT A GLANCE

- OCT can identify and quantify anatomic changes within the retina and abnormal retinal fluids.
- Intraretinal and subretinal fluid volumes on OCT at different points should be considered for retreatment decisions in wet AMD.
- Artificial intelligence-based software may one day reliably and accurately measure fluid activity on OCT volume scans in real-time to promote personalized treatment approaches.

and artificial intelligence (AI)-based studies show that retina specialists have imperfect accuracy and low sensitivity in detecting retinal fluid.[20,22] Qualitative assessment of macular fluids by manual OCT interpretation—usually graded as present or absent and mild or severe—is time-consuming, difficult to standardize, and not feasible in the routine clinic. Considering the growing number of OCT scans necessary for optimal wet AMD management and the increasing OCT volume scan density, accurate fluid assessment may create a significant gap between optimal patient care and efficient workflow in routine clinical practice.[23]

THE POWER OF AI

AI-based segmentation can automatically process OCT scans and accurately identify, localize, and quantify macular fluid.[23-26] AI has proven superior to human experts in terms of the accuracy and speed of fluid analyses in both clinical trial and real-world settings.[23,26-28] As such, quantitative metrics of IRF, SRF, and PED within OCT volume scans can be used as scalable biomarkers in wet AMD, providing substantial advantages to research and clinical practice.[23,26]

Automated segmentation of OCT volumes should greatly improve our understanding of the effect macular fluid has on visual outcomes. It may also offer the opportunity to extract other relevant biomarkers, such as macular atrophy, subretinal hyperreflective material, and fibrosis, to name a few.[26,29] AI-based tools may unveil novel structural-functional correlations in wet AMD, affecting patients' visual prognoses. In the clinic, it may provide a "fluid activity meter" to optimize and personalize wet AMD therapy.[26]

Thus, AI-based software may one day reliably and accurately measure fluid activity on OCT volume scans in real-time to promote personalized treatment approaches. This accurate and user-friendly approach may be able to improve clinical workflow at multiple levels. Patients could benefit from shorter wait times, lower risk of over- or under-treatment, and minimized travel costs and absence from work. For hospital and clinic administrators, it may offer improved resource allocation and enhanced patient access.

FINAL PEARLS

The integrated analysis of functional and structural features allowed by AI-based approaches is a prerequisite to quantify disease progression, improve the therapeutic management of wet AMD, and refine treatment regimens in both real-world practice and clinical trials. Automated algorithms and computational data analysis help extract a wealth of quantitative data from high-resolution OCT imaging, while also reducing the burden of data analysis.

This could ultimately bridge the gap between clinical trial results and real-world outcomes and bring clinical trial quality disease management to routine clinical care.[30] Further research is needed to assess the effect of automated

ARTIFICIAL INTELLIGENCE IN THE REAL WORLD

RetInSight's Fluid Monitor is a first-in-class artificial intelligence-based class IIa medical device recently developed in Europe to help clinicians make treatment decisions and monitor patients with wet AMD. It is compatible with all leading OCT devices, starting from the Heidelberg Engineering ophthalmic imaging platforms and applications (Figure).

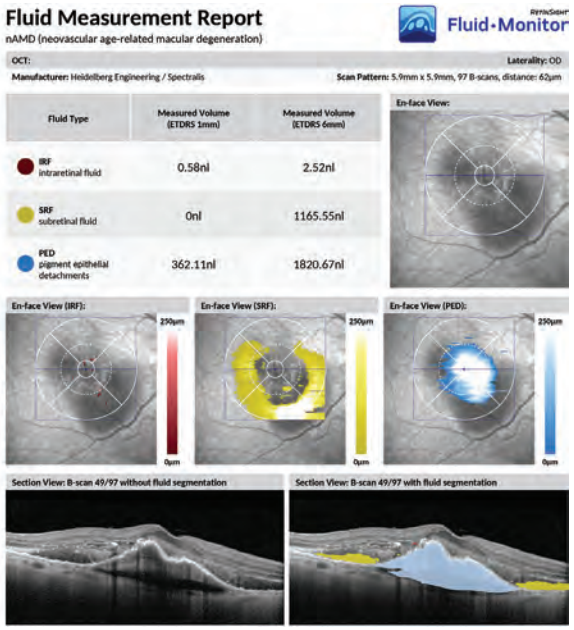


Figure. The RetInSight Fluid Monitor can provide real-time reports during routine OCT imaging and can identify intraretinal fluid, subretinal fluid, and pigment epithelial detachment, as well as the fluid's distribution, quantity in nanoliters, and location within the central 1-mm and 6-mm macular area.

AUTOMATED SEGMENTATION OF OCT VOLUMES SHOULD GREATLY IMPROVE OUR UNDERSTANDING OF THE EFFECT MACULAR FLUID HAS ON VISUAL OUTCOMES.

quantification of fluid in wet AMD in the real-world setting. Continuous innovation, driven by advanced imaging devices, AI-based applications, and novel treatments, is shaping the field of medical retina to improve visual outcomes for patients and reduce the burden of care. ■

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(Continued from page 29)

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CLINICAL TRIAL DESIGNS IN WET AMD: A BRIEF REVIEW

Can newer therapies improve upon visual acuity and other outcomes for patients?

BY CARL D. REGILLO, MD

FDA approval of verteporfin photodynamic therapy (PDT; Visudyne, Novartis) in 1999 marked the era of pharmacotherapy for neovascular conditions of the retina.[1] Soon after, the landscape changed dramatically with the development of biologic therapies that targeted the VEGF family of proteins central to angiogenesis and vascular permeability.[2,3]

Pegaptanib (Macugen, Eyetech Pharmaceuticals), an intravitreally administered pegylated aptamer that targets the 165 isoform of VEGF-A, was the first approved in 2004.[4] It fell out of favor once pivotal trials of newer anti-VEGF-A agents, such as ranibizumab (Lucentis, Genentech/Roche), aflibercept (Eylea, Regeneron), and off-label use of bevacizumab (Avastin, Genentech/Roche), demonstrated more clinically meaningful improvements in vision.

Despite the strides made with standard-of-care intravitreal anti-VEGF-A agents for the treatment of wet AMD, patients' real-world results fall short of those attained in pivotal, phase 3 registration trials.[5-12] Subsequent treatments, also primarily inhibiting VEGF-A, demonstrate noninferiority to earlier agents but have mostly sought to improve durability without showing superior visual results. This article reviews design aspects of these registration trials, including those of next-generation therapeutic approaches.

MARINA AND ANCHOR: SETTING THE STANDARD

The pivotal superiority trials MARINA and ANCHOR compared ranibizumab with sham and PDT, respectively.[13,14] At 12 months, 95% of those randomized to 0.5 mg ranibizumab lost < 15 ETDRS letters versus 62% in the control group. Similarly, in the ANCHOR trial, 96% of the ranibizumab group lost < 15 ETDRS letters versus 64% in the PDT-treated group at 12 months.[15,16] No approved drug has been shown to be superior to monthly ranibizumab, thus setting the bar for newer therapeutic approaches.

NONINFERIORITY TRIALS

Active control studies seek to show that an investigational treatment is no worse than standard of care (ie, statistically noninferior). The specific noninferior margin and trial design affect the strength of the study's findings. Regulators require a functional visual acuity endpoint, which can be categorical (percentage of patients with a 15-letter loss or gain from baseline) or continuous (mean change in BCVA from baseline).

The phase 3 VIEW 1 and 2 studies of aflibercept were largely similar to MARINA and ANCHOR.[17] The primary endpoint analysis assessed noninferiority (margin of 10%) of aflibercept versus ranibizumab in the proportion of patients losing < 15 ETDRS letters at month 12. The aflibercept groups were noninferior to ranibizumab (0.5 mg every 4 weeks) and an integrated analysis found no statistically significant change in mean ETDRS letter improvement at 1 year. The trials demonstrated that 2 mg aflibercept dosed every 4 or 8 weeks (after three monthly loading injections) was noninferior to ranibizumab (0.5 mg every 4 weeks).

Monthly and bimonthly (every 8 weeks after 3-month loading) fixed regimens were used in the registration trials for ranibizumab and aflibercept, respectively. These fixed dosing regimens represent on-label standards of comparison for other follow-on therapies exploring similar or extended dosing schedules.

AT A GLANCE

- Active control studies seek to show that an investigational treatment is no worse than standard of care (ie, statistically noninferior).
- Most current wet AMD trials are designed to demonstrate noninferiority in mean cahnge in BCVA from baseline using extended dosing intervals of newer therapies.
- Combination therapy in wet AMD differs with regards to the primary endpoint; it must demonstrate superiority of effect on visual function outcomes.

The low cost of repackaged bevacizumab led to its widespread off-label use in wet AMD. The landmark CATT trial established the noninferiority of bevacizumab (1.25 mg every 4 weeks) to ranibizumab (0.5 mg every 4 weeks), validating its use in practice.[18]

IMPROVING DURABILITY

A majority of subsequent completed or ongoing trials in wet AMD have been designed to demonstrate noninferiority in mean change in BCVA from baseline using extended dosing intervals of newer therapies compared with fixed dosing with standard-of-care treatment.

Trials of brolucizumab (Beovu, Novartis) and faricimab (Vabysmo, Genentech/Roche) marked the beginning of noninferiority studies of treatment durability for many next-generation therapies, with most employing fixed dosing with aflibercept as a control comparator arm and incorporating designs that tailored the retreatment interval based on protocol-defined disease activity. Key entry criteria largely remained consistent with earlier studies.

The HAWK and HARRIER phase 3 trials investigated 6 mg and 3 mg brolucizumab versus 2 mg aflibercept.[19] A 3-month loading phase was followed by every 12-week dosing for the brolucizumab groups, with an option to decrease to 8-week dosing based on evidence of disease activity. At 2 years, brolucizumab demonstrated noninferiority in mean change in BCVA compared with aflibercept with a similar safety profile. More than half of 6 mg brolucizumab eyes were maintained on dosing every 12 weeks through 48 weeks. Despite better treatment duration, widespread adoption of the drug has been hampered by the risk of occlusive retinal vasculitis and intraocular inflammation.[20]

The phase 3 TENAYA and LUCERNE trial patients were randomized in a 1:1 ratio to 6 mg faricimab or 2 mg aflibercept.[21] Faricimab patients were initially dosed with four injections every 4 weeks up to week 12 and then were assigned dosing intervals of every 8, 12, or 16 weeks based on active disease criteria up to week 60. Both trials met the primary endpoint of mean change in BCVA from baseline, with faricimab showing noninferiority to aflibercept. Faricimab treatment was durable, as 80% of patients in each study achieved at least every 12-week dosing and 45% reached the maximum dosing interval of every 16 weeks by year 1.[21]

It remains to be seen how these extended treatment paradigms from the clinical trial setting perform in the real world, where retreatment decisions vary.

New Drugs Under Investigation

The FDA accepted Regeneron's biologics license application for 8 mg aflibercept based on data from PULSAR that met the primary endpoint of noninferiority in vision gains for both the 12- and 16-week 8 mg aflibercept dosing regimens after initial monthly doses at 48 weeks compared with patients treated with 2 mg aflibercept in an 8-week dosing regimen.[22] A majority of the high-dose treatment patients were able to maintain the dosing regimens. The safety profile was similar to that of the approved aflibercept dose and consistent with the agent's known safety profile.

KSI-301 (Kodiak Sciences) is an anti-VEGF-A antibody biopolymer conjugate with a high molecular weight that is intended to increase residence time in the eye and extend durability. The phase 2b/3 DAZZLE trial randomized patients to either 5 mg KSI-301 on a flexible treatment schedule of 3, 4, or 5 months versus 2 mg aflibercept every 8 weeks following three monthly loading doses. DAZZLE did not meet the primary endpoint of noninferiority of mean change in BCVA from baseline to 12 months. A second trial, DAYLIGHT, is evaluating a more frequent monthly KSI-301 dosing regimen for noninferiority to aflibercept.[23,24]

TKIs and gene therapies hold promise for controlling wet AMD in the maintenance phase of therapy with the potential for greater durability.[25-30] However, these therapies are still in clinical trials, and the relative efficacy and safety of these treatments compared with standard fixed, frequent anti-VEGF-A injections have yet to be shown in large scale, pivotal studies.[31]

SUPERIORITY TRIALS

Combination treatment approaches in wet AMD differ with regards to the primary endpoint, as they need to demonstrate superiority of effect on visual function outcomes (with favorable safety) to be considered for regulatory approval. Key entry criteria are mostly consistent with earlier noninferiority studies; however, patients presenting with worse BCVA at baseline are preferred to avoid any potential ceiling effects of the combination treatment, which could hamper the ability to achieve the superiority primary endpoint.

Despite positive phase 2 data, the results of phase 3 trials of the anti-PDGF molecule, pegpleranib (Fovista, Ophthotech), reported that in combination with ranibizumab or aflibercept/bevacizumab, the primary endpoint of superior mean change in BVCA at 12 months was not met in any of the studies. Reasons for the disappointing data may include changes in trial design from the phase 2 study and potential limited pathophysiological role of PDGF in treatment-naïve disease.[32,33]

OPT-302 (Opthea Limited), an intravitreally administered VEGF-C and -D 'trap' inhibitor biologic, is being investigated in two phase 3 clinical trials in combination with ranibizumab (ShORe) and aflibercept (COAST).[34-36] OPT-302 is given once every 4 or 8 weeks after three monthly loading doses in combination with anti-VEGF-A therapy. Both studies' primary endpoint is superiority in change in BCVA gains from baseline at 12 months for combination therapy versus anti-VEGF-A monotherapy. The completed phase 2b study of OPT-302 plus ranibizumab achieved the primary endpoint of

OLD DRUG, NEW APPROACH

Outlook Therapeutics has an investigational ophthalmic formulation of bevacizumab for the treatment of wet AMD, ONS-5010. The pivotal NORSE TWO trial was designed as a superiority study that compared the safety and efficacy of ONS-5010 (dosed every 4 weeks) against ranibizumab (dosed according to the PIER dosing regimen). The trial met both the primary and secondary endpoints: 41.7% (P = .0052) of patients gained ≥ 15 letters of vision, 56.5% (P = .0016) gained ≥ 10 letters of vision, and 68.5% (P = .0116) gained ≥ 5 letters. The data showed that the drug was well-tolerated, consistent with previously reported data. The FDA accepted the company's biologics license application and set a Prescription Drug User Fee Act goal date of August 29, 2023.[1]

1. Outlook Therapeutics announces acceptance of BLA by FDA for ONS-5010 as a treatment for wet AMD [press release]. Eyewire+. October 28, 2022. Accessed May 1, 2023. eyewire.news/news/outlook-therapeutics-announces-acceptance-of-biologics-license-application-by-fda-for-ons-5010-as-a-treatment-for-wet-amd

a statistically significant mean change in BCVA from baseline to week 24 of +14.2 letters—an additional gain of +3.4 letters (P = .0107) over the ranibizumab plus sham control group.[37]

Phase 2b results also showed that OPT-302 combination therapy had a mean BCVA gain of an additional +5.7 letters over the control group (16.1 vs 10.3 letters) at 24 weeks in a prespecified analysis of treatment-naïve patients with minimally classic and occult lesions. Thus, the phase 3 ShORe and COAST endpoints will be analyzed in a hierarchical fashion, starting with the primary endpoint in these two lesion types (high responders), followed by the total population (including predominantly classic lesions).[34,35]

A LOOK AHEAD

As new therapeutic approaches have been developed for the treatment of patients with wet AMD, pivotal registrational trial designs have evolved to assess for further improvements in efficacy or durability of responses over existing standard of care. Our current anti-VEGF-A therapies work well, but we can still do better to gain back more vision, maintain initial visual gains, or decrease the burden for many patients who currently have a real unmet need for better long-term vision outcomes. ■

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RISING STARS IN RETINA

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

Suzanne Michalak, MD

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

During college and medical school, I thought I was going to pursue neurosurgery. Then I spent a Howard Hughes Medical Institute research year at Boston Children's Hospital, where I met Mary Whitman, MD, PhD, and David Hunter, MD, PhD. They welcomed me into their clinics and showed me that ophthalmology was a better fit. During my residency at Duke, I was fortunate to work with several phenomenal retina attendings and fellows on cutting-edge research and learn from them in the clinic and OR. The complexity of retinal pathology, imaging technology, and the excitement in the field for innovations to restore vision solidified my decision.

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

As is likely the case for most retina fellows, I wouldn't be where I am now without my mentors. At Duke, I was lucky to work closely with Lejla Vajzovic, MD, and Cynthia Toth, MD. They included me in every aspect of the retina department, even as a resident: teaching me vitreoretinal surgical principles, integrating me into weekly vitreoretinal rounds, and showing me how to conduct clinical trials. In fellowship at Stanford, I have been in awe of each member of our retina faculty and consider all of them to be my mentors, particularly my fellowship director, Prithvi Mruthyunjaya, MD. I am constantly impressed by their dedication to teaching while providing exceptional clinical and surgical evidence-based care.

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

One weekend, I received a consult from an outside hospital about a patient with a VA of light perception from endogenous endophthalmitis. Due to a nursing strike, the patient could not be easily transferred, and Darius Moshfeghi, MD, immediately requested emergency privileges so we could perform a bedside tap and inject at the outside hospital. At that time, we noted that the patient also had a retinal detachment. Dr. Moshfeghi and Ehsan Rahimy, MD, worked tirelessly to transfer the patient to Stanford, where we performed bilateral, sequential vitrectomies the following evening. Miraculously, the patient eventually regained his baseline vision.

Other memorable experiences include sailing in a regatta with my mentors in Dubrovnik, Croatia, at the Club Jules Gonin meeting and countless hours discussing cases with my amazing co-fellows.

FIRST CAREER MILESTONE

Dr. Michalak will be practicing adult and pediatric retina at Dartmouth Hitchcock Medical Center in Lebanon, New Hampshire.

RT: What are you hoping to accomplish once you are in practice?

My goals are to provide exceptional, compassionate retina care to patients of all ages and to mentor future generations. I have been very involved in research during residency and fellowship and plan to continue working to further our knowledge as a field.

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

Retina can seem intimidating from the outside, but the field is full of incredible and kind people who are eager to help. In addition to rewarding bread-and-butter retina, you can become an expert in complex proliferative vitreoretinopathy, secondary IOLs, pediatric retina, ocular oncology, or uveitis. There is something for everyone! Please reach out if there's anything I can do to help. ■

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DIAGNOSTIC YIELD IN NON-DILATING PUPILS

Scanning laser ophthalmoscopy-based fundus photography can help to diagnose patients with non-dilating pupils.

BY MANISH NAGPAL, MS, FRCS, FASRS; NAVNEET MEHROTRA, MBBS, DNB, FRF; AKANSHA SHARMA, MBBS, MS; NIVESH GUPTA, MBBS, MS; AND ABHISHEK VERMA, MBBS, DO

The standard for evaluating the peripheral retina is a dilated fundus examination with scleral depression. However, there are some cases of a non-dilating pupil where examination using an ophthalmoscope is impossible. In these cases, scanning laser ophthalmoscope (SLO)-based multimodal fundus imaging could give clinicians a fundus view that is not possible clinically.

In this article, we present the cases of six patients with a non-dilating pupil after instilling tropicamide for a 30-minute period. After performing refraction, IOP assessment, and a slit-lamp examination, we used SLO-based multimodal imaging to capture widefield color photographs, fundus autofluorescence (FAF), fluorescein angiography (FA), ICG angiography (ICGA), and OCT.[1]

CASE NO. 1

A 54-year-old man presented with decreased vision in his left eye for 1 month and a VA of counting fingers at 2 m. On anterior segment examination, we saw multiple keratic precipitates at the back of the cornea with a muddy iris (Figure 1A). The pupil measured 3 mm after instilling topical mydriatic tropicamide for 30 minutes. We also noted mild vitritis.

The widefield imaging showed an exudative retinal detachment (RD) involving 180° of the inferior retina (Figure 1B). FA revealed an altered foveal avascular zone and leakage (Figure 1C), and ICGA showed hypocyanscence (Figure 1D). We advised intravenous methylprednisolone for 5 days followed by oral steroids in a tapering manner prescribed using the patient's weight. The patient's vision did not improve, and we advised bimanual vitrectomy with silicone oil infusion. The patient's VA improved to 6/24 postoperatively.

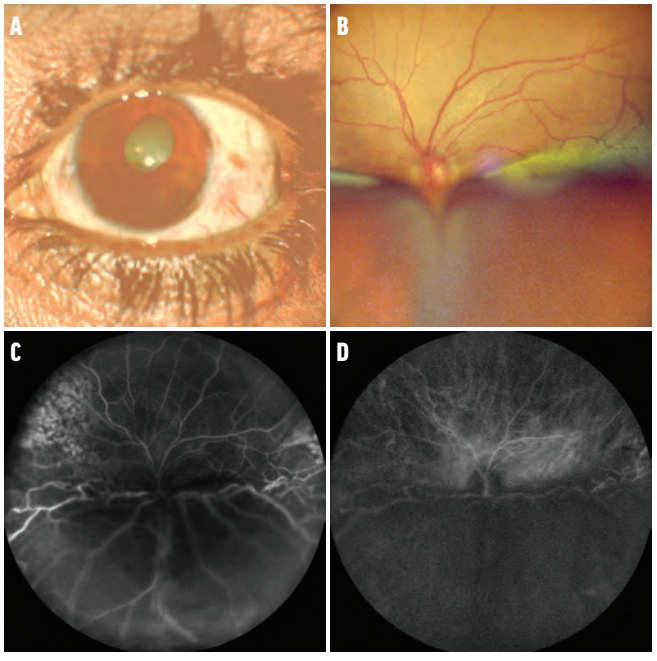

Figure 1. Anterior segment examination revealed keratic precipitates and a muddy iris (A). Widefield imaging showed an exudative RD (B). FA revealed an altered foveal avascular zone and leakage (C). ICGA showed hypocyanscence (D).

CASE NO. 2

A 30-year-old man presented with decreased vision in his left eye for 5 days and a VA of 6/12 in his left eye. His right eye had already been lost due to past ocular

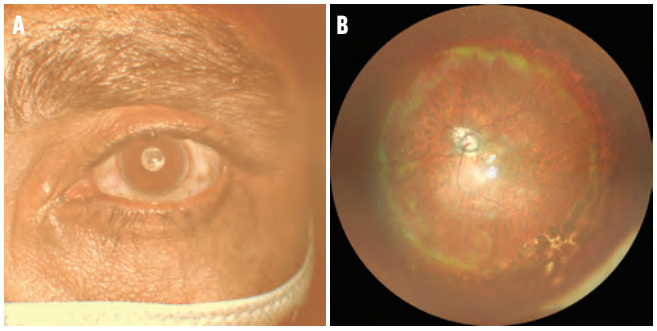

Figure 2. The anterior segment examination showed pseudophakia with an iridotomy (A). Widefield imaging showed disc pallor with cryotherapy marks as well as a 360° retinectomy (B).

trauma. His ocular history was remarkable for cryotherapy in the left eye and bimanual vitrectomy with silicone oil infusion for the treatment of a temporal RD with a giant retinal tear 8 years prior with silicone oil removal performed 6 months postoperatively.

At presentation, the pupil measured 2 mm after instilling topical mydriatic tropicamide for 30 minutes. We noted pseudophakia with an iridotomy at the 12 clock position during the anterior segment examination (Figure 2A). Widefield imaging showed disc pallor with cryotherapy marks at the 5 clock position and a 360° retinectomy (Figure 2B). The patient was observed without further treatment. The retina was well-attached, and the disc was pale, suggestive of optic atrophy.

CASE NO. 3

A 50-year-old man presented with decreased vision in his right eye for 1 month and a VA of counting fingers at 2 m. The anterior segment examination revealed a small non-dilating pupil (Figure 3A). OCT showed a fairly maintained foveal contour with choroidal thickening (Figure 3B).

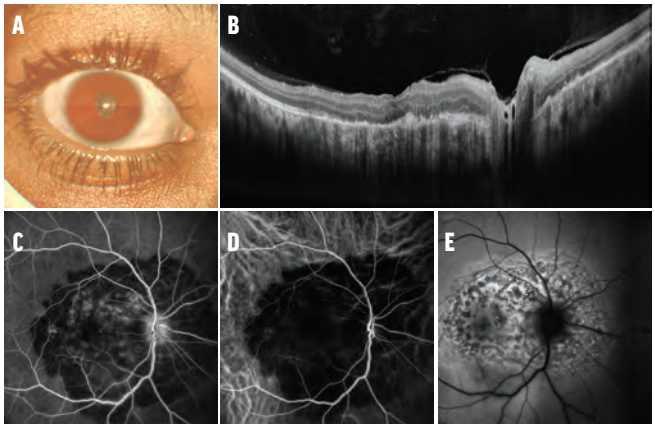

Figure 3. The anterior segment examination showed a small non-dilating pupil (A). OCT showed a fairly maintained foveal contour with choroidal thickening (B). FA showed hyperfluorescence (C). ICGA showed a hypocyanscent in the foveal region (D), and FAF showed hyper- and hypoflourescence (E).

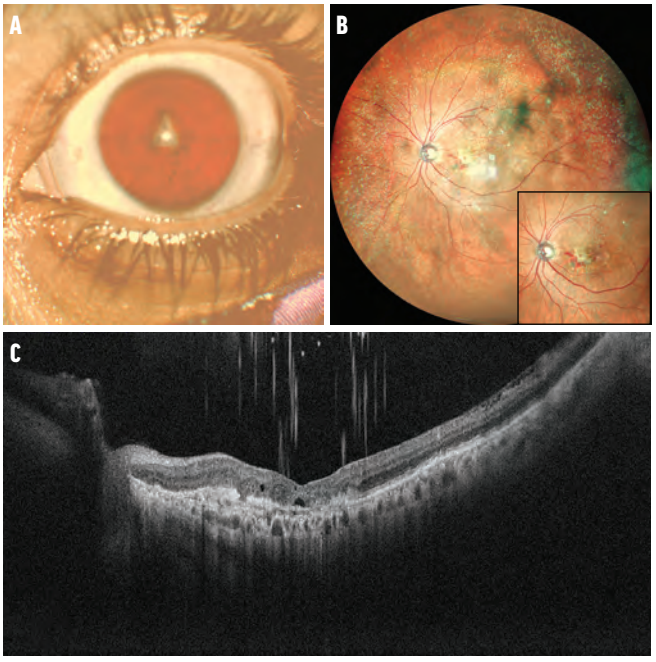

Figure 4. The pupil measured 3.5 mm after instilling topical mydriatic tropicamide for 30 minutes (A). Widefield imaging showed asteroid hyalosis with subretinal blood at the fovea and a juxtapapillary membrane (B). OCT imaging showed a fairly maintained foveal contour with pigmentary changes in the retinal pigment epithelium with a subfoveal subretinal fluid pocket (C).

FA revealed multiple areas of hyperfluorescence in the foveal region increasing in size and intensity from the early to late phase, suggestive of leakage (Figure 3C). ICGA showed this area to be hypocyanscent from the early to late phase (Figure 3D). FAF showed areas of hypo- and hyperautofluorescence in the peripapillary and foveal regions (Figure 3E).

We recommended a complete uveitis workup and started the patient on intravenous methylprednisolone for 3 days followed by oral steroids. The eye responded to the course of steroids, and the inflammation subsided by the 1 month follow up.

CASE NO. 4

A 73-year-old woman presented with decreased vision in her left eye for 15 days and a VA of counting fingers at 1 m. The pupil measured 3.5 mm after instilling topical mydriatic tropicamide for 30 minutes (Figure 4A). The widefield color photography showed asteroid hyalosis with subretinal blood at the fovea and a juxtapapillary membrane (Figure 4B). OCT imaging of the left eye showed a fairly maintained foveal contour with pigmentary changes in the retinal pigment epithelium with a subfoveal subretinal fluid pocket suggestive of a choroidal neovascular membrane (Figure 4C). After three intravitreal anti-VEGF injections, the patient's VA improved to 6/9 OS.

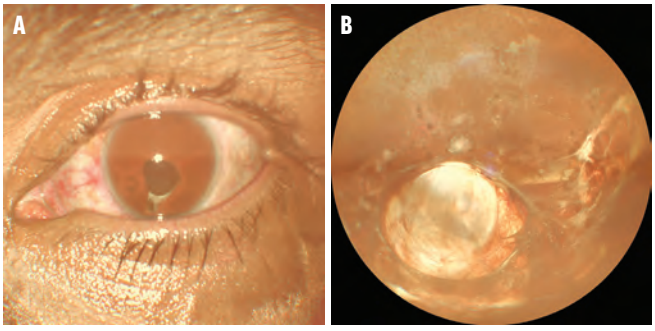

Figure 5. The pupil was non-dilating and maintained a keyhole shape (A). Widefield imaging showed an attached retina with a retinochoroidal coloboma (B).

CASE NO. 5

A 22-year-old man presented with decreased vision in his left eye for 7 days, a VA of light perception, and projection of rays accurate in all four quadrants. During the anterior segment evaluation, we observed microcornea with a typical iris coloboma. His right eye had been lost in childhood. His left eye ocular history was remarkable for scleral buckling with bimanual vitrectomy with silicone oil infusion for the treatment of an RD. Plomb removal was performed due to granuloma formation with silicone oil removal 2 years post-surgery. The patient presented with a redetachment, for which bimanual vitrectomy with silicone oil infusion was done with oil removal 3 years post-surgery.

At the time of presentation, the pupil was non-dilating after instilling topical mydriatic tropicamide and maintained a keyhole shape (Figure 5A). Widefield imaging showed an attached retina with a retinochoroidal coloboma (Figure 5B); the patient's VA was 6/36. The retina was well-attached 1 month postoperatively.

CASE NO. 6

A 37-year-old woman presented with decreased vision in her right eye for 3 years and a VA of 6/60. The anterior segment examination showed posterior synechiae with a festooned pupil and complicated cataract (Figure 6A). The patient noted a history of recurrent attacks and had recently completed a course of oral steroids with immunosuppressants. On OCT, the foveal contour was altered with multiple cystoid spaces in the right eye (Figure 6B). The patient received a dexamethasone intravitreal implant (Ozurdex, Allergan/AbbVie) followed by cataract surgery with synechiolysis.

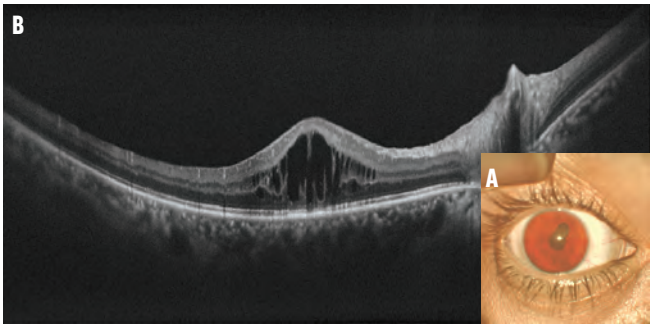

Figure 6. The anterior segment examination showed posterior synechiae with a festooned pupil and complicated cataract (A). OCT showed an altered foveal contour with cystoid spaces (B).

DISCUSSION

To ensure a 140° range of incident light, clinicians need a pupil diameter of at least 2 mm. Because the normal pupil's diameter ranges from 2.5 mm to 4.0 mm, widefield imaging systems can achieve 200° retinal imaging with a non-mydriatic pupil.[2]

Without SLO-based multimodal imaging, fundus examination in non-dilating pupils is extremely difficult. Missing important findings can significantly—and negatively—affect the treatment and follow-up plans. Whether defining the extent of an RD, identifying subretinal bleeds that require anti-VEGF injections, or confirming a leak on FA and planning laser treatment, it's possible with widefield multimodal imaging. ■

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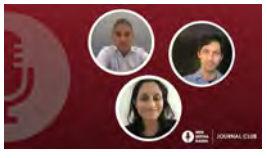

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SPONTANEOUS HYPHEMA FROM SMALL CELL LUNG CANCER METASTASIS

External beam radiation therapy can be a good option to control ocular manifestations when systemic disease is widespread.

BY ERIC LIEN, BS; FERRIS BAYASI, MD; AND CAROL L. SHIELDS, MD

Lung cancer is the leading cause of cancer-related deaths for both men (22%) and women (22%) in the United States.[1] Small cell lung cancer (SCLC) represents only 15% of all lung cancer cases, and nearly 70% of patients with SCLC present with disseminated disease upon diagnosis, which denotes a poor prognosis.[2] Metastasis from any lung cancer most commonly affects the bone (59%), lymph nodes (50%), liver (41%), and brain (32%).[3]

In 2018, Shields et al reported that uveal metastases most often originate from cancer of the breast (37%) or lung (26%), and those from the lung have the poorest 5-year survival rate (13%) following detection of metastasis in the eye.[4] Most intraocular metastases arise in the choroid (88%) and less commonly in the iris (9%) or ciliary body (2%).[5]

Herein, we describe a patient with known SCLC who developed photophobia from hyphema as the initial manifestation of metastasis to the iris.

CASE REPORT

A 66-year-old White man with a 14-month history of SCLC and known metastasis to the brain, bone, and liver presented to his primary care physician for photophobia in each eye, although it was worse in the right eye. At that time, he was diagnosed with allergic conjunctivitis and was given an oral antihistamine and topical erythromycin ointment. Later, a visit to the ophthalmologist revealed hyphema and a possible iris mass in his right eye. The patient was referred to the Ocular Oncology Service.

He had been diagnosed with SCLC in May 2021 and treated with radiotherapy and carboplatin, etoposide, and atezolizumab. He was a former cigarette smoker and had discontinued smoking 10 years earlier.

At the initial examination, his BCVA was 20/70 OD and 20/40 OS. IOP was 23 mm Hg OD and 17 mm Hg OS. The anterior segment of the right eye revealed moderate conjunctival and scleral injection with 20% hyphema overlying a milky-white, fluffy-appearing solid vascularized mass involving 6 clock hours of the iris and angle inferiorly (Figure 1). Anterior segment OCT documented the mass in the angle with endothelial touch (Figure 2).

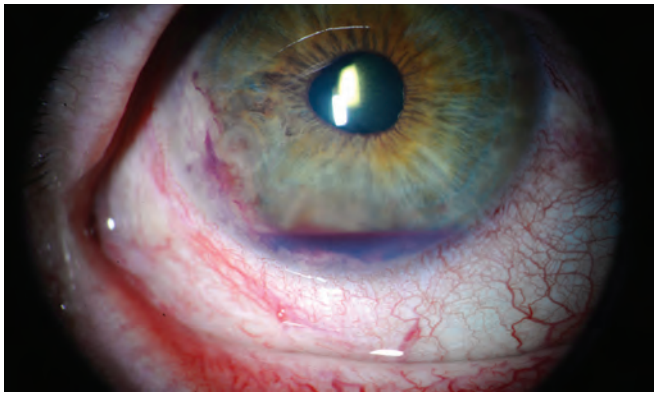

Figure 1. Slit-lamp examination of the right eye documented hyphema, corectopia, and a solid vascularized mass in the inferotemporal angle.

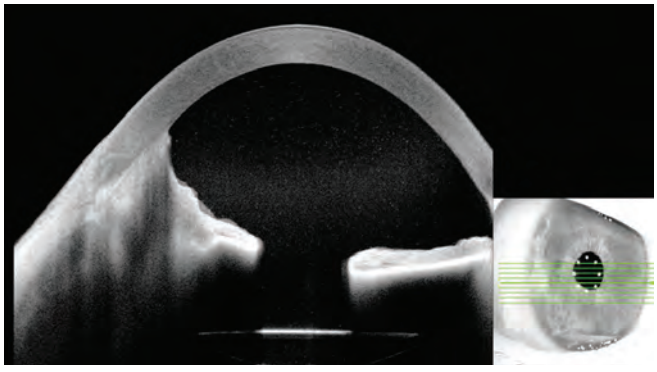

Figure 2. On anterior segment OCT, the transverse cross-section of the right eye showed the tumor at the anterior chamber angle adherent to the corneal endothelium.

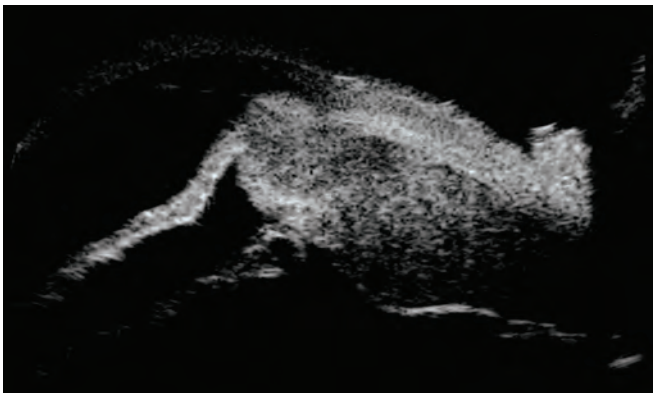

Figure 3. Ultrasound biomicroscopy of the right eye highlighted ciliary body involvement.

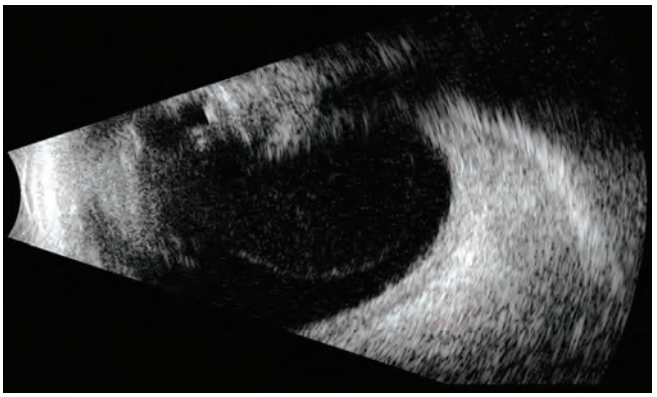

Figure 4. B-scan ultrasonography of the right eye showed posterior extension of the mass into the choroidal region.

On ultrasonography, the mass extended into the ciliary body and the choroid, measuring 24 mm in basal diameter and 6.2 mm in thickness (Figures 3 and 4). The left eye was unremarkable. Given the solid iridociliary tumor and systemic evidence of metastasis, the patient was suspected to have iridociliary metastasis from SCLC. Confirmation via fine needle aspiration biopsy was discussed with the patient, but given the poor systemic status, biopsy was ultimately avoided in favor of treating him directly with external beam radiation therapy (EBRT) to the eye.

INCIDENCE AND CLINICIAL PRESENTATION

Of 3,680 cases of iris tumors, solid nonmelanocytic lesions accounted for only 11% of cases, with 2% of all iris tumors representing metastases.[6] Most patients with uveal metastasis complain of blurred or decreased vision, while some present with uveitis, episcleritis, or glaucoma-like symptoms due to iris neovascularization or trabecular meshwork blockage.[7]

In a retrospective review of 104 patients with iris metastasis from systemic cancers, the most common symptoms were corectopia (37%), pain (32%), blurred vision (30%), and secondary glaucoma (30%).[8] In 78% of these patients, the metastasis was unifocal and unilateral, as in our case.[8] While clinical presentation of both iris melanoma and metastasis can be similar, the diagnosis of iris metastasis is primarily reliant on a history of cancer and evidence of systemic involvement.[7,8] However, the definitive diagnosis often requires fine needle aspiration biopsy.[7,8]

MANAGEMENT OF UVEAL METASTASES

Treatment for patients with iridociliary metastasis from SCLC is generally limited to palliative care. The presence of uveal metastasis frequently indicates widespread systemic disease, as in our patient with brain, bone, and liver metastases.[9] One sample of patients with choroidal metastases found synchronous brain metastases in 13% of patients (24 of 188), with an additional 14% (26 of 188) later developing cerebral metastases.[9]

Our Approach

Systemic chemotherapy and immunotherapy were discontinued in our patient due to idiopathic thrombocytopenia, but he continued to receive palliative radiotherapy for his primary lung cancer. Options to treat his iridociliary metastasis included EBRT, iodine-125 plaque radiotherapy, or enucleation.[10] Due to the size and extent of the tumor and his numerous systemic conditions, plaque radiotherapy was avoided, considering the need for surgery and risk of complications with this large tumor.[7,11,12] Palliative treatment with EBRT was performed with the aim of preserving vision and preventing intractable pain that could require enucleation.

Benefits of EBRT

There is considerable data on outcomes of EBRT for choroidal metastases, with globe preservation rates as high as 98%.[9] One study involving 27 patients with choroidal metastasis from lung cancer treated with EBRT showed 20 (74%) patients who experienced complete regression, three (12%) whose tumor was stabilized, and four (15%) who experienced further growth.[11]

In another study of 155 eyes with choroidal metastases of various origins, 89 (57%) experienced improved vision or maintained navigational vision (20/60 to 20/200) following EBRT. Among 47 participants who were legally blind (ie, VA worse than 20/400) before EBRT, 17 (36%) experienced improvement to a VA of 20/50 or better or achieved navigational vision.[9] Factors associated with a positive response to EBRT included initial VA < 20/50, age < 55 years, White race, and tumor basal diameter < 15 mm.[9] One or more radiation-related complications were noted in 28 eyes (12%) and these included radiation retinopathy, optic neuropathy, cataract, neovascularization, exposure keratopathy, and narrow angle glaucoma.[9]

An additional study focused on the rates and associated factors of complications with EBRT for patients with choroidal and ciliary body metastases.[13] Biopsy at the time of diagnosis increased the likelihood of developing complications.[13] There was no difference in cataract formation rates between

a lens-sparing technique and whole-globe irradiation.[13] The median survival time of patients with complications was significantly longer than those who did not experience any complications (25.9 months vs 7.4 months, $P = .002$), reflecting the relatively late onset of complications.[13] In patients with choroidal/ciliary body metastases, these consequences were less likely to occur due to their preexisting unfavorable prognosis.[13]

CONTROL SYMPTOMS WITH MINIMAL SIDE EFFECTS

While outcomes for iris and iridociliary metastasis were comparatively limited due to less frequent occurrence, EBRT remains a valuable therapeutic option for effectively controlling symptoms of uveal metastases with minimal treatment-associated complications.[13] ■

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.

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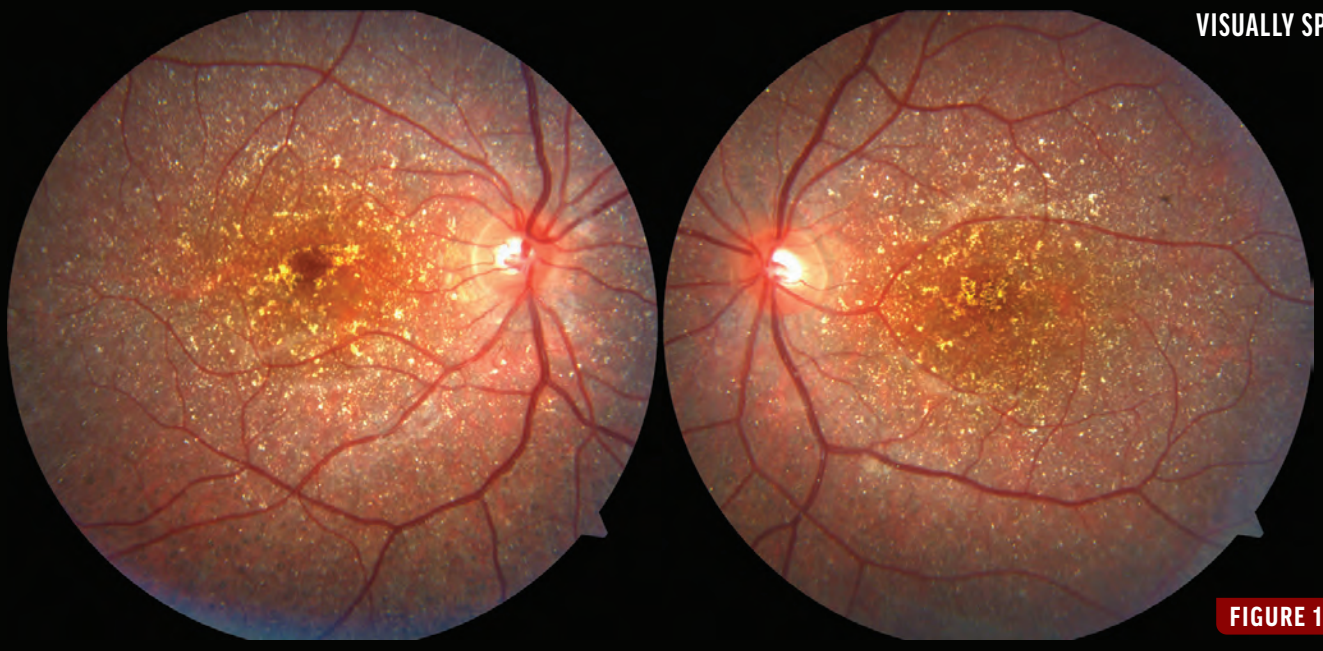


FIGURE 1

CATCHING BIETTI CRYSTALLINE DYSTROPHY EARLY

Prominent retinal deposits in the early stage may be helpful for diagnosis.

BY M. GIRAY ERSOZ, MD, FEBO; ROUZBEH ABBASGHOLIZADEH, MD; AND METIN SULEYMANZADE, MD

A 12-year-old girl presented to our clinic with poor vision at night. Her BCVA was 20/25 OD and 20/25 OS, and she had a family history of hereditary retinal dystrophy.

The anterior segment examination of each eye was unremarkable. Color fundus photography revealed diffuse, glistening, yellow-white crystalline deposits at the posterior pole of the retina in each eye (Figure 1). Fundus autofluorescence (FAF) also showed hyperautofluorescent deposits at the posterior pole of each eye (Figure 2).

OCT revealed hyperreflective spots (Figure 3, white arrowhead) in the inner retinal layers, bright reflective deposits (white arrow) on top of the retinal pigment epithelium (RPE)-Bruch membrane complex, and absence of outer retinal tubulations in each eye. Disruption of the ellipsoid zone, interdigitation zone, and RPE was more prominent on the parafoveal OCT sections. Presence of prominent crystalline retinal deposits, along with FAF and OCT findings, led us to the diagnosis of early-stage Bietti crystalline dystrophy (BCD).

DISCUSSION

BCD is an uncommon progressive retinal degenerative disease that has an autosomal recessive inheritance pattern. Mutation of the *CYP4V2* gene leads to defective fatty acid metabolism in the RPE and formation of retinal deposits.[1-3]

The presentation usually occurs between the second and third decades of life. The initial symptoms of BCD include gradual reduction in visual acuity, decreased night vision, and visual field loss.

The glistening yellow-white retinal crystalline deposits that are evident in the early stages of the disease are gradually replaced by RPE atrophy.[4,5] Because our patient's case was at a very early stage of the disease, the crystalline deposits were more prominent and outer retinal tubulations were absent.

Although the diagnosis of BCD is mainly based on the presence of distinctive retinal crystalline deposits, multimodal imaging techniques, such as OCT and FAF, are also useful to elucidate the diagnosis and disease course. ■

FIGURE 2

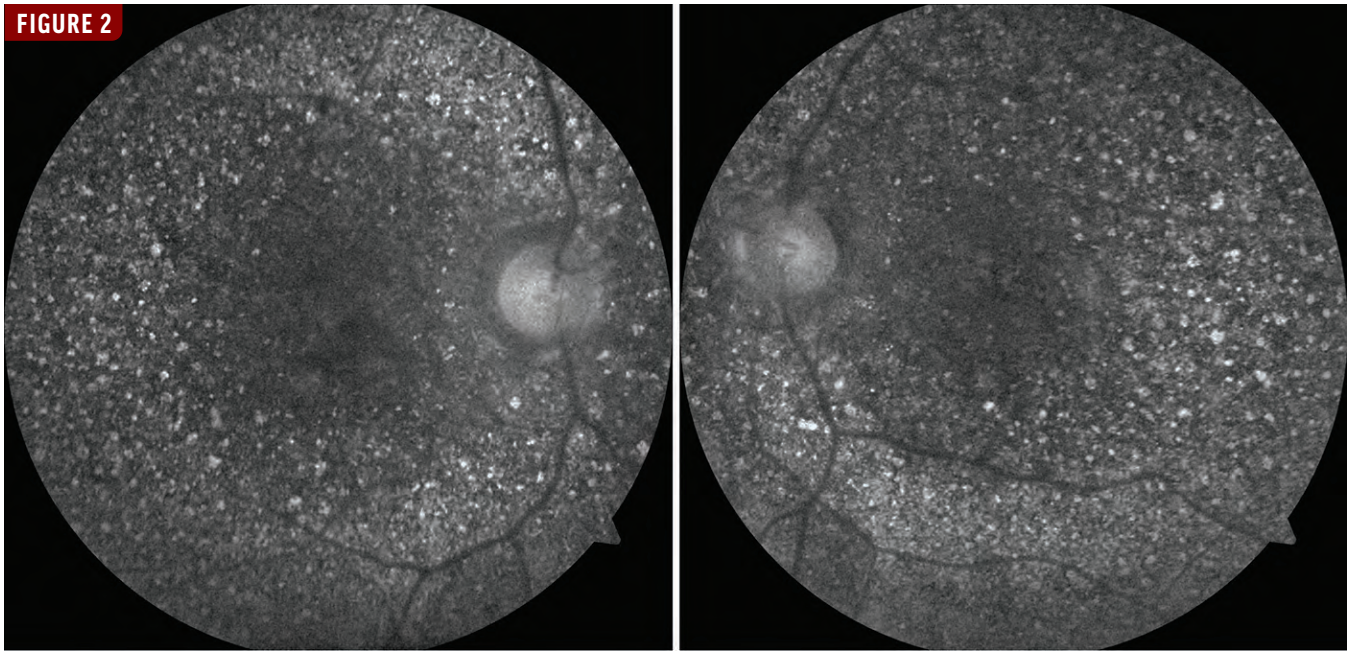
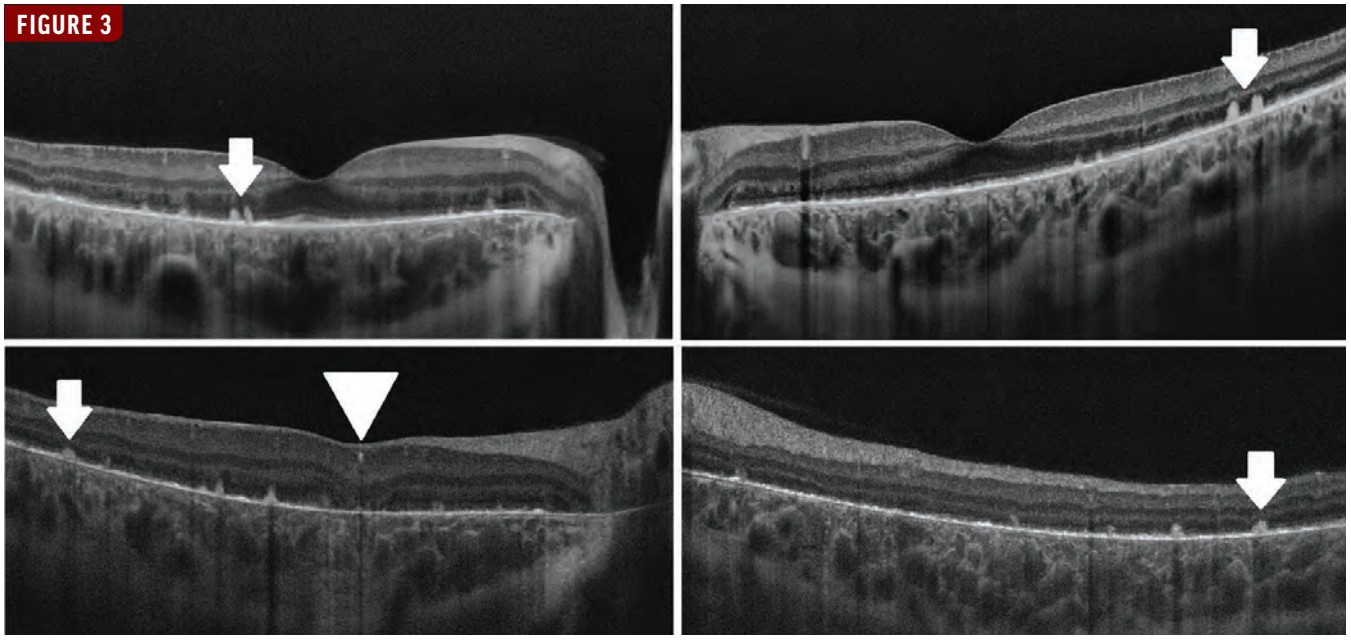


FIGURE 3



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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.

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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:
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U.S. License No.: 1048

M-US-00013249(v2.0) 2/23

Start with the power of 2

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

*Primary endpoint of non-inferiority vs aflibercept was defined as the mean change from baseline in BCVA (measured by the ETDRS letter score) to 1 year (average of weeks 40, 44, and 48 in nAMD and weeks 48, 52, and 56 in DME) and was tested for non-inferiority using a margin of 4 letters.[1]
†After 4 or 6 monthly loading doses.[1] Please see below for more information.
‡Verana Health data from Q1–Q4 2022.[6]

Discover 2 years of DME data at vabysmo-hcp.com/start

†Dosing Information:
DME dosing: 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). nAMD dosing: 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.[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 Brief Summary of full VABYSMO Prescribing Information on the following page.

References: 1. VABYSMO [package insert]. South San Francisco, CA: Genentech, Inc; 2023. **2.** Beovu® (brolucizumab-dbll) injection [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2022. **3.** Eylea® (aflibercept) [package insert]. Tarrytown, NY: Regeneron Pharmaceuticals, Inc; 2022. **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. **6.** Data on file. South San Francisco, CA: Genentech, Inc.

BCVA=best corrected visual acuity; ETDRS=Early Treatment Diabetic Retinopathy Study; OCT=optical coherence tomography; Q4W=every 4 weeks; Q8W=every 8 weeks; Q12W=every 12 weeks; Q16W=every 16 weeks.

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