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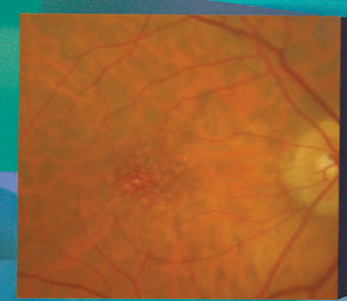
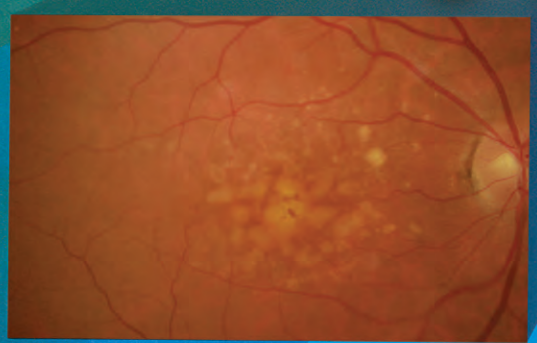
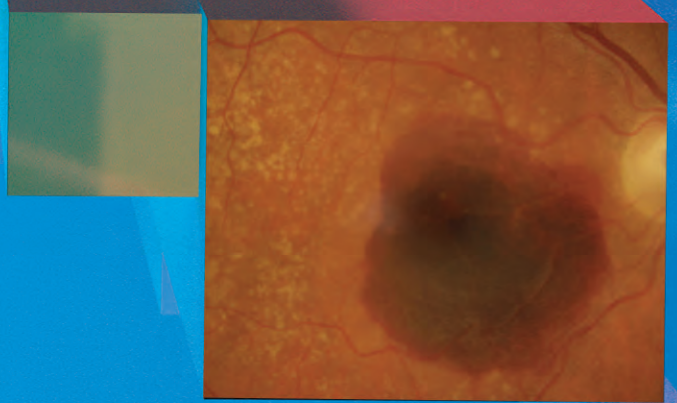
eyetube

ADVANCES IN AMD CARE







A look at the new staging, monitoring, and treatment options heading your way.

AT-HOME MONITORING IN YOUR OFFICE

RETHINKING OUR AMD NOMENCLATURE

AMD GENE THERAPY CHECK-IN

PROGRESSION IN GEOGRAPHIC ATROPHY IS RELENTLESS AND IRREVERSIBLE[1-4]

While GA progression may appear to move slowly, it can affect your patients faster than you think[1,4-6]

The consequences of Geographic Atrophy (GA) are too critical to be ignored[7-9]

IN A MEDIAN OF ONLY 2.5 YEARS,
GA lesions encroached on the fovea according to a prospective AREDS study (N=3640)[2*]

2 OUT OF 3 PATIENTS
lost the ability to drive in a median time of <2 years according to a retrospective study (n=523)[10†]

GA lesions can lead to visual impairment even before they reach the fovea[1,5,6]

See the effect of GA progression on your patients

*Data sourced from the Age-related Eye Disease Study (AREDS) Report #26—a long-term, multicenter, prospective study examining progression of GA area in a cohort of 3640 patients with signs of early and more advanced forms of AMD.

†A retrospective cohort analysis (N=1901) of a multicenter electronic medical record database examining disease burden and progression in patients in the United Kingdom with bilateral GA secondary to AMD.

BCVA=best-corrected visual acuity.

References: 1. Boyer DS et al. *Retina*. 2017;37:819-835. 2. Lindblad AS et al, and AREDS Research Group. *Arch Ophthalmol*. 2009;127(9):1168-1174. 3. Holz FG et al. *Ophthalmology*. 2014;121(5):1079-1091. 4. Sunness JS et al. *Ophthalmology*. 2007;114(2):271-277. 5. Kimel M et al. Invest *Ophthalmol Vis Sci*. 2016;57(14):6298-6304. 6. Sadda SR et al. *Retina*. 2016;36(10):1806-1822. 7. Singh RP et al. *Am J Ophthalmic Clin Trials*. 2019;(1):1-6. doi:10.25259/ajoct-9-2018. 8. Sivaprasad S et al. *Ophthalmol Ther*. 2019;8(1):115-124. 9. Patel PJ et al. *Clin Ophthalmol*. 2020;14:15-28. 10. Chakravarthy U et al. *Ophthalmology*. 2018;125:842-849.

Apellis

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WINDS OF CHANGE


For those of you who missed it, this year's Vit-Buckle Society (VBS) meeting included an inspiring three-way debate on wet AMD therapy options: the port delivery system (PDS) with ranibizumab (Susvimo, Genentech/Roche) versus gene therapy versus intravitreal anti-VEGF injections (Figure). Despite excellent presentations on the PDS by Ashley M. Crane, MD and gene therapy by yours truly, R.A., the room overwhelmingly decided Esther Lee Kim, MD, won the debate with her rousing support for intravitreal injections.

Figure. The wet AMD debate panel brought to light the challenges with anti-VEGF injections and the ways second-generation options are seeking to overcome them. From left to right: Esther Lee Kim, MD; Ashley M. Crane, MD; debate moderators Tarek S. Hassan, MD, and Sandra R. Montezuma, MD; and Robert L. Avery, MD.

The outcome was to be expected, of course, and Dr. Kim had something of an unfair advantage. I (R.A.) am trying not to let the defeat get to me. A simple in-office anti-VEGF injection can stave off progression and improve vision for many patients—all without much in the way of a safety concern, at least for most agents. The treatment burden is high with anti-VEGF injections, but it *works* and has undoubtedly been a game changer for our wet AMD patients.

However. Most striking to us was the fact that we could even have that type of debate in the first place. After more than a decade of relatively stagnant treatment approaches to wet AMD, the winds of change are upon us. In fact, it feels as if almost every aspect of AMD care is shifting beneath our feet. VBS and other conference halls (finally crowded with friendly faces) have been ringing with questions: what do we *do* with all this innovation? Who is it going to help? How is it going to affect our day-to-day clinical practice?

Everyone is looking to leaders in the field for advice on how to incorporate the PDS, faricimab (Vabysmo, Genentech/Roche), biosimilars, and maybe gene therapy one day, into their treatment paradigms. Equally important, clinicians are wondering how to prepare for the potential approval of a therapy for geographic atrophy. Sure, we follow these patients now, but what if we could actually treat them? What would that mean for diagnostic timing? Disease staging? Long-term monitoring? Clinic flow?

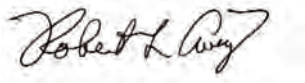
Only clinical experience—and many more debates—will help us better understand how these new therapies fit into our practices. Who knows, maybe that same debate will have a different outcome in a few years.

This issue of *Retina Today* is dedicated to answering at least some of these questions for you. Within these pages, you will find advice on incorporating the new therapies, as well as a robust discussion on proper AMD nomenclature and a look at the biosimilar market.

As if new treatment options weren't enough, we also have at-home monitoring to consider, and the possibility of artificial intelligence affecting how we diagnose and follow patients in the near future. Both topics are included in this issue to help you prepare for changes that are likely just around the corner.

While we do our best to absorb the onslaught of new information reshaping our clinics, we must turn right around and educate our patients on those very same changes. They have the right to be informed about all their treatment options, and it's up to us to guide them toward the best management strategy. For many patients, it's likely going to be a quick conversation simply making them aware that two new therapies exist; after all, our standard of care remains an exceptional option. But we all have a few patients for whom a longer-duration option just might be the change they need, and they will require an in-depth discussion of the benefits and risks of switching therapies. The newly approved therapies, tools, and techniques now provide a more personalized approach for patients who struggle with the treatment burden or aren't seeing a benefit with the tried-and-true.

Charles C. Wykoff, MD, PhD, said it best in this issue's roundtable discussion: We must instill within our patients a drive to maintain the best vision possible using today's therapies because next-generation treatments are going to be even better. ■

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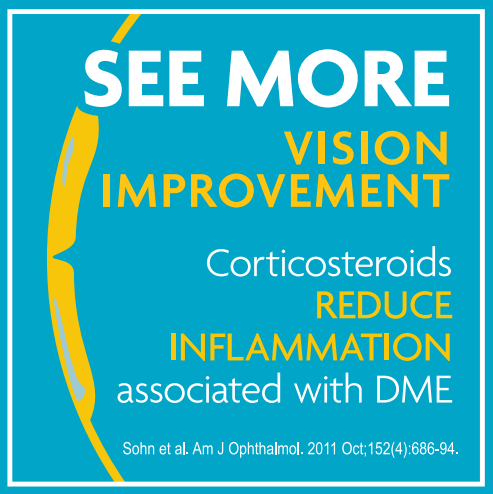
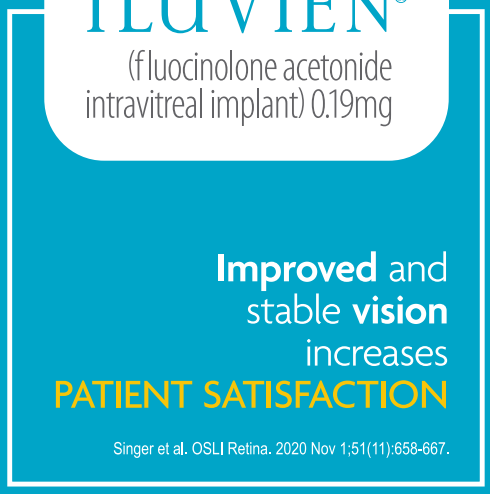




ILUVIEN with CONTINUOUS MICRODOSING™ can reduce the recurrence of edema by treating the underlying inflammation that drives DME.[1,2]

Learn More at hcp.ILUVIEN.com

INDICATION

ILUVIEN® (fluocinolone acetonide intravitreal implant) 0.19 mg is indicated for the treatment of diabetic macular edema (DME) in patients who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure.

Important Safety Information

CONTRAINDICATIONS

- ILUVIEN is contraindicated in patients with active or suspected ocular or periocular infections including most viral disease of the cornea and conjunctiva including active epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections and fungal diseases.
- ILUVIEN is contraindicated in patients with glaucoma who have cup to disc ratios of greater than 0.8.
- ILUVIEN is contraindicated in patients with known hypersensitivity to any components of this product.

WARNINGS AND PRECAUTIONS

- Intravitreal injections, including those with ILUVIEN, have been associated with endophthalmitis, eye inflammation, increased intraocular pressure, and retinal detachments. Patients should be monitored following the intravitreal injection.
- Use of corticosteroids including ILUVIEN may produce posterior subcapsular cataracts, increased intraocular pressure and glaucoma. Use of corticosteroids may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses. Corticosteroids are not recommended to be used in patients with a history of ocular herpes simplex because of the potential for reactivation of the viral infection.
- Patients in whom the posterior capsule of the lens is absent or has a tear are at risk of implant migration into the anterior chamber.

ADVERSE REACTIONS

- In controlled studies, the most common adverse reactions reported were cataract development (ILUVIEN 82%; sham 50%) and intraocular pressure elevation of ≥ 10 mm Hg (ILUVIEN 34%; sham 10%).

Please see brief summary of Prescribing Information on the following page. You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

[1]Deuchler SK, et al., Arch Clin Exp Ophthalmol. 2022 Mar 3. doi: 10.1007/s00417-022-05564-2. Epub ahead of print.

[2]Singer M, et al. Ophthalmology. 2022. doi: 10.1016/j.ophtha.2022.01.015. Online ahead of print.

Alimera

BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

ILUVIEN® (fluocinolone acetonide intravitreal implant) 0.19 mg
For Intravitreal Injection

INDICATIONS AND USAGE

ILUVIEN® (fluocinolone acetonide intravitreal implant) 0.19 mg is indicated for the treatment of diabetic macular edema in patients who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure.

CONTRAINDICATIONS

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

Glaucoma: **ILUVIEN** is contraindicated in patients with glaucoma who have cup to disc ratios of greater than 0.8.

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

WARNINGS AND PRECAUTIONS

Intravitreal Injection-related Effects: Intravitreal injections, including those with **ILUVIEN**, have been associated with endophthalmitis, eye inflammation, increased intraocular pressure, and retinal detachments. Patients should be monitored following the intravitreal injection.

Steroid-related Effects: Use of corticosteroids including **ILUVIEN** may produce posterior subcapsular cataracts, increased intraocular pressure and glaucoma. Use of corticosteroids may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses.

Corticosteroids are not recommended to be used in patients with a history of ocular herpes simplex because of the potential for reactivation of the viral infection.

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

ADVERSE REACTIONS

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

Adverse reactions associated with ophthalmic steroids including **ILUVIEN** include cataract formation and subsequent cataract surgery, elevated intraocular pressure, which may be associated with optic nerve damage, visual acuity and field defects, secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera.

ILUVIEN was studied in two multicenter, randomized, sham-controlled, masked trials in which patients with diabetic macular edema were treated with either **ILUVIEN** (n=375) or sham (n=185). Table 1 summarizes safety data available when the last subject completed the last 36-month follow-up visit for the two primary **ILUVIEN** trials. In these trials, subjects were eligible for retreatment no earlier than 12 months after study entry. Over the three-year follow-up period, approximately 75% of the **ILUVIEN** treated subjects received only one **ILUVIEN** implant.

Table 1: Ocular Adverse Reactions Reported by ≥1% of Patients and Non-ocular Adverse Reactions Reported by ≥5% of Patients

Adverse Reactions	ILUVIEN (N=375) n (%)	Sham (N=185) n (%)
Ocular		
Cataract[1]	192/235[2] (82%)	61/121[2] (50%)
Myodesopsia	80 (21%)	17 (9%)
Eye pain	57 (15%)	25 (14%)
Conjunctival haemorrhage	50 (13%)	21 (11%)
Posterior capsule opacification	35 (9%)	6 (3%)
Eye irritation	30 (8%)	11 (6%)
Vitreous detachment	26 (7%)	12 (7%)
Conjunctivitis	14 (4%)	5 (3%)
Corneal oedema	13 (4%)	3 (2%)
Foreign body sensation in eyes	12 (3%)	4 (2%)
Eye pruritus	10 (3%)	3 (2%)
Ocular hyperaemia	10 (3%)	3 (2%)
Optic atrophy	9 (2%)	2 (1%)
Ocular discomfort	8 (2%)	1 (1%)
Photophobia	7 (2%)	2 (1%)
Retinal exudates	7 (2%)	0 (0%)
Anterior chamber cell	6 (2%)	1 (1%)
Eye discharge	6 (2%)	1 (1%)

Table 1 (continued)

Adverse Reactions	ILUVIEN (N=375) n (%)	Sham (N=185) n (%)
Non-ocular		
Anemia	40 (11%)	10 (5%)
Headache	33 (9%)	11 (6%)
Renal failure	32 (9%)	10 (5%)
Pneumonia	28 (7%)	8 (4%)

[1] Includes cataract, cataract nuclear, cataract subcapsular, cataract cortical and cataract diabetic in patients who were phakic at baseline. Among these patients, 80% of **ILUVIEN** subjects vs. 27% of sham-controlled subjects underwent cataract surgery.

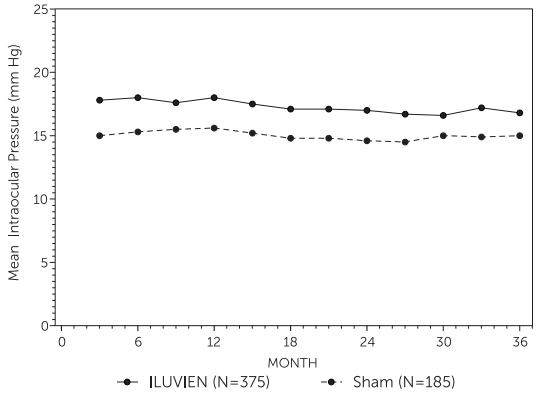
[2] 235 of the 375 **ILUVIEN** subjects were phakic at baseline; 121 of 185 sham-controlled subjects were phakic at baseline.

Increased Intraocular Pressure

Table 2: Summary of Elevated IOP-Related Adverse Reactions

Event	ILUVIEN (N=375) n (%)	Sham (N=185) n (%)
Non-ocular		
IOP elevation ≥ 10 mm Hg from baseline	127 (34%)	18 (10%)
IOP elevation ≥ 30 mm Hg	75 (20%)	8 (4%)
Any IOP-lowering medication	144 (38%)	26 (14%)
Any surgical intervention for elevated intraocular pressure	18 (5%)	1 (1%)

Figure 1: Mean IOP during the study



Cataracts and Cataract Surgery

At baseline, 235 of the 375 **ILUVIEN** subjects were phakic; 121 of 185 sham-controlled subjects were phakic. The incidence of cataract development in patients who had a phakic study eye was higher in the **ILUVIEN** group (82%) compared with sham (50%). The median time of cataract being reported as an adverse event was approximately 12 months in the **ILUVIEN** group and 19 months in the sham group. Among these patients, 80% of **ILUVIEN** subjects vs. 27% of sham-controlled subjects underwent cataract surgery, generally within the first 18 months (Median Month 15 for both **ILUVIEN** group and for sham) of the studies.

Post-marketing Experience: The following reactions have been identified during post-marketing use of **ILUVIEN** in clinical practice. Because they are reported voluntarily, estimates of frequency cannot be made. The reactions, which have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to **ILUVIEN**, or a combination of these factors, include reports of drug administration error and reports of the drug being ineffective.

USE IN SPECIFIC POPULATIONS

Pregnancy: Pregnancy Category C.
There are no adequate and well-controlled studies of **ILUVIEN** in pregnant women. Animal reproduction studies have not been conducted with fluocinolone acetonide. Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. **ILUVIEN** should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Systemically administered corticosteroids are present in human milk and could suppress growth and interfere with endogenous corticosteroid production. The systemic concentration of fluocinolone acetonide following intravitreal treatment with **ILUVIEN** is low. It is not known whether intravitreal treatment with **ILUVIEN** could result in sufficient systemic absorption to produce detectable quantities in human milk. Exercise caution when **ILUVIEN** is administered to a nursing woman.

Pediatric Use: Safety and effectiveness of **ILUVIEN** in pediatric patients have not been established.

Geriatric Use: No overall differences in safety or effectiveness have been observed between elderly and younger patients.

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ADVANCES IN AMD CARE

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DEPARTMENTS

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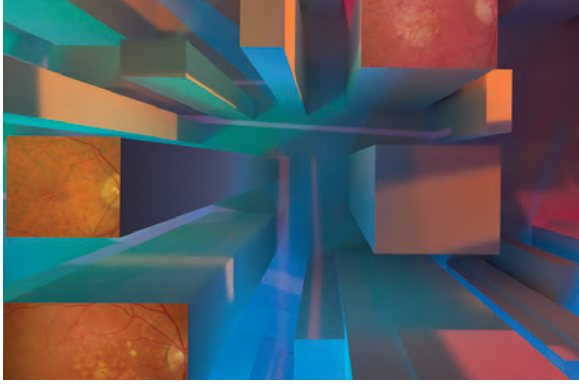

10-YEAR DATA SUPPORTS UTILITY OF REMOTE MONITORING

A recent study with 10 years of data shows that patients with dry AMD had better visual acuity at the time of conversion to wet AMD when they used a remote AMD monitoring system (ForeseeHome, Notal Vision) compared with standard in-office monitoring, according to a press release from Notal Vision.[1]

The retrospective study followed 2,123 dry AMD patients (3,334 eyes) who were monitored with the remote system for 10 years. Among these patients, median VA was 20/30, 20/39, and 20/32 at baseline, at conversion to wet AMD, and after an average of 2.7 years of treatment for those whose conversion was detected early, respectively.[2] By contrast, the AAO's IRIS Registry reports that the mean VA is 20/83 at the time of conversion to wet AMD for patients being monitored through in-office visits and patient self-reported symptoms, according to the press release.[1]

The remote monitoring system works by using a peripheral hyperacuity perimetry test that can detect small changes in retinal structure that may suggest conversion from dry to wet AMD. Patients can use ForeseeHome to perform the test remotely between regular appointments; the Notal Vision Monitoring Center receives the results and notifies the patient's physician of any abnormal findings that may require intervention.

Amid the recent buzz in AMD management, at-home monitoring is becoming yet another potential option to discuss with patients who may be at risk of converting to wet AMD.

1. Retrospective study covering 2,000 patients over 10 years using ForeseeHome AMD remote monitoring shows substantially better outcomes for patients [press release]. Notal Vision. April 26, 2022. Accessed May 10, 2022. www.globenewswire.com/news-release/2022/04/26/2429162/0/en/Retrospective-study-covering-2-000-patients-over-10-years-using-ForeseeHome-AMD-remote-monitoring-shows-substantially-better-outcomes-for-patients.html
2. Mathai M, Reddy S, Elman MJ. Analysis of the long-term visual outcomes of ForeseeHome remote telemonitoring: the ALOFT study. Preprint. Published online April 25, 2022. *Ophthalmol Retina*.

NEW LCA THERAPY SHOWS EARLY PROMISE

Results of a phase 1b/2 clinical trial published in *Nature Medicine* show that sepofarsen, an RNA antisense oligonucleotide targeting a specific variant in the *CEP290* gene, met its primary endpoint for manageable safety profile and secondary endpoint for preliminary efficacy in the treatment of Leber congenital amaurosis type 10 (LCA10).[1]

In the open-label, multicenter, 12-month trial, 11 patients (five adult and six pediatric) received at least four intravitreal injections of sepofarsen in their worse-seeing eye. Six of 11 patients received the 160 µg/80 µg dose, and the other five received the 320 µg/160 µg dose.

Ten patients experienced ocular adverse events in their treated eye, as well as one patient in their untreated eye (5/6 with 160 µg/80 µg vs 5/5 with 320 µg/160 µg). Eight eyes developed cataracts, and six cases were categorized as serious and required lens replacement (2/3 with 160 µg/80 µg vs 4/5 with 320 µg/160 µg). Once the 160 µg/80 µg dose was found to have the superior risk-benefit profile, the higher doses were either discontinued or not started.

In addition to these safety data, a post-hoc analysis showed clinically meaningful improvements in BCVA (-0.3 logMAR) on either the Early Treatment of Diabetic Retinopathy Study vision chart or the Berkeley Rudimentary Vision Test in five of 11 patients (45%), and seven patients (64%) experienced BVCA improvements of at least -0.2 logMAR.[1]

The authors concluded that these findings suggest the value of continuing to develop sepofarsen as a potential treatment for LCA10.

1. Russell SR, Drack AV, Cideciyan AV, et al. Intravitreal antisense oligonucleotide sepofarsen in Leber congenital amaurosis type 10: a phase 1b/2 trial. Preprint. Published online April 4, 2022. *Nat Med*.

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WET AMD EYE

ANTI-VEGF

Therapy yields better long-term VA results when wet AMD detected with good VA[1]

FELLOW EYE

20/79 VA

Mean VA of fellow eyes at wet AMD diagnosis according to real-world data[1]

Over 60% of wet AMD "fellow eyes" lose too much vision[1]– even with frequent treatment visits

Detect Early. Treat Early.

ForeseeHome is a **remote monitoring** program for at-risk wet AMD fellow eyes that helps **detect conversion** at 20/40 or better in 83% of patients.[2]

- FDA Cleared
- Medicare Covered

ForeseeHOME™
AMD Monitoring Program

Introduce your patients to ForeseeHome during an injection visit and offer them an extra level of protection.

Our Monitoring Center works with your staff to easily implement an "inject and protect" protocol into your practice workflow that requires minimal effort or additional time.

The Key to Successful Home Monitoring

NOTAL VISION MONITORING CENTER

- Engagement & Education
- Benefits Verification & Authorization
- Continuous Monitoring

NOTAL VISION™
Monitoring Center

- Practice Workflow Implementation
- Remote Patient Management
- Vision Alert Management

References: 1. Ho AC, Kleinman DM, Lum FC, et al. Baseline Visual Acuity at Wet AMD Diagnosis Predicts Long-Term Vision Outcomes: An Analysis of the IRIS Registry. *Ophthalmic Surg Lasers Imaging Retina*. 2020;51:633-639. **2.** Real-World Performance of a Self-Operated Home Monitoring System for Early Detection of Neovascular AMD (ForeseeHome device), presented by Allen Ho, American Society of Retina Specialist Meeting 2020.

See website for FDA Indication for Use.

SM-125.2

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DME TREATMENT RECEIVES EUROPEAN COMMISSION APPROVAL

Last month, Novartis announced that its treatment for diabetic macular edema, 6 mg brolucizumab (Beovu), was approved by the European Commission.

This decision was based on 1-year data from two phase 3 clinical trials showing noninferior BCVA gains with use of the investigational drug compared with 2 mg aflibercept (Eylea, Regeneron). In each trial, the initial loading phases consisted of five intravitreal injections 6 weeks apart; after this phase, more than 50% of the patients in each trial were able to remain on a 12-week dosing interval for 1 year.[1]

"With the potential to address unmet needs, this approval is significant for people living with [diabetic macular edema (DME)], many of whom are of working age and struggle with adherence due to the need to manage multiple comorbidities related to diabetes," explained Novartis in an email to *Retina Today*. The approval is an important step toward lightening the treatment burden for some patients.

1. Novartis announces European Commission approval of Beovu for people living with diabetic macular edema [press release]. Novartis. March 31, 2022. Accessed May 10, 2022. www.novartis.com/news/media-releases/novartis-announces-european-commission-approval-beovu-people-living-diabetic-macular-edema

INVESTIGATION OF DME AMONG MINORITY POPULATIONS UNDERWAY

Genentech/Roche recently announced the launch of its phase 4, multicenter, open-label, single-arm Evelatum clinical trial to evaluate the use of faricimab (Vabysmo, Genentech/Roche) for the treatment of DME specifically in underrepresented racial/ethnic patient populations.[1]

The goal of the study is to better understand how patients in certain racial/ethnic groups respond to treatment with the recently-approved bispecific antibody. Historically, clinical trials have posed barriers to participation for minority patients. Although it is well-known that diabetes affects Black, Hispanic, Latinx, and Indigenous individuals more frequently, placing them at a higher risk of developing DME, these racial/ethnic groups have been underrepresented in clinical trials of DME and in medical research broadly.

"We designed the Elevatum study to specifically address this issue and evaluate treatment response to Vabysmo in patients with DME from underrepresented patient populations," said Manuel Amador, MD, medical director at Genentech/Roche who is helping to lead the study, in an email to *Retina Today*.

Results from the trial are expected in 2024.

1. National Institutes of Health. A study to investigate faricimab treatment response in treatment-naive, underrepresented patients with diabetic macular edema (ELEVATUM). Clinicaltrials.gov. May 2, 2022. Accessed May 10, 2022. clinicaltrials.gov/ct2/show/NCT05224102?term=NCT05224102&draw=2&rank=1

GEOGRAPHIC ATROPHY ASSOCIATED WITH HIGH EMOTIONAL BURDEN

Vision loss due to geographic atrophy (GA) can have serious effects on emotional and mental health, according to the results of a recent global survey conducted by The Harris Poll and sponsored by Apellis.[1] The Geographic Atrophy Insights Survey results indicate that individuals with GA often experience significant negative effects in their everyday lives, as well as gaps in knowledge about the disease.

The survey included 203 adults with GA across nine countries. Most respondents reported that their visual decline has affected their independence and quality of life in worse ways than they expected (68%); that they must rely on a caregiver for support (70%); and that their ability to perform functions of daily life such as driving (95%), reading (96%), and traveling (88%) have been negatively affected. A large proportion also reported emotional burdens such as feelings of anxiety (46%), powerlessness (39%), and frustration (33%), and 35% reported withdrawing from social activities for reasons related to their condition.

The survey also revealed a need for improved education about GA; in fact, 76% of respondents believed their vision loss was a part of natural aging before receiving a diagnosis, and 91% reported a desire to be provided with more information relevant to their disease.

Potential Therapy on the Horizon

There's promising news from Apellis for these patients. This year at ARVO, the company announced detailed and longer-term data from the phase 3 DERBY and OAKS trials of intravitreal pegcetacoplan showing continued safety and efficacy at 18 months for the treatment of patients with GA.

Each trial individually showed a significant reduction in the growth of extrafoveal and foveal lesions with both monthly and every-other-month intravitreal injections of pegcetacoplan. In a combined analysis of the two clinical trials, treatments given monthly and every-other-month reduced extrafoveal lesion growth by 26% ($P < 0.0001$) and 21% ($P = 0.0006$), respectively, and reduced foveal lesion growth by 13% in each treatment group ($P = 0.0070$ and $P = 0.0069$, respectively).[2]

The 18-month data also continue to show favorable safety and tolerability, according to the press release.[2] The company plans to submit a new drug application to the FDA in the second quarter of 2022. ■

1. Apellis announces results from new global survey conducted by the Harris Poll revealing the emotional burden and impact on independence caused by geographic atrophy (GA) [press release]. Apellis. April 21, 2022. Accessed May 10, 2022. investors.apellis.com/news-releases/news-release-details/apellis-announces-results-new-global-survey-conducted-harris

2. Apellis announces detailed 18-month results from phase 3 DERBY and OAKS studies of pegcetacoplan for geographic atrophy (GA) at ARVO annual meeting [press release]. Apellis. May 2, 2022. Accessed May 10, 2022. investors.apellis.com/news-releases/news-release-details/apellis-announces-detailed-18-month-results-phase-3-derby-and

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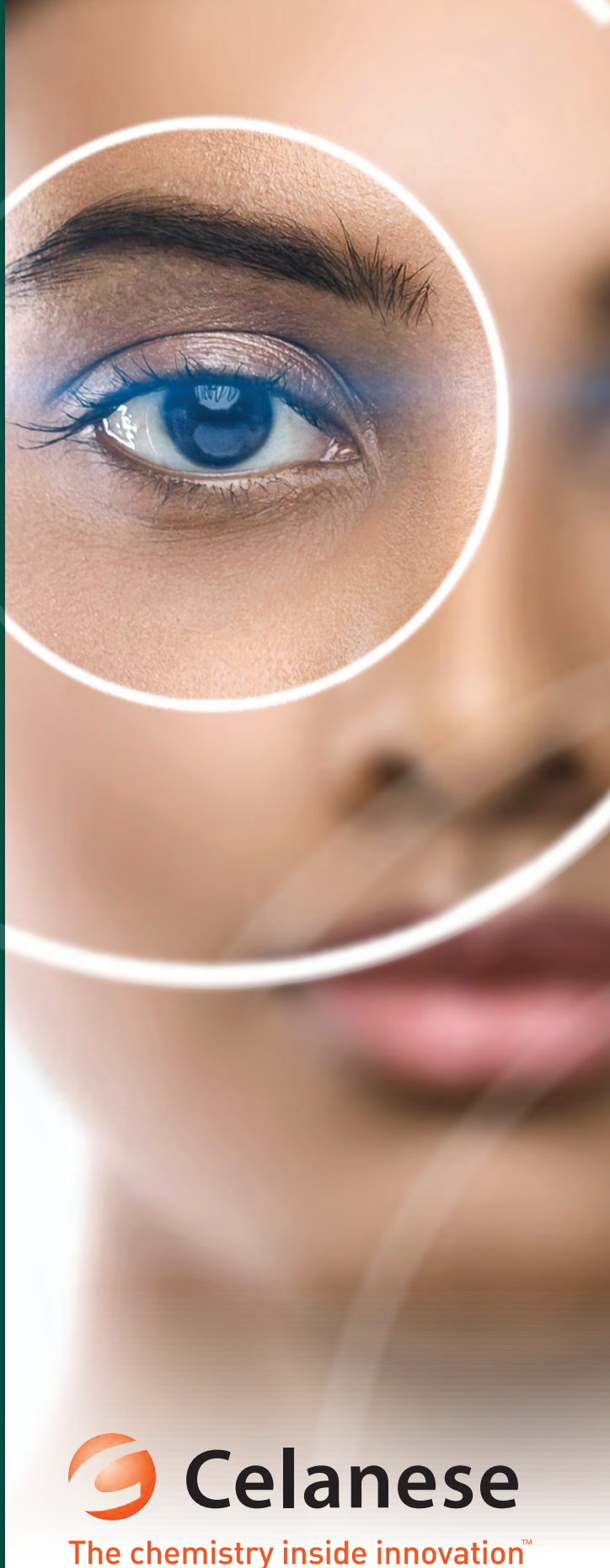

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ARVO HOT TAKES

With so much cutting-edge research rolling out of ARVO, it's hard to keep up. Here, we summarize some of the newest data presented in Denver, April 30 to May 12, 2022.

- After evaluating Medicare reimbursements for 20,730 ophthalmologists (75.8% men) between 2013 and 2019, researchers at Harvard Medical School and Tufts University School of Medicine discovered that women receive lower reimbursements than men—$20,239.80 less, to be exact, after adjusting for covariates such as years of experience, location, and socioeconomics. In addition, women performing vitreoretinal surgery earn 0.27 cents for each dollar earned by men, the researchers found.[1]
- A poster presentation showed that patients with polypoidal choroidal vasculopathy (PCV) type choroidal neovascularization treated with OPT-302 (Opthea Limited) in combination with ranibizumab (Lucentis, Genentech/Roche) experienced an additional 6.7-letter gain compared with patients treated with ranibizumab monotherapy. Jason Slakter, MD, a clinical professor in the Department of Ophthalmology at NYU Grossman School of Medicine, presented the poster, which concluded that more patients with PCV gained ≥ 10 and ≥ 15 letters from baseline, or achieved a VA of at least 20/40.[2]
- Using Ora's Variable Contrast Flicker test, researchers found that patients with early and intermediate AMD had significantly higher contrast thresholds for the intermediate flicker rate (between 10-20 Hz) at low- and high-mesopic background luminance levels, suggesting impairment. The poster, presented by John Rodriguez, PhD, director of the Ora Retina Institute, concluded that such a repeatable test over time may become a reliable, reversible functional endpoint for future clinical trials.[3] Ora also shared data on its Reading Passages test, which showed that participants with early and intermediate AMD had reading speed impairment that correlated with contrast (ie, the lower the contrast, the more significant the reading speed impairment).[4]
- Several posters shared data on the recently approved suprachoroidal triamcinolone acetonide injectable suspension (Xipere, Bausch + Lomb), including findings that suggest the new treatment provides significant improvements in BCVA and central subfield thickness, regardless of baseline disease characteristics, for patients with macular edema associated with uveitis.[5]
- A retrospective cohort analysis of patients with GA who were followed for 3 years in clinical practice found that the rate of vision loss was similar regardless of whether lesions were nonsubfoveal or subfoveal at baseline. The poster, presented by M. Ali Khan, MD, also noted that eyes that began the study with good vision lost more letters over the 3-year period compared with eyes with poor vision at baseline. In addition, within 1 year, 20% of study eyes may no longer meet BCVA eligibility criteria for driving—which increased to 35% at year 3.[6]
- Researchers have discovered detectable but severely dysfunctional photoreceptors in the central and midperipheral retina of patients with Leber congenital amaurosis (LCA5-LCA), which points to potential targets for gene augmentation. Subretinal delivery of a novel gene therapy, AAV8-hLCA5, in nonhuman primates revealed the therapy was safe at 1E10 vg with mild inflammation at 1E11 vg, providing guidance for the dosing in future trials.[7]
- To help differentiate choroidal nevi from melanomas, a team of investigators in Zurich used multimodal imaging (fundus photography, OCT, autofluorescence, and ultrasonography) with visual acuity assessment to create a risk score; patients with an increased cumulative score should be referred to ocular oncologists, the poster concluded.[8]
- A survey of participants in a mentorship program for underrepresented minority (URM) premedical undergraduate students showed that the program increased interest in ophthalmology by 90%, in medicine generally by 83%, and in research by 68%. The poster concluded that the program, initially launched at Massachusetts Eye and Ear during the COVID-19 pandemic, may serve as a model for other institutions.[9] ■

1. Halawa O, Sekimitsu S, Boland M, Zebardast N. Gender-based differences in Medicare reimbursements among ophthalmologists persist across time. Paper presented at ARVO; May 3, 2022; Denver, Colorado.
2. Slakter JS, Coleman H, Wykoff CC, et al. Efficacy and safety of OPT-302 in combination with ranibizumab for polypoidal choroidal vasculopathy. Poster presented at ARVO; May 1, 2022; Denver, Colorado.
3. Gherghel D, Bensinger E, Dieter KC, Rodriguez J, Wallstrom G, Abelson MB. Variable contrast flicker in patients with non-advanced age-related macular degeneration: results from the 3rd year follow-up. Poster presented at ARVO; May 1, 2022; Denver, Colorado.
4. Dusharm M, Bensinger E, Dieter KC, Rodriguez J, Wallstrom G, Abelson MB. A novel test of low contrast reading in non-advanced age-related macular degeneration: a potential functional endpoint for clinical trials. Poster presented at ARVO; May 1, 2022; Denver, Colorado.
5. Singer M, Kapik B, Ciulla T. Suprachoroidal triamcinolone acetonide injectable suspension for macular edema associated with uveitis: effect of disease characteristics on clinical outcomes. Poster presented at ARVO; May 3, 2022; Denver, Colorado.
6. Retrospective cohort analysis of patients with geographic atrophy (GA) secondary to age-related macular degeneration followed for 3 years in clinical practice. Poster presented at ARVO; May 1, 2022; Denver, Colorado.
7. Margaritis P, Bennett J, Chomistek S, et al. Preparation for a gene therapy trial for LCA5-associated retinal degenerations: treatment potential in patients and dose-ranging studies in non-human primates. Poster presented at ARVO; May 4, 2022; Denver, Colorado.
8. Zweifel S, Geiger F, Said S, et al. Assessing choroidal nevi, melanomas and indeterminate melanocytic lesions using multimodal imaging – a retrospective chart review. Poster presented at ARVO; May 1, 2022; Denver, Colorado.
9. Bannerman A, Lu E, Bryant D, Miller J. Creating a mentorship, research, and virtual shadowing program for underrepresented minority undergraduates during COVID-19. Poster presented at ARVO; May 2, 2022; Denver, Colorado.

THE GREAT VBS ABSTRACT ROUNDUP

The 2022 scientific posters teemed with research that pushed attendees to reassess some of their clinical approaches.

BY SHIVANI V. REDDY, MD

The 10th annual Vit-Buckle Society (VBS) meeting was the bee's knees. The 2022 Great Gatsby-themed event, which had many of us seeing each other in person for the first time in 2 years, roared like the 20s. The sessions and exhibit hall exploded with VBS energy. New surgical techniques, management of rare cases, wild clinical videos, and truly addressing diversity in ophthalmology and retina were at the forefront of this year's meeting.

The scientific poster session followed this trend, with projects shedding light on a variety of topics, from diversity and inclusion to rare dystrophies. Here's a look at what this year's scientific poster winners brought to the party (Figure).

RESIDENT WINNER: YUXI ZHENG, MD

The pathologic vitreomacular interface remains a mystery and raises a host of unanswered questions. How long do we monitor patients with vitreomacular adhesion (VMA) and vitreomacular traction (VMT)? Which patients will have release? Can we predict visual outcomes? Why won't the posterior hyaloid just let go? Zheng et al used OCT to analyze 328 eyes with VMA and 263 eyes with VMT and found that, in cases of VMA, increased time to release was significantly associated with the presence of posterior hyaloid membrane hyperreflectivity (PHMH) and vitreofoveal interface hyperreflectivity (VIH). A decreased rate of VMT release was associated with PHMH, increased central subfield thickness (CST), and cystoid retinal changes. Factors associated with worse visual acuity included inner retinal surface disturbances, ellipsoid zone disruption, and cystoid changes; however, no difference in visual acuity was found after 3 months. They concluded that OCT characteristics indicating stronger tractional forces (PHMH and VIH) or ongoing traction (CST and cystoid changes) were associated with a decreased rate of vitreomacular separation, longer time to VMA/VMT release, and short-term poorer visual acuity in VMT.

FELLOW WINNER: ADITYA BANSAL, DNB

In a world where single-surgery success in rhegmatogenous retinal detachment (RRD) repair is all-important, the idea of retinal displacement, or low-integrity retinal attachment (LIRA), pushes us to think beyond anatomic indicators of success and more deeply consider quality of vision post-reattachment surgery in our surgical planning. Multimodal imaging, especially fundus autofluorescence (FAF), is an important tool to integrate this metric into clinical practice.

Bansal et al assessed the sensitivity and specificity of FAF imaging when used for LIRA detection following RRD repair. This retrospective review of eight patients included infrared (IR) images before and after RRD occurrence and FAF images post-RRD repair. Using OCT software, they marked at least four corresponding retinal pigment epithelium (RPE) and choroidal landmarks on all IR images and created pre- and post-RRD repair image overlays using a python code to align the images and compute a homography. They used the patients' contralateral normal eyes to validate the technique, and all contralateral images had perfect alignment. Using IR overlay images as the standard, FAF showed 78.6% sensitivity and 100% specificity when detecting LIRA. However, the IR overlays detected a far greater extent of retinal displacement compared with FAF. They found IR overlay imaging to be a better qualitative and quantitative measure of retinal displacement and suggested that lower sensitivity may be the reason for variability across LIRA studies that use FAF.

MEDICAL STUDENT WINNER: LUKE NELSON, BS

This project sheds light on the potential pathophysiology of Stargardt disease. The mutated ABCA4 protein, an adenosine 5'-triphosphate (ATP)-binding cassette transporter implicated in Stargardt disease, has long been thought to be localized to the photoreceptor outer segments (POS). The defective ABCA4 protein in these photoreceptors leads to a downstream accumulation of degenerative byproducts in the RPE, causing RPE dysfunction and photoreceptor loss. Although researchers know that ABCA4 is present in the RPE, its function in the visual cascade is not well-defined.

Nelson et al aimed to understand the colocalization of ABCA4 in the RPE cells and characterize its movement following exposure to the lab-created POS regimen. The team used healthy donor fibroblasts reprogrammed to induced pluripotent stem cells (iPSCs) that were differentiated into RPE cells. After they cultured the iPSC-RPE cells, the researchers studied the ABCA4 localization within these

VIT-BUCKLE SOCIETY

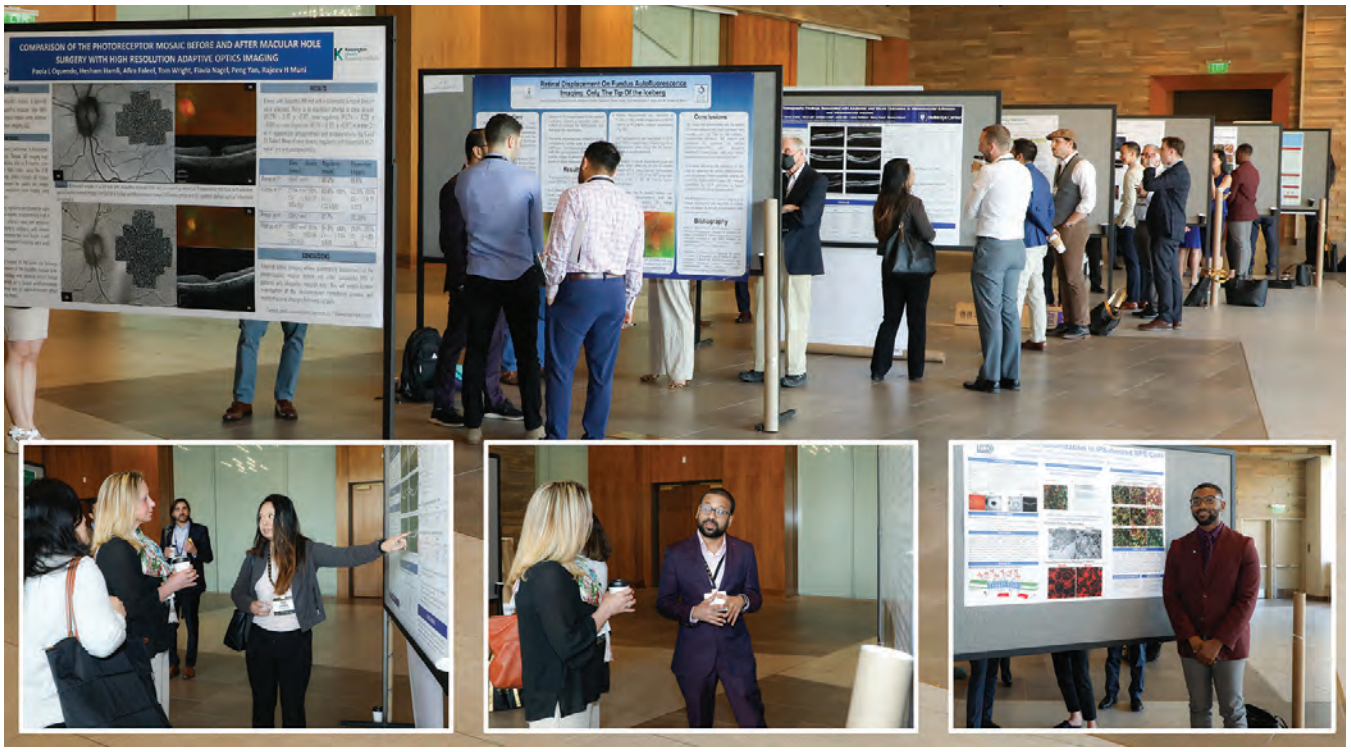

Figure. The 2022 VBS scientific poster presenters were available throughout the meeting and had enriching discussions with the conference attendees. The winners were (insets left to right) Yuxi Zheng, MD; Aditya Bansal, DNB; and Luke Nelson, BS.

cells in unfed (30 minutes) and fed (4 hours) POS conditions. They found that ABCA4 transitions from the apical membrane to the subcellular after exposure to POS. On the apical side, ABCA4 colocalizes with the sodium-potassium pump (Na-K ATPase) via immunostaining. They also found that ABCA4 colocalizes with RAB5, RAB7, and caveolin-1 at different timepoints. These findings provide a more detailed understanding of the functional role of ABCA4 in the RPE cells and its contribution to visual processing.

POSTER SNAPSHOTS

Brinson et al studied disparities in eye care usage across vision impairment and diabetes status in the United States from 2010 to 2018. They found that older patients with diabetes, females, and patients of Asian and White races were more likely to use eye care. They also found eye care usage was overall steadily increasing among patients with diabetes.

Diaz et al presented a nontraumatic hyperoxic retinopathy model in mice to study the formation of tractional retinopathy and preretinal membranes in retinal detachments (RD). They found that oxygen fluctuations can lead to an upregulation of myofibroblast progenitor cells, contributing to the development of preretinal membranes and RDs.

Hucko et al used self-reported data to study the trends in racial and ethnic diversity of US allopathic residency programs from 2011 to 2019. They found that the increase in the number of underrepresented minority residents has not kept pace with the demographic changes in the United States. More efforts are needed to address the persistent lack of representation for racial and ethnic minorities.

Watane et al presented results of a retrospective review of surgical techniques and complications of IOL exchanges, a case series of scleral-sutured enVista MX60 (Bausch + Lomb) dislocations, and a structural integrity study of lens eyelets and haptic-optic junctions. They found a simple-pass suture allowed for greater force on MX60 eyelets before fracture compared with the cow-hitch suture. Yamane scleral-fixated IOLs were associated with the greatest tilt, while iris-sutured IOLs had the highest subsequent dislocation. The haptics of the CT Lucia three-piece IOL (Carl Zeiss Meditec) required 2.8x greater force to break than the MX60 haptics.

Venincasa et al presented a survey study exploring the impact of COVID-19 on resident perceptions of their training and personal lives. After surveying 193 applicants to the Bascom Palmer residency program between 2016 and 2019, the authors noted a significant impact on surgical and clinical ophthalmic training during the pandemic. Residents also reported personal stressors such as worsened friendships with fellow residents and increased time away from family.

Rahman et al presented a retrospective review of six patients treated with low-dose oral methotrexate (MTX) as a preventative measure against proliferative vitreoretinopathy (PVR). Patients with RD with high-risk characteristics for

(Continued on page 45)

RT Retina Today ONE TO Watch

AVNI P. FINN, MD, MBA

Please share with us your background.

I was born in London and moved to Claremont, California, when I was young. I went to college at Stanford University where I earned my Bachelor of Arts in Human Biology with a minor in Spanish. I have always been interested in science, with a particular interest in health care policy and international health. This led me to working in health care policy for a year before realizing that I really needed be face-to-face with patients, so I applied to medical school.

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

As a resident at the Mass Eye and Ear Infirmary, some of the most challenging cases I saw, both medical and surgical, were tackled by vitreoretinal surgeons. I saw them as the "last stop" eye surgeons. If there was a complicated surgery or a unique systemic manifestation, it usually involved a retina specialist. This was both intimidating and intriguing as a resident. As my examination and surgical skills developed, it became less intimidating and more exciting. I knew vitreoretinal surgery would be challenging yet very fulfilling—no surgery is the same and there is an art to treating each patient.

Who are your mentors?

I have been very fortunate in my training to have many excellent mentors; they have instilled in me a passion for retina and have contributed to helping me succeed within our field. To mention a few: Joan W. Miller, MD; Dean Eliott, MD; Glenn J. Jaffe, MD; Cynthia A. Toth, MD; Lejla Vajzovic, MD; and Sharon Fekrat, MD. Mentorship, however, doesn't just end in training. I know I will continue to find surgeons and friends who will provide support and mentorship.

Describe your current position.

I am an assistant professor at the Vanderbilt Eye Institute where I practice vitreoretinal surgery and am involved in clinical care, research, and teaching on a daily basis. I work with residents and fellows in my clinic and in the OR. Working with trainees keeps me on my toes—you get to see things through a different set of eyes and figure out how to best teach skills to others. As a surgeon, this has me continuously evolving my techniques. My research endeavors are focused on big data and imaging to better understand biomarkers of surgical retinal disease in the hopes that this can guide visual prognosis and surgical decision making.

What has been the most memorable experience of your career thus far?

One of the most memorable experiences of my career was discussing a new surgical technique in clinic, putting it into practice in the OR, and seeing the surgical success with improved vision for a patient. This was a unique internal limiting membrane flap that my team and I planned for a difficult myopic macular hole case, which we called the "internal limiting membrane retracting door" technique. I performed this surgery during my fellowship with Tamer Mahmoud, MD, PhD, and we subsequently published our technique in *Retina*.[1] I think of this case often, as it epitomizes surgical innovation and how we can do better for our patients.

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

Attend meetings, remain curious, and collaborate with your colleagues. Focusing on these three things has been really fulfilling for me and can create new opportunities. ■

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- Financial disclosure: Advisory Board (Allergan/AbbVie, Genentech/Roche); Consultant (Apellis Pharmaceuticals)

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A CASE OF MEWDS FOLLOWING COVID-19 INFECTION

Research on post-COVID-19 cases of this white dot syndrome may lend insight into its pathogenesis and the work-up of COVID-19 patients with visual symptoms.

BY TRAVIS PECK, MD; OBADAH MOUSHMOUSH, MD; AND ARTHI VENKAT, MD

Multiple evanescent white dot syndrome (MEWDS) is a typically acute-onset, unilateral syndrome that manifests with decreased vision, scotomas, photopsias, or a combination of all three. On fundoscopy, numerous gray, white, or yellow-white dots can be seen at the level of the outer retina or retinal pigment epithelium, most often in the posterior pole. A mild anterior chamber reaction and vitritis may also be noted in some patients. The etiology remains unclear, and no hereditary predilection has been reported; however, the syndrome most commonly affects healthy women from 15 to 50 years of age.[1] When there is suspicion for MEWDS, multiple imaging modalities can help elucidate the syndrome. For example, fluorescein angiography (FA) can reveal a wreath-like pattern of punctate, hyperfluorescent dots, as well as late-leakage and staining of the optic nerve head.

Approximately one-third of patients with MEWDS report a viral prodrome prior to onset of visual symptoms. The underlying pathogenesis of MEWDS may involve an immune response to viral antigens that have gained access to the retinal receptor cells. In the literature, there has been one case report of atypical MEWDS following infection with COVID-19, as well as multiple case reports of MEWDS following COVID-19 vaccination.[2] Here, we report a case of MEWDS shortly after infection with COVID-19 and review the literature surrounding MEWDS and other retinal conditions related to COVID-19.

CASE REPORT

A previously healthy 28-year-old White male patient presented to the retina clinic with a 1-week history of blurred peripheral vision in his left eye. He stated that everything was fuzzy in a specific area of his temporal visual field. Ocular history was remarkable for myopia, and medical history was unremarkable other than COVID-19 infection 2 weeks prior to the onset of his visual symptoms. He reported cough, chills, and myalgias for approximately 4 days while infected.

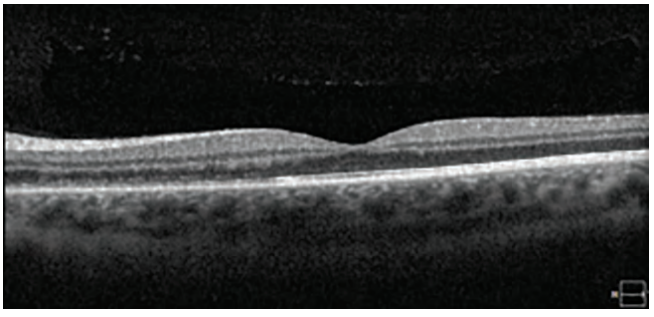

Figure 1. At presentation, the patient's left eye OCT revealed attenuation at the levels of the ellipsoid and interdigitation zones nasally.

On examination, VA was 20/20 OU. There was no afferent pupillary defect, and IOP and visual fields were within normal limits in each eye. Anterior segment examination was unremarkable; notably, there was no anterior chamber inflammation in either eye. Fundoscopic examination revealed subtle deep, yellow lesions in the peripapillary retina of the left eye. OCT demonstrated attenuation of the ellipsoid and interdigitation zones in the nasal macula (Figure 1). Fundus autofluorescence (FAF) revealed a wreath-like configuration of hyperfluorescence around the optic nerve with numerous noncontiguous, smaller areas of hyperfluorescence throughout the macula and midperipheral retina (Figure 2). FA also demonstrated a confluent area of hyperfluorescence centered around the optic nerve, which increased in intensity in the later frames, consistent with staining (Figure 3).

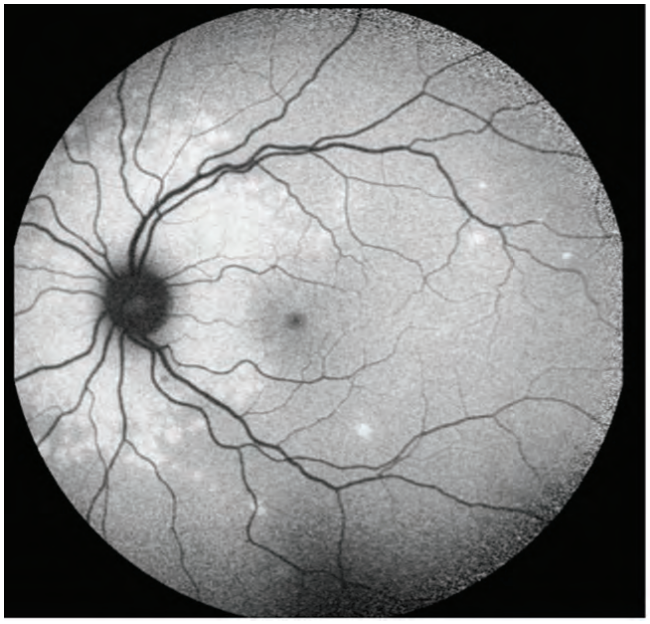

Figure 2. On initial presentation, the left eye demonstrates a ring of circumpapillary hyperautofluorescence and surrounding, scattered smaller foci of hyperautofluorescence on FAF.

Differential Diagnosis

The differential diagnosis included infectious etiologies, such as syphilis and tuberculosis (TB), and inflammatory causes, such as sarcoidosis. The outer retinal findings were suspicious for white dot syndromes, such as MEWDS or acute posterior multifocal placoid pigment epitheliopathy (APMPPE). Workup included rapid plasma reagin, Treponema pallidum antibody, and TB testing with QuantiFERON Gold (Qiagen), which were negative. Complete blood count and comprehensive metabolic panel were also unremarkable.

Management and Follow-up

The patient was monitored off therapy and instructed to return in 1 week. Upon follow-up, he felt that his symptoms had worsened, and imaging revealed slight progression of the previously described findings. Given the negative infectious workup and progression of his symptoms and findings, he was started on 60 mg oral prednisone daily and given instructions to taper by 10 mg weekly.

At follow-up 11 days later, the patient reported a decrease in his peripheral scotoma in the left eye and improved vision. Examination showed a decrease in the prominence and number of the deep retinal yellow lesions. At 2 months, OCT demonstrated reconstitution of the ellipsoid zone, and FAF showed a decrease in the size and intensity of the hyperfluorescence (Figure 4). He was advised to continue the planned prednisone taper.

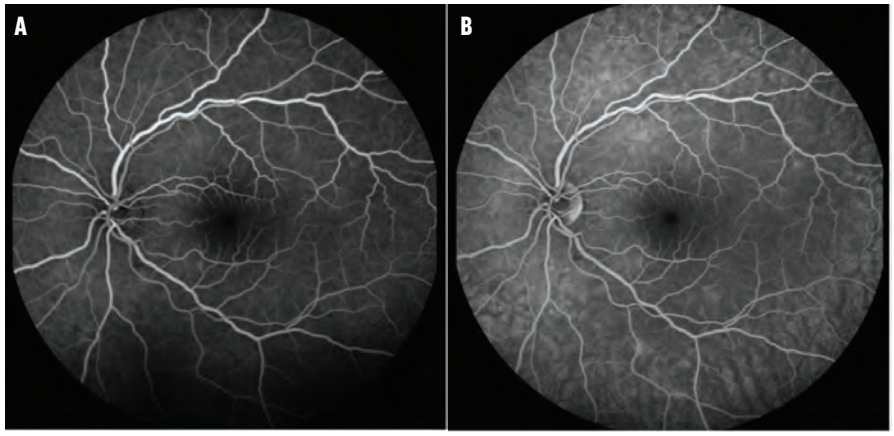

Figure 3. Peak (A) and late (B) phase FA at initial presentation in the left eye demonstrate circumpapillary hyperfluorescence with smaller hyperfluorescent lesions throughout the macula, corresponding to the areas seen on autofluorescence.

DISCUSSION

MEWDS is an uncommon, typically unilateral condition that is most often seen in young myopic women.[3] Our patient's unilateral, temporal photopsias with hyperfluorescent dots in a wreath-like configuration on fundus examination and FAF; focal loss of the ellipsoid zone on OCT following a known viral infection; and negative infectious/inflammatory workup were consistent with a MEWDS diagnosis. APMPPE was considered less likely given the small size of the peripapillary lesions, presence of hyperfluorescent (rather than hypofluorescent) lesions on early-phase FA, and unilateral presentation.

Two competing theories have been postulated as to the pathogenesis of MEWDS. Gass et al suggested that a virus invades photoreceptors through cell-to-cell transmission after entering through either the ora serrata or optic disc margin.[4] The authors suggested that symptoms manifest following loss of retinal receptor function secondary to a delayed host immune response to the invading virus.

Jampol et al suggested that MEWDS may be a discrete autoimmune disease that manifests in patients with specific genetic loci that are susceptible to environmental triggers, rather than a direct invasion of the virus.[5] Discerning the correct pathophysiology may shed light on the management of MEWDS.

Currently, no intervention is recommended in the management of MEWDS, with complete resolution expected in several weeks following diagnosis. In prolonged cases or those with more significant vision loss, systemic corticosteroids are often employed.[3] A prednisone taper was trialed in our patient due to subjectively worsening vision and photopsias. Our patient improved symptomatically after starting prednisone; however, it is unclear if his improvement was a result of the medication or the natural history of the disease. Steroid response may

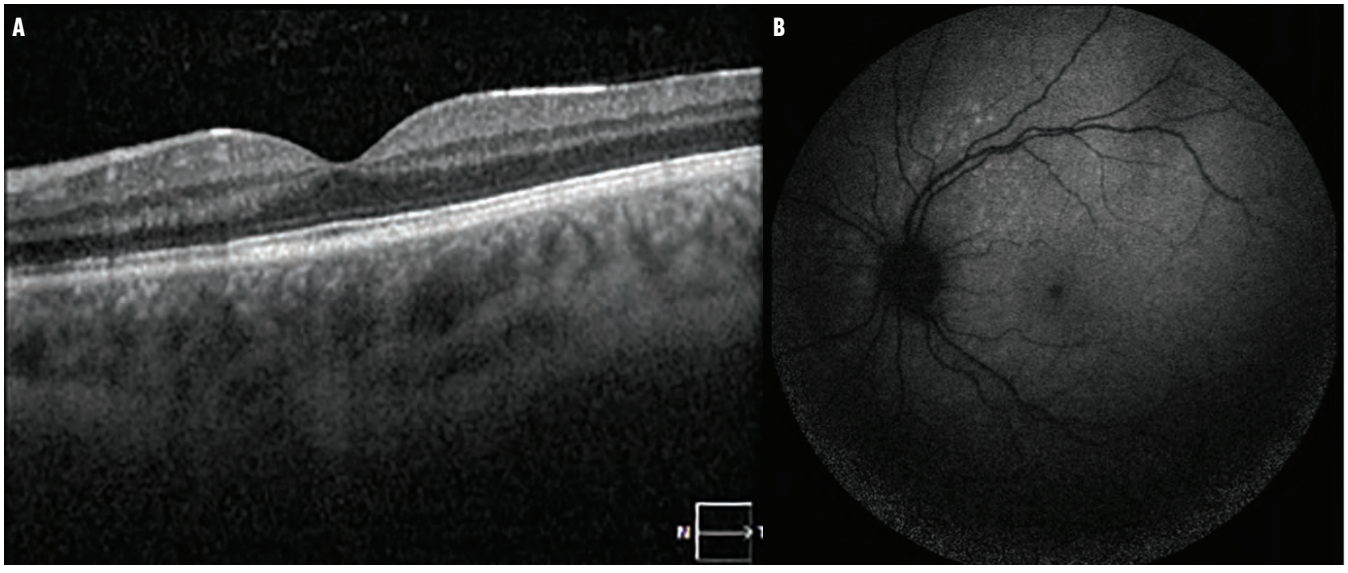

Figure 4. At the 2-month follow-up, the left eye presented with reconstitution and partial recovery of the ellipsoid zone on OCT (A), as well as decreased intensity of hyperautofluorescence on FAF (B).

favor an autoimmune pathophysiology for MEWDS. Further research is needed to analyze whether COVID-19 causes MEWDS through direct invasion or secondary to triggering an autoimmune process.

COVID-19 INVOLVEMENT

Several cases of MEWDS have been reported following the first and second doses of COVID-19 vaccination.[6,7] However, there is only one other reported case of MEWDS after COVID-19 infection.[2] This unusual case, reported by De Salvo et al, occurred 2 weeks following infection, and intermediate phase ICGA revealed multiple hyperfluorescent lesions rather than the typical hypofluorescent lesions seen in MEWDS.[2] The authors argue that because COVID-19 has unprecedented effects throughout the body, it is not surprising to have unusual retinal findings in post-COVID-19 MEWDS. Although we did not obtain ICGA, the findings on multimodal imaging were classic for MEWDS in our case.

In our case and that of De Salvo et al, there was a 2-week period between symptomatic COVID-19 infection and onset of visual symptoms. Both patients also experienced clinical worsening for the first week after diagnosis. It may be that post-COVID-19 MEWDS initially follows a more progressive course; therefore, clinicians should not consider worsening symptoms to be incompatible with a diagnosis of MEWDS in cases of recent COVID-19 infection.

Other retinal changes following COVID-19 infection have been identified, including hyperreflective lesions at the level of the ganglion cell and inner plexiform layers, as well as cotton-wool spots and microhemorrhages along the retinal arcade.[8] Ocular manifestations, such as chemosis, epiphora, and conjunctival hyperemia, have been reported in as many as 31.6% of patients presenting with COVID-19 infection.[9] Numerous uveitis cases have been reported following COVID-19 vaccination.[6,10] Further research on the association between both the virus and vaccination with MEWDS may clarify the pathogenesis of this ocular complication. ■

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TACKLING PEDIATRIC OPTIC DISC PIT MACULOPATHY

An internal limiting membrane plug can help improve visual acuity quickly.

BY ROSA L. PINHEIRO, MD; FILIPE HENRIQUES, MD; JOÃO FIGUEIRA, PHD; MÁRIO ALFAIATE, MD; AND JOAQUIM N. MURTA, PHD

An optic disc pit is a congenital malformation that can cause decreased visual acuity due to an accumulation of intraretinal and/or subretinal fluid (SRF). Because clinical onset of optic disc pit maculopathy is uncommon in children, there is no standard surgical approach apart from pars plana vitrectomy (PPV).[1] Many authors have described various techniques, concluding that sealing the pit leads to a faster improvement of visual acuity, including for pediatric cases.[2,3] Rapid visual recovery is important, especially for children younger than 12 years of age who are at risk of developing amblyopia. Three cases of pediatric optic disc pit maculopathy with and without internal limiting membrane (ILM) plugging, along with a review of the literature, highlight the benefits of each surgical technique.

CASES

The first case involved a 14-year-old boy diagnosed with optic disc pit maculopathy with a VA of 20/400 OD due to macular detachment. A 23-gauge PPV was performed, followed by an incomplete posterior vitreous detachment (PVD) due to strong vitreoretinal adhesion. Low-fluence argon endolaser photocoagulation was applied to the temporal edge of the optic disc. After fluid-air exchange, the vitreous cavity was filled with 14% C_3F_8. SRF gradually decreased over the following months, and 3 years later, the patient attained a VA of 20/20 OD.

Ten years after the initial presentation, the patient was scheduled for a second surgery due to VA worsening to 20/63 OD and recurrence of macular detachment. During reoperation, we removed a portion of the residual posterior hyaloid and used a free ILM piece to fill the pit; the remaining ILM flap was inverted over the pit. After fluid-air exchange, we filled the eye with 15% SF_6. One month later, there was no SRF on spectral-domain OCT (SD-OCT), and VA improved to 20/40 OD over 15 months.

The second case involved a 15-year-old boy with optic disc pit maculopathy in his left eye. Preoperative VA was 20/63 OS. The patient underwent 23-gauge PPV with PVD. We peeled the ILM, used a free ILM flap to plug the optic pit, and filled the eye with 15% SF_6. Four months after surgery, there was complete macular reattachment. VA improved to 20/25 OS and was stable until last follow-up 4 years after the intervention.

The third case involved a 13-year-old girl with optic disc pit maculopathy and VA of 20/50 OD due to a large macular detachment. We performed PPV and PVD and used a free ILM flap to fill the pit. After fluid-air exchange, we filled the vitreous cavity with 20% SF_6 (Video). Three months postoperatively, VA reached 20/25 OD and SRF progressively disappeared over 9 months (Figure). Two years later, visual acuity and macular integrity remained stable.

DISCUSSION

In the cases described above, each patient experienced significant improvements in visual acuity, but those who underwent ILM plugging experienced a faster visual recovery. In the first case, reoperation with the ILM plugging technique resulted in rapid resolution of SRF, as previously described,[4] despite insufficient recovery of visual acuity. One explanation for recurrent SRF in the first patient could be the incomplete PVD due to strong vitreoretinal adhesion, a common intraoperative finding in pediatric patients.

Endolaser photocoagulation was performed in the first patient without complications, and other surgeons have reported successful treatment with endolaser in children.[5] Nevertheless, there is a risk of damaging the papillomacular bundle, and there are reports of effective surgical treatment without endolaser in pediatric patients.[6]

TABLE. PEDIATRIC PATIENTS WITH OPTIC DISC PIT MACULOPATHY WHO UNDERWENT SURGERY, INCLUDING SEALING OF THE PIT

First Author (Year of Publication)	Patient Age (Years)	Initial VA	Surgical Technique	Final VA	Time To Full Recovery (Months)
Muftuoglu et al (2021)[1]	9	20/50	23-gauge PPV + PVD + air-PFCL exchange + C_3F_8	20/32	11
	14	20/200	23-gauge PPV + PVD + air-PFCL exchange + C_3F_8	20/125	25
D'Souza et al (2021)[2]	16	20/125	PPV + PVD + fovea-sparing ILM peeling + ILM plug + 20% SF_6 or 14% C_3F_8	20/63	< 12
	11	20/125	PPV + PVD + fovea-sparing ILM peeling + ILM + 20% SF_6 or 14% C_3F_8	20/40	< 12
Babu et al (2020)[3]	14	20/63	25-gauge PPV + PVD + ILM peeling + SRF drainage + ILM plug + SF_6	20/40	< 12
	16	20/63	25-gauge PPV + PVD + ILM peeling + SRF drainage + ILM plug + SF_6	20/63	< 12
	17	20/80	25-gauge PPV + PVD + ILM peeling + SRF drainage + ILM plug + SF_6; postoperative macular hole	20/63	< 12
	16	20/63	25-gauge PPV + PVD + ILM peeling + SRF drainage + scleral plug + SF_6	20/63	< 12
Pastor-Idoate et al (2019)[4]	8	20/200	23-gauge PPV + inverted ILM plug + endolaser + 12% C_3F_8	20/200	6
	12	20/50	23-gauge PPV + endolaser + ILM plug + 12% C_3F_8	20/20	13
Dhiman et al (2019)[5]	15	< 20/400	PPV + ILM peeling + ILM plug	> 20/80	< 9
Nadal et al (2015)[6]	18	20/40	PPV + PVD + autologous platelet concentrate plug + 15% C_3F_8	20/25	< 72
	15	20/200	PPV + PVD + autologous platelet concentrate plug + 15% C_3F_8	20/63	12
	13	20/200	PPV + PVD + autologous platelet concentrate plug + 15% C_3F_8	20/40	< 144
Travassos et al (2013)[7]	15	20/200	Clear lens extraction + 25-gauge PPV + SRF drainage; reoperation with SRF drainage + homologous scleral tissue flap filling of the pit + 14% C_3F_8	20/40	24
	11	< 20/400	25-gauge PPV + SRF drainage + homologous scleral tissue flap filling of the pit + 14% C_3F_8	20/200	12

Abbreviations: ILM, internal limiting membrane; PFCL, perfluorocarbon liquid; PVD, posterior vitreous detachment; PPV, pars plana vitrectomy (23- or 25-gauge); SRF, subretinal fluid.

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For each ILM plugging procedure, there were no surgical complications, but these can include mechanical damage and toxicity of different materials to the optic nerve fibers and formation of macular holes after ILM peeling.[2,3,7] The latter can be avoided with fovea-sparing ILM peeling.

Studies have found that vitrectomy is the only surgery with proven benefit in the management of optic disc pit maculopathy,[1,8] and others conclude that sealing the pit hastens visual recovery even if it does not lead to better results.[9]

Several materials have been used to plug the pit, including scleral autograft, fibrin sealant, amniotic membrane, and autologous platelets. ILM is a good option because it does not cause inflammation and it is already in place. Peeling of the ILM can ensure complete hyaloid removal and eliminate traction. ILM can act as a scaffold for the proliferation of Müller cells and consequential gliosis, further contributing to the barrier.[7]

In a literature review, we found 16 pediatric patients with optic disc pit maculopathy who underwent surgery that included plugging of the pit (Table). VA improved to at least 20/63 in 12 cases; the children who did not achieve a VA of at least 20/63 had a preoperative VA of 20/200 or worse, two

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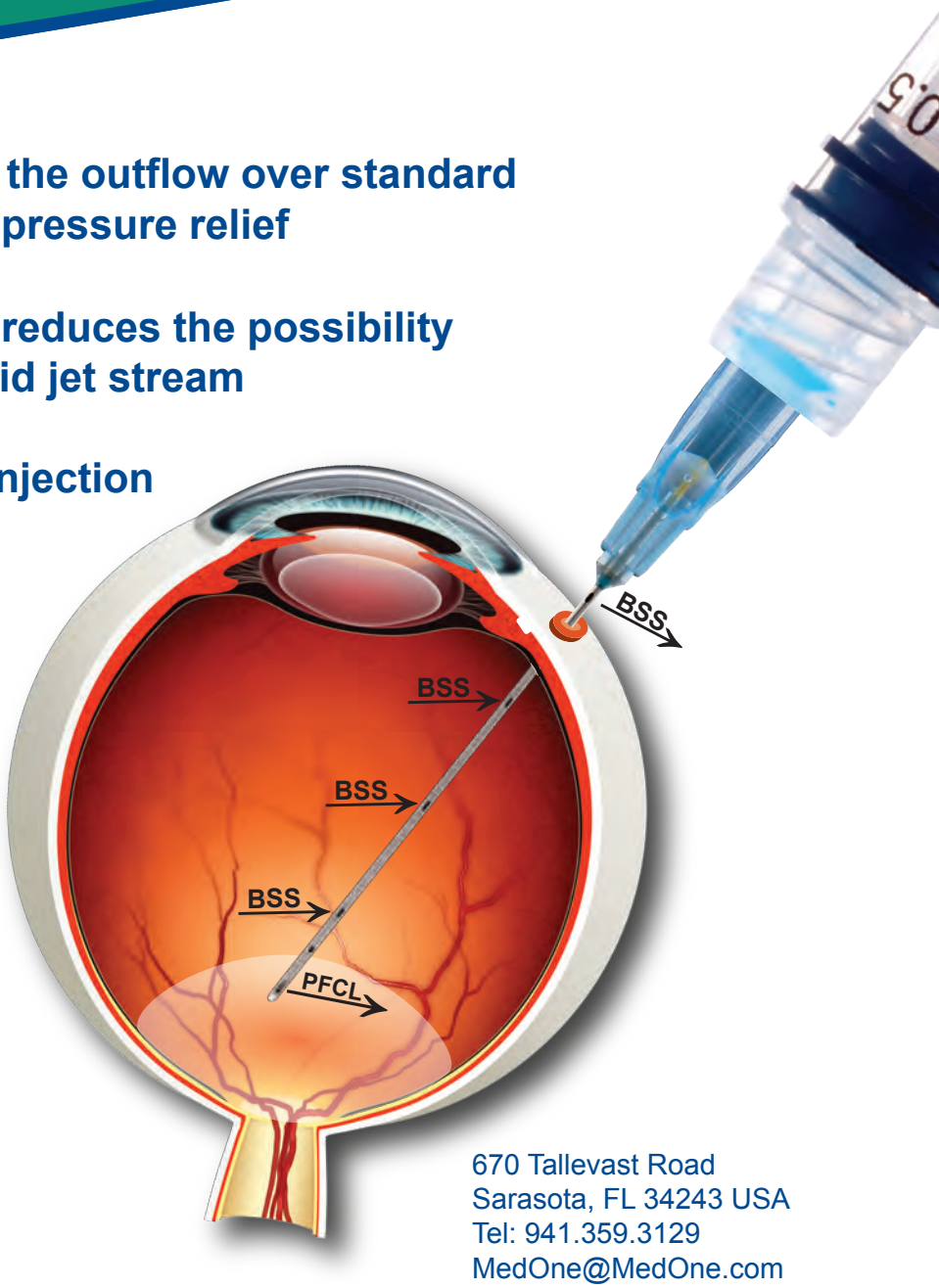

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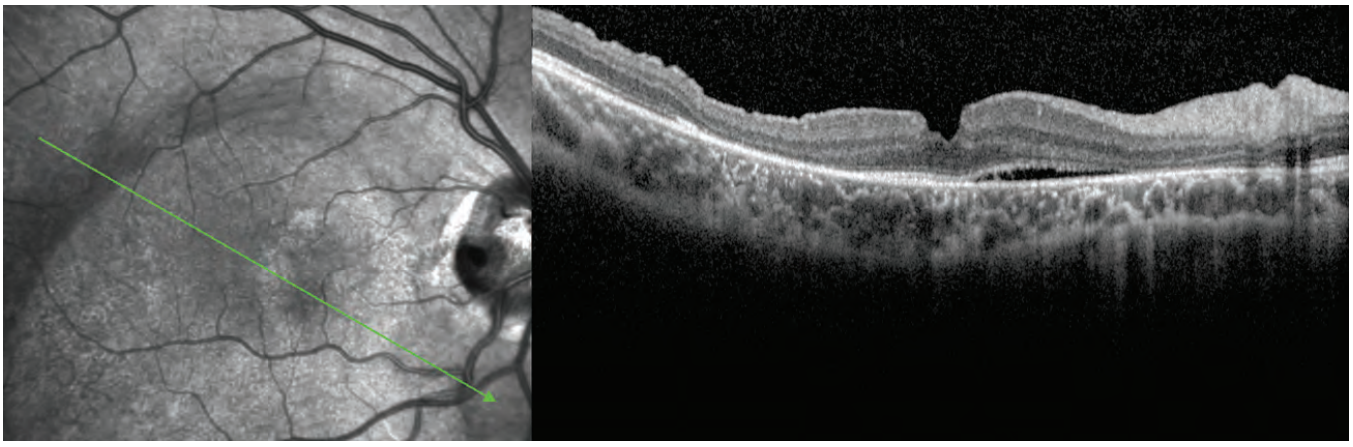

Figure. SD-OCT B scan of the third patient (13-year-old girl) 9 months after surgery, showing almost complete macular reattachment, except for a line of subretinal fluid.

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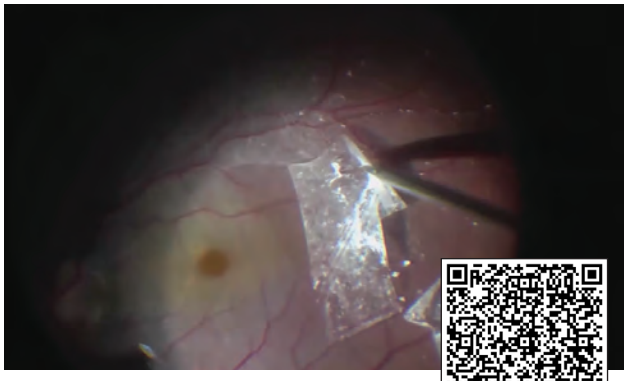

Video. Surgical Technique for Pediatric Optic Disc Pit Maculopathy

of whom were younger than 12 years and may have already developed amblyopia. Twelve of 16 patients achieved their best postoperative visual acuity within 13 months.

TAKE-HOME

Childhood onset of optic disc pit maculopathy is rare, and few studies focus on surgical management in this population. ILM plugging and use of other materials to seal the pit are effective adjuncts to vitrectomy and may lead to faster visual acuity recovery, but further reports on treatment of optic disc pit maculopathy in children are warranted. ■

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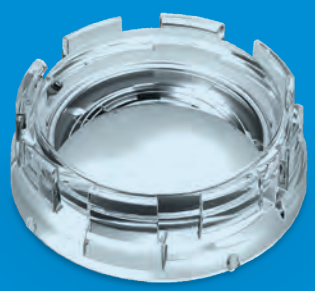

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INTEGRATING NEW AMD THERAPIES INTO THE CLINIC

Experts weigh in on how the growing armamentarium will affect patient care.

A DISCUSSION WITH ROBYN GUYMER AM, MBBS, PHD, FRANZCO, FAHMS; CHARLES C. WYKOFF, MD, PHD; AND DIANA V. DO, MD; MODERATED BY ALLEN C. HO, MD




Anti-VEGF therapy, a staple in our clinics for 16 years now, has been transformational for patients with conditions such as wet AMD, diabetic retinopathy (DR), diabetic macular edema (DME), retinal vein occlusion, and myopic choroidal neovascularization. We are now on version 2.0 as we move into more durable therapies, more mechanisms of action, and combination therapies. But how are we going to use these new therapies in our practices? To answer that question, I sat down with some of the best and brightest medical and surgical retina specialists to share their perspectives and pearls.

- Allen C. Ho, MD

DR. HO: HOW DO YOU THINK THE NEW THERAPIES WILL FIT INTO YOUR ARMAMENTARIUM FOR WET AMD?

Robyn Guymer AM, MBBS, PhD, FRANZCO, FAHMS: Faricimab (Vabysmo, Genentech/Roche) adds an extra choice to our standard options, and it will fit in nicely. We will likely use it in a treat-and-extend protocol and start with cases that are currently being treated but for whom we haven't been able to extend past 8 weeks.

Recent experience with other new treatments is likely to make us a little bit more hesitant now, so I don't think we will change everyone over immediately. In Australia, we will be fortunate to have real-world experience from the United States before we are able to start with these new treatments, which will hopefully be later this year or early next year.

The port delivery system (PDS) with ranibizumab (Susvimo, Genentech/Roche) is very different because it requires surgical intervention. In Australia, many AMD patients are treated by a medical retina specialist like myself, so we will have to figure out how to manage patients back and forth with our vitreoretinal colleagues and who will do the refills moving forward. Medical retina specialists don't want to hand over the care of these patients, so it will be interesting to see how we manage this change. The PDS won't be for every patient with wet AMD; as with faricimab, it's likely we will start with those who aren't able to extend.

AT A GLANCE

- The panelists speculate that most clinicians will recommend the new longer-duration therapies first to AMD patients who have been unable to extend treatment beyond 8 weeks on their current anti-VEGF therapy.
- Even though the port delivery system refill-exchange usually occurs at 6-month intervals, routinely following patients is still necessary to watch for disease activity and because there is a higher risk of endophthalmitis with the device.
- The success of any geographic atrophy therapy will hinge on patient selection and education because many patients may cease treatment if they do not perceive any benefit.

DR. HO: DIANA, YOU ARE A VITREORETINAL SURGEON AND A MEDICAL RETINA SPECIALIST; HOW WILL THESE THERAPIES FIT INTO YOUR TOOLBOX?

Diana V. Do, MD: Office-based therapies will remain my first choice because they are convenient for the patient and offer immediate treatment. As for the PDS, it's the first wet AMD treatment in more than 15 years to provide an alternative to our current standard of care office-based intravitreal injections. The PDS with ranibizumab continuously delivers medicine into the eye through a refillable implant, and it may help people with wet AMD maintain their vision with as few as two treatments per year, which is unheard of with our standard of care. The phase 3 Archway clinical trial showed that refill-exchanges of the PDS every 6 months sustained vision compared with eyes that received monthly ranibizumab (Lucentis, Genentech/Roche).[1]

Even though the refill usually occurs at 6-month intervals, routinely following patients is still necessary and important because there is a higher risk of endophthalmitis with the PDS. In the clinical trials, there was almost a threefold higher rate of endophthalmitis in eyes that received the PDS compared with those that received intravitreal ranibizumab injections.[2] The PDS is a foreign device placed in the pars plana and covered by the Tenon's and conjunctiva. The surgery must be done very precisely to prevent the risk of conjunctival retraction or erosion, which would expose the implant to potential harmful bacteria.

DR. HO: PERHAPS THAT THREEFOLD RISK WILL BE MITIGATED AS WE EVOLVE THE SURGICAL TECHNIQUE. CHARLIE, CAN YOU GIVE US SOME PEARLS?

Charles C. Wykoff, MD, PhD: It's valuable to have additional tools in our toolbox, and it's fantastic from a patient perspective to have more choices and a highly differentiated approach to wet AMD management. For clinicians, I recommend being aware of the options and educating patients on your perception of the benefits and risks of each. Even if you are reluctant to use the PDS because of the safety profile and associated boxed warning included on the package insert, it's important that your patients at least hear of it and hear your perspective; it's better that they learn about it from you than from someone else.

Meticulous attention to the surgical technique—in the OR when implanting the device and during the in-office refill-exchange—is crucial to optimize the local anatomy and minimize risks of side effects associated with the device. The specific details of the procedure are extremely well-defined by the manufacturer. We have evolved the surgical technique substantially over time and may continue to do so by incorporating past learnings. The two most important points to appreciate during the implantation are to deeply respect conjunctiva and Tenon's capsule manipulation and make the scleral incision length exactly 3.5 mm and not any larger.

Dr. Ho: Those are great pearls from someone who has done a lot of PDS implantations, and many clinicians have probably had their patients ask about this procedure. I tell patients that the current safety profile is evolving and that it requires a trip to the OR. We do our patients a service by discussing the option—it's just good practice.

DR. HO: HOW ARE YOU GOING TO FOLLOW PATIENTS, AND TO WHOM ARE YOU GOING TO OFFER THE DEVICE?

Dr. Wykoff: We are still learning which patients are the best candidates. I have been fortunate to be able to implant a lot of these devices and have been actively managing dozens of patients with the PDS for years at this point. In my experience, most patients who do not have any adverse events are extremely happy with it, and it is highly effective. Before the phase 2 and 3 data were available, I was skeptical that a protein placed at body temperature would maintain biological activity for months to years; but the trials have clearly demonstrated that ranibizumab maintains activity for many months after implantation and refill-exchanges. For most, the efficacy demonstrated through the phase 2 Ladder trial, the phase 3 Archway trial, and the long-term extension study of wet AMD patients has been remarkably strong.

While the protocol in the phase 3 program is to perform refill-exchanges every 6 months, based on the phase 2 data it appears that many patients may be able to achieve the same clinical outcomes while receiving refill-exchange far less frequently. Among the PDS patients I am managing outside of clinical trials, I am using a treat-and-extend approach.

DR. HO: AS FOR VABYSMO, I WAS A LITTLE DISAPPOINTED THAT THIS DUAL MECHANISM DIDN'T IMPROVE EFFICACY. MAYBE THERE IS SOME SIGNAL OF DURABILITY, BUT WERE YOU A LITTLE SURPRISED BY THE EFFICACY?

Dr. Wykoff: That's an understandable perspective. The phase 3 trials used very strong control arms with fixed 8-week dosing of Eylea (aflibercept, Regeneron) after the monthly loading doses. From an efficacy perspective, noninferiority with aflibercept was achieved with faricimab in both DME and wet AMD with an indication of differentiated durability with faricimab, with about 78% of patients at every 12- or 16-week dosing in the DME program at the end of 2 years in the personalized treatment interval arms. More directly relevant to clinical practice, though, is that in the DME trials, many of the OCT-based anatomic outcomes assessing fluid status favored faricimab, including change in central subfoveal thickness, the proportion of patients

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A LOOK AT SHORT-PULSE LASER TO SLOW PROGRESSION OF INTERMEDIATE AMD

Commentary by Robyn Guymer AM, MBBS, PhD, FRANZCO, FAHMS

We conducted the Laser in Early Stages of AMD (LEAD) study, which used a nanosecond laser to target intermediate AMD.[1] In a post hoc analysis, we found that most patients with intermediate AMD, those without reticular pseudodrusen, who had this laser treatment every 6 months for 3 years experienced a significant slowing of their progression compared with those who had reticular pseudodrusen, which was a quarter of the intermediate AMD patients at baseline. Overall, there was no difference, but when we subdivided patients into those two groups, there was a significant difference. There is something important we still need to know about reticular pseudodrusen, which we currently don't understand.

Remember that nanosecond laser is different from traditional thermal laser; it does not damage the neural retina. The concept is that the short-pulse laser rejuvenates the retinal pigment epithelium either through cell division, which certainly happens in animal models, or through cell rejuvenation. It also appears that you can detect changes in the peripheral blood, indicating an immune response, after laser, which may bring about a bilateral effect of a unilateral treatment. We don't know all the mechanisms of laser therapy, but it seems the nanosecond laser triggers a local effect as well as a systemic immune response.

We are working with the regulatory authorities to conduct another study in the United States and internationally. The problem is the trial design around an endpoint. Ideally an intermediate AMD trial would follow cases longitudinally to an earlier endpoint of the beginning of atrophy, but currently this endpoint is not accepted. In LEAD, we enrolled patients with intermediate AMD and tried to stop the development of nascent GA (nGA), the OCT sign of early cell death. We know that nGA has a 78-fold increased risk of GA;[2] thus, if we can stop nGA, we can stop GA, but for registration we have to prove that we can stop GA. That means a very long and large study.

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achieving central subfoveal thickness < 325 µm, and the proportion of patients achieving absence of intraretinal fluid.

In clinical practice, this improved drying capacity may translate to better outcomes. My hope is that once we get into the real world where patients, on average, do not receive every-other-month dosing, a more durable agent may translate into a more sustained visual benefit.

Dr. Guymer: Also, the faricimab trial was somewhat artificial in that after a certain number of weeks, patients were split into 16-, 12-, or 8-week treatment arms, and once they were in these categories, they had to stay there. In the real world, we change the regimen based on how the patient is doing. Thus, in terms of efficacy, we may see better results in the real world when we can change the interval depending on response. In addition, the true benefit may well come in the medium term, as we know that many patients continue to lose vision in the real world, and results don't match the clinical trials. Part of the loss of vision is because of the development of atrophy and fibrosis. The hope is that, with an anti-VEGF and an anti-angiopoietin-2, there may be an opportunity to have persistent good vision, which we don't currently see in our real-world outcomes.

DR. HO: SPEAKING OF ATROPHY, WHAT ARE YOU TELLING YOUR PATIENTS ABOUT THE APELLIS PROGRAM FOR GEOGRAPHIC ATROPHY (GA)?

Dr. Do: It is exciting that we have new therapeutic options potentially coming to the clinic for GA. Many of these clinical trials are investigating complement inhibitors, and pegcetacoplan is being evaluated in the phase 3 DERBY and OAKS clinical trials. These pivotal trials are looking at whether this intravitreal C3 inhibitor, given every month or every 8 weeks, could slow the progression of atrophy. One of the clinical trials met the primary endpoint, but the second trial did not.

The sponsor is continuing to follow these study patients through 18 months and beyond to determine if the benefits seen in the phase 2 clinical trial bear out with longer follow-up in this pivotal trial study population. The challenge with these complement inhibitors is that they cannot reverse the atrophy that has already happened. Thus, the goal is not to improve vision, but to slow down the expansion of the atrophy area, and that will make adherence to a frequent administration protocol a challenge for our patients. It will be hard to motivate our patients to come back for monthly or bimonthly treatment because they will not be experiencing an improvement in vision.

DR. HO: CHARLIE, HOW DO YOU THINK THIS GA THERAPY WILL BE USED IN PRACTICE IF IT IS APPROVED?

Dr. Wykoff: Patients who present with vision loss from an exudative retinal disease like DME and wet AMD typically notice an improvement in visual function following treatment. GA is a completely different situation. Even though *we* understand that vision is not going to improve with treatment, it is going to be very hard to communicate this

to patients regardless of what we say because patients are hopeful by nature. We can tell them their vision is not going to get better, but they will still be disappointed when it does not improve after a few shots. It's going to be a challenge to maintain consistent dosing, and our current data suggests that long-term, repeated therapy is going to be necessary to maximize the benefit. Patient education will be critical to long-term success.

These treatments are a start, an important step forward, and I hope these products receive regulatory approval. There are many patients who are motivated to initiate treatment. We must start somewhere, and I'm hopeful that next-generation therapies will be even better.

Dr. Guymer: I agree that it's going to be an individual patient discussion because it's not clear who will take to this therapy. What is useful is the concept of fovea-threatening GA, and we must find a way to define it because I can't imagine the authorities are going to pay for everybody to get treatment for GA. The question is, who would we suggest to start treatment? I would, for example, recommend treatment for a patient who has atrophy that is threatening the fovea within, say, the next 2 years, if we could predict that. Thus, we should be following patients now as we anticipate treatment, so that we can show patients their own change over time, which will likely help predict when their central vision is going to be threatened.

For example, if you have a few years of prior imaging to show change over time, it's going to be easier to educate and discuss with patients as to whether they are good candidates for treatment. I encourage our colleagues to start taking fundus autofluorescence images if possible, or OCT, so that we can have that conversation with the individual patients. As a profession, we would like to start before there is cell loss, and once these agents get approved, there will be patients who will want to start earlier and earlier.

But the trial design makes it hard to start trials earlier in the disease process. We have been very active in trying to identify and define OCT signs of the first evidence of cell loss. Even though these signs may not be regulatory-approved endpoints, at least companies can start doing early-phase studies to see which drugs and techniques to take forward.

DR. HO: ANY LAST THOUGHTS FROM THE PANEL?

Dr. Do: I'm thrilled to be in the field of ophthalmology and retina, because there is so much innovation here; just in the past year we have two new FDA-approved therapies for wet AMD. I'm excited to educate patients about them and start using them for certain patients. In the future, I'm hopeful that we will address some of our unmet needs with the novel molecules in early-stage clinical trials.

Dr. Guymer: Fancy being in a field where we have been able to reduce the rate of legal blindness in more than half of our population with wet AMD. Any treatment for atrophic AMD will be a huge step forward. We will get better at the delivery of the treatment, but we have to start somewhere.

Dr. Wykoff: It's great to have new opportunities and tools in the toolbox. Looking down the pipeline, I believe that we will continue to see innovation and improved options for patients. There are many promising agents currently in phase 2 trials exploring new molecular pathways.

It's important that we communicate with patients the value of maintaining optimal outcomes with current treatments today so that they can reap the benefits of the next-generation treatments that are going to be even better tomorrow.

Dr. Ho: We are in a very rich ecosystem of pharmacologic, biologic, and device options all focused on doing better for patients. We are lucky that patients value vision because many of these treatments are not inexpensive. Vision is one of the most important aspects of a patient's health, particularly for aging patients and working-age diabetics. ■

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THE BIOSIMILAR MARKET: WHAT YOU NEED TO KNOW

Understanding the development process may be fundamental to determining how to integrate these therapies into your clinical practice.

BY REBECCA HEPP, EDITOR-IN-CHIEF; REVIEWED BY SUSAN BRESSLER, MD

Anti-VEGF therapy, the mainstay for many retinal diseases commonly seen in a retina practice, can prevent additional vision impairment and restore visual function for many patients with wet AMD, diabetic retinopathy, and macular edema from retina vein occlusion (RVO). Today's approved agents—ranibizumab (Lucentis, Genentech/Roche), aflibercept (Eylea, Regeneron), and brolucizumab (Beovu, Novartis)—dominate the retina therapeutic market, with ranibizumab sales topping $1.6 billion in 2020 in the United States, and aflibercept approaching $5 billion. Not only that, but the anti-VEGF market remained steady despite the COVID-19 pandemic and a dip in clinic visits.[1]

Such numbers also highlight how pricy anti-VEGF therapy can be. Thus, several companies are working on biosimilars to compete with these originator biologics. In late 2021, the FDA approved the country's first biosimilar in the ophthalmic space, ranibizumab-nuna (Byooviz, Samsung Bioepis/Biogen) for the treatment of wet AMD, macular edema following RVO, and myopic choroidal neovascularization.

At least 11 other anti-VEGF biosimilars are in various stages of clinical research, setting the stage for a significant shift in how retina specialists treat patients in need of anti-VEGF injections.[2] This article details the growth of the biosimilar market, the differences between an originator biologic and its biosimilar, and what it all means for treating patients.

WHAT'S DIFFERENT

Biologics, generics, and biosimilars each have their own development pathways and research approaches (see *The Regulatory Pathway: Biologics Versus Biosimilars*). Understanding the similarities and differences between originator biologics and biosimilars will help clinicians make informed decisions about how best to integrate biosimilar products in their patient populations. The entire biosimilar ecosystem involves novel scientific development and legislation, considering biologics (other than vaccines) only appeared in 1982 and the FDA didn't approve the first biosimilar agent until 2015.[3,4]

A biologic is a genetically engineered protein that is derived from human genes; those genes are expressed in cell lines that are being asked to produce a large protein. Each biologic has a unique manufacturing process within a living cell line. Researchers first identify the gene sequence that codes for the desired protein and then find an appropriate vector to insert the gene into a cell. The final drug substance has unique biophysical characteristics that may be altered during a detailed manufacturing process.

Because it's a living system, any given biologic may change over time, creating within-product lot-to-lot variation. In practice, this means a vial of aflibercept manufactured in 2022 may be different from a vial of aflibercept manufactured 1 or 2 years ago. Thus, when a biologic is approved

AT A GLANCE

- A biosimilar is a large molecule considered highly similar (not identical) to the originator biologic.
- Researchers speculate that, between 2020 and 2024, the US health care system could save an estimated $100 billion by using biosimilars as compared to the originator biologics.
- The question of biosimilar adoption within the US ophthalmic community may not ultimately be the clinicians' choice; payers will likely lead the way as a cost-saving measure.

by the FDA, it's approved for certain indications and its manufacturing process to limit within-product variation.

The entire development process for an originator biologic, the reference product, takes 10 to 15 years and anywhere between $1.2 and $2.5 billion.[5]

When creating a generic drug, the chemical formula for the original small-molecule drug is in the public domain, and the manufacturer can chemically synthesize an identical twin. A generic drug does not have to be tested for safety or efficacy; developers only must show that it is a bioequivalent agent in healthy volunteer humans. Developing a generic drug takes 3 to 5 years and an investment of approximately $1 to $5 million.[5]

A biosimilar, however, is a large molecule that is considered highly *similar* (not identical) to the originator biologic. The manufacturer must demonstrate that a proposed biosimilar is comparable in terms of its physiochemical properties, pharmacokinetic behavior in humans, and pharmacodynamics; a biosimilar must have similar immunogenicity, safety, and efficacy. This is no small feat, considering the complicated development steps for a biologic are not in the public domain—only the gene sequence is.

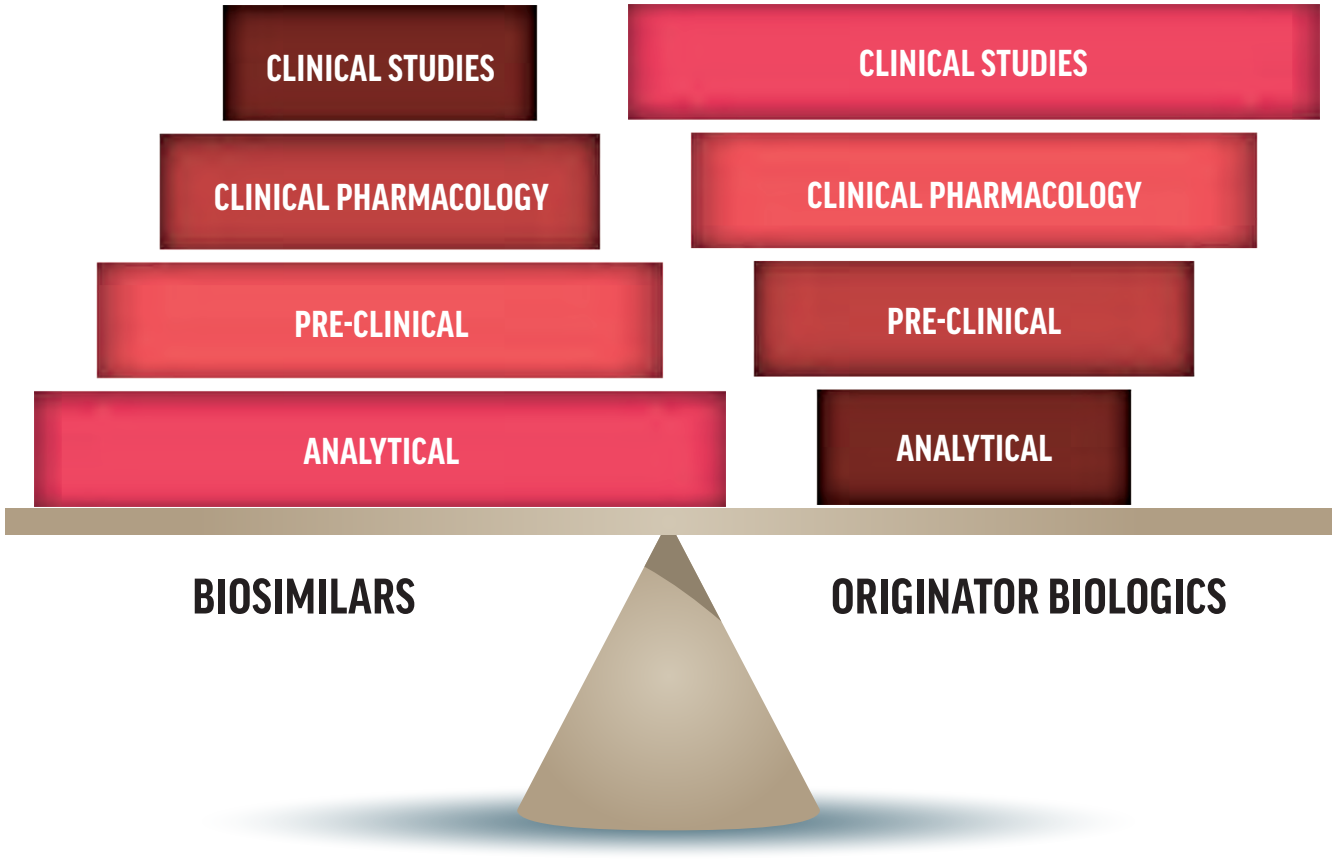
Rather than simply copying a small-molecule, chemically synthesized drug as generic drugs do, a biosimilar manufacturer must reverse engineer to create a final substance that behaves in a biosimilar fashion. This process may create an agent that has differences from the originator biologic. However, those differences must be in parts of the molecule that do not result in clinically meaningful differences between the proposed biosimilar and the reference product. The manufacturer also must demonstrate a manufacturing process that limits the within-product variability, same as the obligation for the originator biologic.

The research and development required for a biosimilar takes 8 to 12 years and costs $100 to $200 million.[5]

NOVEL DEVELOPMENT APPROACHES

The bulk of the investment for a biosimilar is in the laboratory research demonstrating the analytical similarity between the proposed biosimilar and the reference product. The development process only requires one randomized clinical trial of the proposed biosimilar compared with the originator in a sensitive disease population using a sensitive clinical endpoint. Data evaluating the pharmacokinetics of the proposed biosimilar are gathered on a subpopulation of clinical trial participants.

THE REGULATORY PATHWAY: BIOLOGICS VERSUS BIOSIMILARS



Typically, the clinical trial will be performed on a patient population for which the reference product has FDA approval. In retinal diseases, the comparator trial often uses change in visual acuity relative to baseline with a primary endpoint at week 8, rather than week 52—a very new concept for the ophthalmic community. Researchers use an 8-week primary endpoint because the rate of improvement for the originator biologic is particularly steep in those first 8 weeks, which ought to improve the odds of seeing a true difference between the efficacy of a proposed biosimilar and its originator biologic, should one exist. Researchers continue to follow trial participants beyond the primary outcome time point, generally out to 1 year, to enhance the safety database. This also provides longer-term efficacy data, which may provide some comfort to clinicians.

Once a manufacturer shows bioequivalence in one indication, it can apply for *extrapolation*, which may extend approval for the biosimilar to be used for other indications held by the reference product. Regulators look over an entire portfolio of information for the originator biologic and the biosimilar and determine if they are comfortable granting approval with extrapolation to other disease indications.

If a biosimilar is granted the designation of *interchangeability* by the FDA, the drug can then be substituted for the originator biologic at the pharmacy level, at least in states in which this is permitted.

To apply for interchangeability, the biosimilar manufacturer must submit data from one or more switching studies; that means: 1) taking patients who are on the originator biologic, like ranibizumab, and switching them to the biosimilar, 2) switching them back to the originator biologic, and 3) switching them back to the biosimilar and comparing the data to those maintained on the originator biologic throughout a similar interval. The goal of the study is to demonstrate results that are as good for switched patients as they are for patients who remained on the originator biologic.

While the FDA may grant interchangeability, it is also governed at the state level, and not all states allow it without a physician specifically prescribing the biosimilar agent.

WHAT BIOSIMILARS BRING TO THE TABLE

Biosimilars offer the prospect for an excellent return on investment for the manufacturer, but they likely provide significant benefits to patients as well. Biologics are very expensive, and biosimilars are likely to enter the market as a more affordable treatment option in the United States and abroad. For example, when biosimilars outside of ophthalmology (most of which are in the field of rheumatology) have launched in the United States, their initial list price has been anywhere from 15% to 30% lower than the originator biologic.[6] That reduced price, allegedly, expands the access for that drug to more patients and may improve adherence to treatment schedules because of the lower out-of-pocket cost for patients.

Researchers speculate that, between 2020 and 2024, the US health care system could save an estimated $100 billion by using biosimilars rather than the originator biologics.[7]

ADOPTION

The question of adoption within the US ophthalmic community may not ultimately be the clinicians' choice. Payers, both private and government, will likely lead the way as a cost-saving measure mandating the use of biosimilars in lieu of the originator biologics. For example, outside of ophthalmology, biosimilars are set to reach nearly 60% of the volume share of their markets by the end of their second year of availability.[7] Whether that will be the case in ophthalmology remains to be seen.

Although the biosimilar development pathway has a sound rationale, the process includes a limited number of patients exposed to the drug from a safety standpoint. Thus, it's possible that one or more severe adverse events may be associated with a proposed biosimilar that are not identified during the development process. If the true incidence of a severe adverse event is low, it may not be recognized until the biosimilar is used more broadly in community practice. Clinicians should carefully monitor information and share their experiences as biosimilars start to gain traction in the retina community. Growing experience will bring to light any previously unidentified safety signals—and if not, clinicians' confidence in the new therapeutics will likely grow.

KNOWLEDGE IS POWER

Many of the principles governing the development, approval, and adoption of biosimilars are different from what the retina community is accustomed to for the originator biologics. Thus, education is the first step to prepare clinicians to properly interpret data about biosimilars and determine their place in clinical care. ■

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RETHINKING OUR AMD NOMENCLATURE

It's time we agree on how to define signs of atrophy as potential therapies inch closer to approval.

BY ROBYN GUYMER AM, MBBS, PHD, FRANZCO, FAHMS

We appear to be on the cusp of a new era that will include novel treatments to slow the growth of atrophic lesions in AMD. Soon, we may be able to treat the disease before clinically visible signs of atrophy are present because the first signs of cell death are discernible on OCT imaging. To ensure we are all ready for these advances, we must share a common terminology to describe the anatomical signs that are present in retinal images, as well as have a common understanding of their significance.

To start, we need to use the same framework to describe the clinical phenotypes and stages of AMD. The Beckman Initiative for Macular Research Classification Committee published a consensus paper in 2013, outlining a clinical classification of AMD that was designed to provide definitions that were universally accessible to all clinicians (Table, Figure 1).[1] The Beckman classification only requires either a clinical examination or color fundus image to classify AMD patients. Despite this initiative, a lack of uniformity on how we classify AMD disease stages remains.

TIME TO GET ONBOARD

On the verge of a therapy for geographic atrophy (GA), it is crucial that we all adopt the Beckman classification to avoid ambiguity as to the staging of AMD. Based on this classification, the stages of AMD are early, intermediate, and late. Late AMD has two forms: neovascular and GA. The Beckman classification recognizes an increasing risk of developing late AMD and includes categories of *no apparent aging change* and *normal aging change*, both of which signify very low risk of vision loss from AMD.

The Beckman group considered the terms *wet* and *dry* as lay terms that should only be used to describe the two late forms of AMD, neovascular (wet) and GA (dry), rather than earlier stages of AMD. Agreeing to use this terminology and refraining from the use of terms such as *early dry AMD* would end much confusion. This is an essential step forward as we begin to identify patients for trials and interventions designed to enroll only at a certain stage of progression.

OCT NOMENCLATURE

Advances in multimodal imaging provide more insight into patients' disease severity and risk of progression to late AMD, and we can now go further than the Beckman classification in determining stages of AMD. OCT has become an essential imaging tool to evaluate the macula and is now ubiquitous in retinal clinics. OCT macular images have revealed near histological details of what appear to be the first signs of cell loss and the beginning of atrophy in eyes with AMD that only have drusen and pigmentary abnormalities (ie, in patients with early/intermediate AMD) before clinically apparent signs of GA.

An international group of retina specialists, image reading

AT A GLANCE

- It is crucial that we all adopt the Beckman classification of AMD to avoid ambiguity as to the staging of AMD.
- The Classification of Atrophy Meetings have provided the consensus terminology and criteria for defining atrophy based on OCT imaging.
- Nascent GA is a strong predictor of the development of GA and may be a potential surrogate endpoint in future clinical trials.

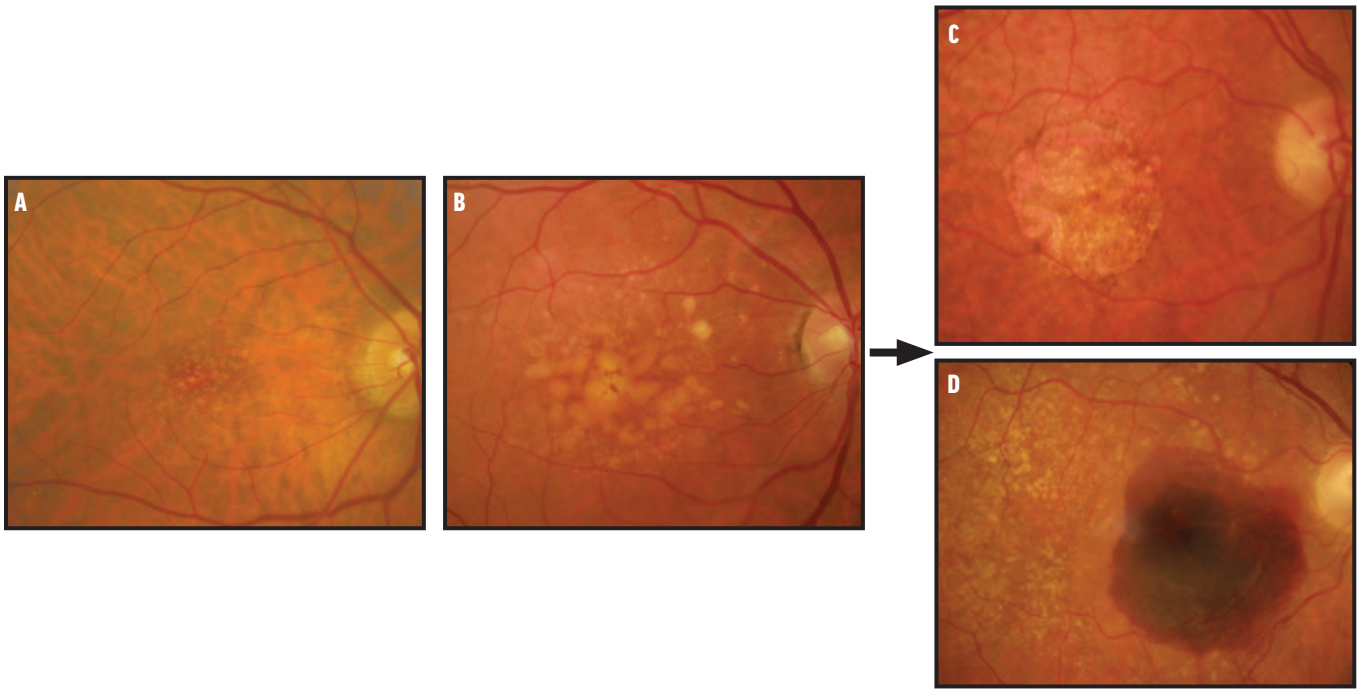

Figure 1. These fundus images demonstrate each of the Beckman stages: early AMD (A), intermediate AMD (B), and late AMD, either GA (C) or neovascular AMD (D).

center experts, retinal histologists, and optics engineers convened to agree upon the nomenclature to describe these changes. The Classification of Atrophy Meetings (CAM) have garnered several manuscripts that describe the consensus terminology and criteria for defining atrophy based on OCT imaging.[2,3] The group surveyed the literature, performed masked analyses of longitudinal multimodal imaging, and met to identify areas of agreement. The CAM group then proposed a classification system based on OCT as the reference image. In addition, other imaging modalities, such as fundus autoflourescence (FAF), near-infrared reflectance, and color fundus photography, were included to provide complementary and confirmatory information.

The result was a lexicon around the anatomical signs that portend the development of GA and relate to the loss of photoreceptors and retinal pigment epithelium (RPE). The terms *complete RPE and outer retinal atrophy* (cRORA) and *incomplete RPE and outer retinal atrophy* (iRORA) were proposed. The specific OCT criteria that designate a lesion as cRORA are:

1. a region of hypertransmission at least 250 µm in diameter,
2. a zone of attenuation or disruption of the RPE at least 250 µm in diameter,
3. evidence of overlying photoreceptor degeneration, and
4. absence of scrolled RPE or other signs of an RPE tear.

The criteria for iRORA are identical to cRORA, except that the dimensions of the RPE and choroidal hypertransmission are less than 250 µm. The CAM investigators also recognized that even before all four criteria of cRORA/iRORA are present, there will be OCT scans in which some, but not all, signs are present. These eyes should be considered as having risk factors for the progression to GA.

The CAM classifications are a more granular representation of AMD changes than those detectable in color fundus photography alone. They will allow us to better follow the course of disease progression, stage it more precisely, and determine subsequent risk of progression.

By providing a common lexicon, the CAM group hopes to enable the research community to explore these novel anatomical signs and collect longitudinal information to determine the increased risk of vision loss.

NASCENT GA: A POTENTIAL SURROGATE ENDPOINT

Currently, the rate of enlargement of atrophy as determined by FAF is a regulatory agency-approved anatomic endpoint for clinical trials. Thus, trial designs require the presence of a reliably measurable atrophic lesion on FAF imaging at baseline so that its enlargement can be accurately determined over time. As such, intervening any earlier in the disease process still requires investigators to follow the trial participants until this FAF endpoint can be demonstrated. Such a trial design would require many participants who are followed for many years, which is not feasible and comes with significant costs. However, OCT may be able to demonstrate anatomical changes in individuals with intermediate AMD to provide robust earlier anatomical endpoints for clinical trials, facilitating earlier disease clinical trial design.

TABLE. BECKMAN CLASSIFICATION OF AMD

Disease Stage	Definition
No apparent aging changes	- No drusen - No AMD pigmentary abnormalities*
Normal aging changes	- Only small drusen ≤ 63 µm - No AMD pigmentary abnormalities*
Early AMD	- Medium drusen > 63 µm and ≤ 125 µm - No AMD pigmentary abnormalities*
Intermediate AMD	Large drusen > 125 µm and/or any AMD pigmentary abnormalities*
Late AMD	Neovascular AMD and/or GA

*AMD pigmentary abnormalities: any definite hyper- or hypopigmentary abnormalities associated with medium or large drusen but not associated with known disease entities.

In 2014, our group described changes on OCT imaging that we believe stand as robust biomarkers for the potential risk of developing GA; we coined the term *nascent GA* (nGA) based on our findings. The data we used were collected from a large cohort of participants with drusen greater than 125 µm in at least one eye, who were assessed cross-sectionally and longitudinally, with a subset of participants seen every 3 months for up to 30 months.

The signs observed in regions that went on to develop atrophy (and are required for nGA to be present) were subsidence of the outer plexiform layer and inner nuclear layer and/or development of a hyporeflective wedge-shaped band within Henle fiber layer, within the limits of the outer plexiform layer (Figure 2).[4] Upon further analysis of data from the Laser in Early Stages of AMD (LEAD) study,[5] we found that, following detection of nGA, the probability of progression to GA after 24 months was 38%. The development of nGA was associated with a markedly increased risk of progression to GA compared with those who did not develop nGA (adjusted hazard ratio, 78.1; $P < .001$). In addition, the development of nGA explained 91% of the variance in the time to GA development.[4] Thus, this study demonstrated that nGA was a strong predictor of the development of GA, providing supportive evidence of its potential value as a surrogate endpoint in future trials for early stages of AMD.

In CAM 3, the group suggested that we continue to use the term GA, but only in a subset of cRORA in the absence of choroidal neovascularization (CNV) and where evident in color fundus photographs. The group recommended *macular atrophy* as the term to encompass atrophy both with and without CNV. Thus, nGA was suggested to be used as a more general term to describe iRORA in the absence of CNV. However, nGA, as originally defined, required specific signs of photoreceptor loss and comes with a high rate of progression to GA. Not all cases of iRORA have these signs, and iRORA appears more frequently in a cohort of patients with intermediate AMD compared with nGA, as originally defined.

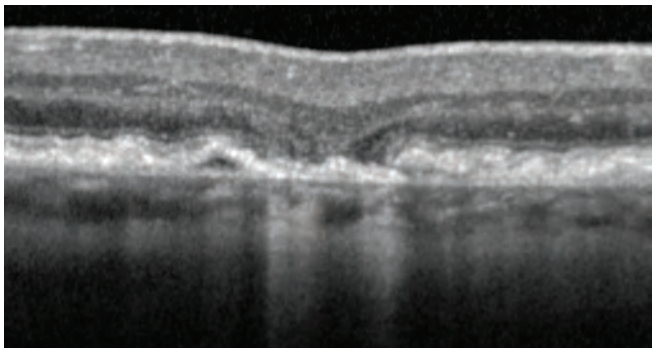

Figure 2. nGA showing the required features of subsidence of the outer plexiform layer and inner nuclear layer and/or development of a hyporeflective wedge-shaped band within Henle fiber layer, within the limits of the outer plexiform layer.

NEXT STEPS

Moving forward, the field will likely rely on artificial intelligence and algorithms that segment each layer of the retina. Studies and clinical trials will need to define which signs of cell loss to include or exclude from their cohorts and what changes would constitute evidence of progression.

Until then, we must be able to reliably grade each of the signs that are required for these definitions. The CAM 6 paper, which reports on inter-reader agreement when assessing these OCT signs, begins to address this issue.[6]

Regulatory authorities will likewise need to consider these new AMD staging characteristics and determine which changes provide robust biomarkers to act as surrogate endpoints, once their relationship with GA is well-established.

For now, we must all become familiar with these OCT signs of atrophy to help everyone prepare for treatments that are surely headed our way. ■

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GENE THERAPY CHECK-IN: WET AMD AND GA

Early data from phase 1/2 trials are promising, with more work underway.

BY KYLE D. KOVACS, MD, AND SZILÁRD KISS, MD


After a decades-long journey, the 2017 FDA approval of voretigene neparvovec (Luxterna, Spark Therapeutics) provided proof of concept and renewed interest in the retina as an ideal gene therapy target.[1,2] Researchers have turned their attention to gene therapies for other monogenic inherited retinal dystrophies (IRDs), as well as more prevalent acquired retinal diseases such as wet AMD and geographic atrophy (GA).

Unlike IRD gene therapy, in which functional proteins are expressed in target cells where they are otherwise absent or aberrant, AMD gene therapies are applied in a gene agnostic fashion. The therapy promotes the formation of an ocular biofactory in which proteins not normally created within the eye are produced (or normal proteins are over-produced). This approach targets either well-established pathophysiologic pathways or theoretically relevant targets. Not treating a specific genetic mutation, as is the case for IRDs, allows potential translation to larger populations.

There are three delivery approaches under investigation: subretinal, suprachoroidal, and intravitreal. Each has certain advantages and requirements based on the features of a specific vector and the potential for triggering an inflammatory response. For example, the challenge of an adeno-associated virus-2 (AAV2) vector is to bypass the internal limiting membrane. Recently, long-term findings in patients dosed with subretinal voretigene neparvovec have furthered interest in alternative delivery approaches, particularly in the case of nonspecific gene therapy.[3] Ongoing AMD trials are exploring novel vector constructs and delivery made possible by not needing to target specific cells and their respective monogenic mutations.

Here, we review some of the efforts that are moving translational medicine forward (Table).

WET AMD

Wet AMD has long been an area of interest for gene therapy. Some of the earliest work looked at intravitreal and subretinal delivery of an AAV2 construct promoting expression of a soluble fms-like tyrosine kinase 1, which decreases endogenous levels of VEGF.[4,5] Other work investigated endostatin and angiostatin targets via subretinal delivery of a lentivirus construct.[6]

While safety and some efficacy were demonstrated, insufficient effectiveness halted further development. More recent

AT A GLANCE

- RGX-314 (Regenxbio) for wet AMD is moving into pivotal phase 2b/3 trials comparing subretinal delivery with monthly intravitreal ranibizumab (Lucentis, Genentech/Roche) and bimonthly aflibercept (Eylea, Regeneron).
- The phase 1/2 FOCUS trial of GT005 (Gyroscope Therapeutics) for geographic atrophy (GA) shows that the treatment is well tolerated, without significant inflammation, and provides sustained complement factor I levels.
- HMR59 (Hemera Biosciences/Janssen Pharmaceuticals) aims to create endogenous expression of an antiinflammatory protein that is under-expressed in retinal cells of patients with both wet AMD and GA.

TABLE. AMD GENE THERAPY CHEAT SHEET

Gene Therapy Candidate	Disease State	Mode of Delivery	Trial Status
RGX-314 (Regenxbio)	Wet AMD	Subretinal	Phase 2b/3 (ATMOSPHERE and ASCENT)
		Suprachoroidal	Phase 2 (AAVIATE)
ADVM-022 (Adverum)	Wet AMD	Intravitreal	Phase 1 complete, phase 2 in development
GT005 (Gyroscope Therapeutics)	Geographic atrophy	Subretinal	Phase 2 (EXPLORE and HORIZON)
HMR59 (Hemera Biosciences/ Janssen Pharmaceuticals)	Wet AMD	Intravitreal	Phase 1 (complete)
	Geographic atrophy	Intravitreal	Phase 1 (enrolling)

efforts are showing promise, although the threshold for success remains high due to the proven standard of care with repeated intravitreal anti-VEGF therapy.

RGX-314

RGX-314 (Regenxbio), in which an AAV8 vector encodes for a monoclonal anti-VEGF antibody fragment, is being investigated with both subretinal and suprachoroidal delivery in wet AMD. The subretinal delivery program completed phase 1/2a in 42 patients with 2 years of follow-up and has demonstrated tolerability, stable to improved vision and retinal thickness, and a meaningful reduction in injection burden with higher doses (patient cohorts 3-5).[7] Two pivotal phase 2b/3 trials are enrolling patients: ATMOSPHERE comparing subretinal RGX-314 with monthly intravitreal ranibizumab (Lucentis, Genentech/ Roche) and ASCENT (run in partnership with Allergan/ AbbVie) comparing subretinal RGX-314 with bimonthly aflibercept (Eylea, Regeneron).

Suprachoroidal delivery moves gene therapy to the office setting and avoids the associated risks of vitrectomy and iatrogenic retinal detachment with subretinal injection. Suprachoroidal delivery of RGX-314 is under investigation in the phase 2 AAVIATE trial, in which patients with wet AMD undergo in-office suprachoroidal injection of RGX-314 with the SCS Microinjector (Clearside Biomedical). Initial results show that suprachoroidal delivery of RGX-314 is well tolerated (n = 50, across three cohorts) and contributed to a 6-month reduction in patient injection burden (cohort 1, n = 15, 75.9% reduction); researchers noted four cases of mild inflammation that resolved with topical steroid drops in cohort 1.[8]

ADVM-022

ADVM-022 (Adverum) is a novel AAV2.7m8 vector designed to allow enhanced retinal transduction across the internal limiting membrane despite being delivered via a single intravitreal injection for wet AMD. The phase 1 investigation of wet AMD is complete with 30 subjects enrolled across four cohorts. The data show a more than 80% reduction in intravitreal injection burden with sustained aflibercept expression and mild (with one moderate) cases of inflammation, all of which were responsive to topical steroid drops.[9] Adverum recently announced that, following FDA feedback, it anticipates completing its investigational new drug amendment mid-2022 with dosing of the first patient in a phase 2 trial of ADVM-022 in the third quarter of 2022.[10] This trial is designed to evaluate the previously used $2x10^{11}$ vg/eye dose and a new, lower $6x10^{10}$ vg/eye dose of ADVM-022, along with new enhanced prophylactic steroid regimens, including local steroids and a combination of local and systemic steroids, in patients with wet AMD.[10]

GEOGRAPHIC ATROPHY

GA is an appealing disease target for gene therapy, considering there are no approved therapies for it; therefore, the high threshold for approval in wet AMD does not exist for GA. However, identification of molecular targets for gene therapy has been challenging in the absence of a clinically validated and FDA-approved therapeutic pathway.

GT005

GT005 (Gyroscope Therapeutics) is an AAV2 vector being delivered to the subretinal space via the proprietary Orbit Subretinal Delivery System (Gyroscope Therapeutics) as well as the traditional transvitreal subretinal bleb approach. This gene therapy construct promotes expression of complement factor I (CFI) in the treatment of GA and has been found to be well tolerated without significant inflammation and sustained CFI expression in a phase 1/2 trial (FOCUS).[11] Separate phase 2 studies are investigating GT005 in patients

GENE AGNOSTIC APPROACHES TO THERAPIES FOR ACQUIRED RETINAL DISEASES HAVE COME A LONG WAY OVER THE LAST DECADE, WITH NUMEROUS TARGETS SHOWING PROMISE AS CLINICAL TRIALS PROGRESS.

with rare CFI variants (EXPLORE) and a larger GA population (HORIZON).[12,13] These studies aim to document whether the sustained CFI expression noted thus far translates into clinically relevant slowing of GA progression with continued tolerability and safety.

DUAL TARGETS

HMR59 (Hemera Biosciences/Janssen Pharmaceuticals) is an AAV2 vector that is delivered via a single intravitreal injection. The therapy aims to create endogenous expression of soluble CD59, an antiinflammatory protein that is underexpressed in retinal cells of patients with both wet AMD and GA. For GA, a phase 1 dose-escalating safety and tolerability study (HMR-1001) that enrolled 17 patients is complete with data pending.[14]

For wet AMD, a phase 1 proof of concept study of a single intravitreal administration of HMR59 (HMR-1002) has enrolled 25 treatment-naïve patients with newly converted wet AMD.[15] Interval updates and data are forthcoming.

Because this is a new pathway for wet AMD therapy, all patients meeting the enrollment criteria are treated with a single intravitreal injection of an anti-VEGF agent at day 0 and then treated with HMR59 at day 7. Patients will continue monthly anti-VEGF therapy as needed throughout the 12-month study period.[15]

HOPE FOR THE FUTURE

Gene agnostic approaches to therapies for acquired retinal diseases have come a long way over the last decade, with numerous targets showing promise as clinical trials progress. Nonetheless, given the excellent safety profile of current anti-VEGF therapies, the threshold for defining success remains high for wet AMD. Refinement of vectors and therapeutic target selection and improvements in vector delivery (both surgical technique refinement and route of administration) have yielded some early phase 1/2 promise. Time will tell if the safety and efficacy profiles prove favorable for these agents and their alternative routes of delivery.

Retina specialists and the broader medical community are eagerly watching. ■

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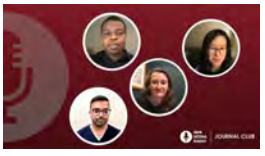

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AT-HOME MONITORING IN YOUR OFFICE

Two cases demonstrate how this new tool can help you track patients between office visits.

BY DAVID S. CHIN YEE, MD, AND MIGUEL BUSQUETS, MD, FACS

Following patients with early and intermediate AMD feels a bit like watching them walk a tightrope sometimes, doesn't it? Patients can present for years with no progression; yet, in mere months they might have conversion with significant vision changes. While careful education on the possible symptoms of conversion can help patients understand when to call the office between routine follow-up, it's often not enough. According to these two experts, at-home monitoring for AMD can provide the safety net these patients need. Here, David S. Chin Yee, MD, and Miguel Busquets, MD, FACS, share cases to highlight exactly how at-home monitoring helped to catch changes early and ensure a prompt shift in care.

– Rebecca Hepp, Editor-in-Chief

LEFT EYE ALERT

By David S. Chin Yee, MD

A 72-year-old man with long-standing wet AMD in the right eye (diagnosed in 2017) who had undergone previous treatment with anti-VEGF therapy with a disciform scar (Figure 1) was now being observed with VA of 20/800 OD and intermediate AMD in the left eye with VA of 20/25 (Figure 2). Due to the high risk of conversion to wet AMD in the left eye and the monocular status, the patient was referred for at-home monitoring with the ForeseeHome AMD Monitoring Program (Notal Vision). The patient began using the device in July 2018 and was monitored in-office every 6 months.

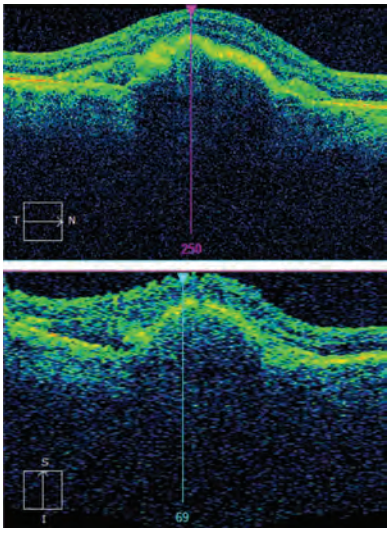


Figure 1. At presentation, the patient's right eye had wet AMD, a disciform scar, and VA of 20/800.

In July 2021, the system alerted my office to changes to the patient's left eye testing. The patient was called and scheduled for an immediate appointment. On examination, his VA was 20/30 OS. The anterior segment examination was unremarkable, while dilated fundus examination of the left eye showed subretinal fluid and new choroidal neovascularization (CNV). Based on this, the patient was diagnosed with conversion to wet AMD with CNV in the left eye (Figure 3). The patient received anti-VEGF injection on the initial visit and continued monthly injections. Currently, he is extended to receive treatment every 8 weeks with VA improved to 20/25 OS and resolution of CNV (Figure 4).

AT A GLANCE

- At-home AMD monitoring may offer clinicians a reliable way to track patients between office visits.
- The ForeseeHome AMD Monitoring Program (Notal Vision) alerts clinicians to changes in a patient's testing, prompting in-office evaluation at the earliest stages of conversion to wet AMD.
- Two authors share their experiences with the home monitoring program, and how the system caught patients' conversion from intermediate AMD to wet AMD.

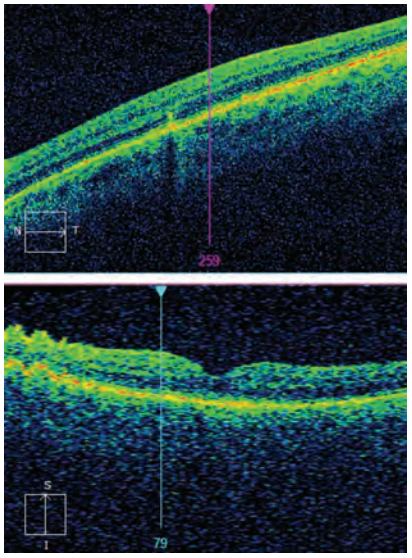


Figure 2. At the time that the patient began at-home monitoring, his left eye had intermediate AMD with a VA of 20/25.

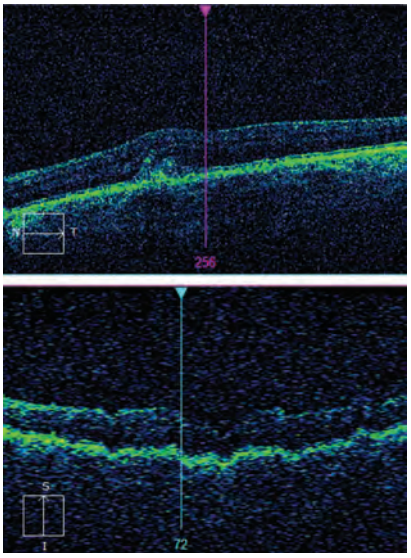


Figure 3. Changes in the at-home testing prompted an immediate in-office visit, which revealed new choroidal neovascularization and conversion to wet AMD.

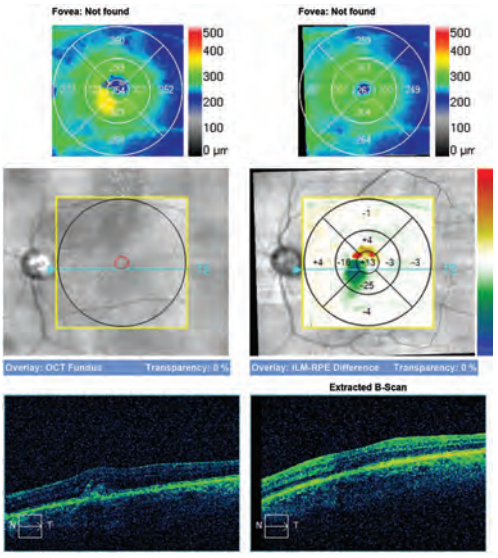


Figure 4. Intravitreal anti-VEGF injections improved the patient's VA to 20/25 OS and led to the resolution of the choroidal neovascularization.

Gotta Catch Them Both

By Miguel Busquets, MD, FACS

In October 2019, a new female patient presented for an AMD evaluation, stating that she had been diagnosed with AMD 3 years prior. She had a cataract in each eye with VA of 20/50 OD and 20/30 OS. Her dilated fundus examination revealed high-risk medium-sized to large drusen and retinal pigment epithelial changes in both eyes, but no fluid or hemorrhage in either eye. OCT imaging confirmed these findings (Figure 5).

The patient was counselled on taking AREDS2 vitamins, sun safety, and the importance of a healthy diet. She was also referred for at-home monitoring with the ForeseeHome AMD Monitoring Program and for a cataract surgery consult.

In February 2021, the patient presented for her regularly scheduled dry AMD follow-up with no new complaints. She had undergone cataract surgery the year prior and presented with VA of 20/20 OU. Dilated fundus examination showed dry drusenoid changes, also noted on OCT. She was scheduled to return in 6 months for a typical follow-up.

In June 2021, my office was alerted to changes to her at-home testing in the right eye. The patient was seen in the office the day after the alert—still with 20/20 vision—at which time she described metamorphopsia and blurred vision in her right eye that started about 1 week prior. Dilated fundus examination revealed new CNV with intraretinal fluid confirmed by OCT (Figure 6). She was diagnosed with conversion to wet AMD with active CNV in the right eye, received an intravitreal injection of anti-VEGF therapy, and was scheduled for monthly injections. She continued at-home monitoring for her left eye.

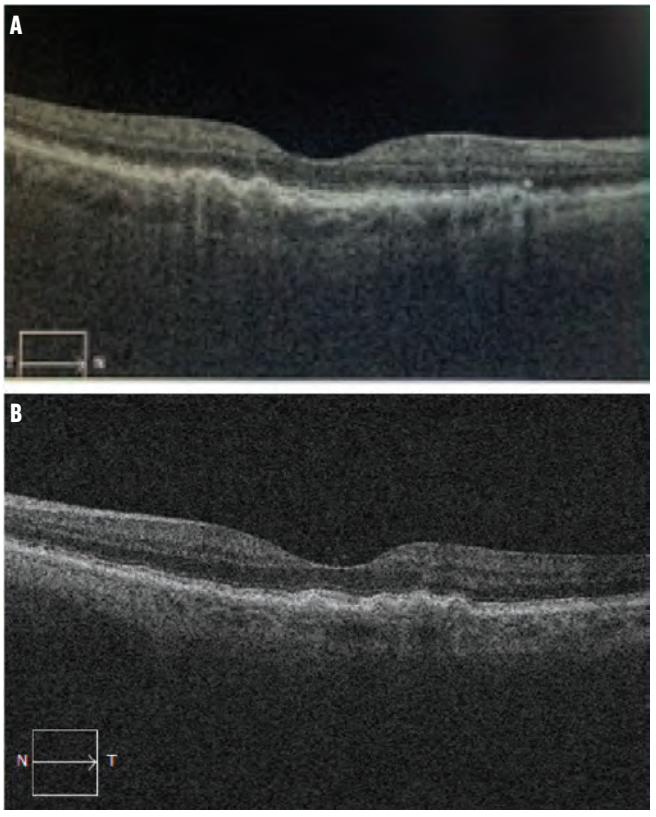
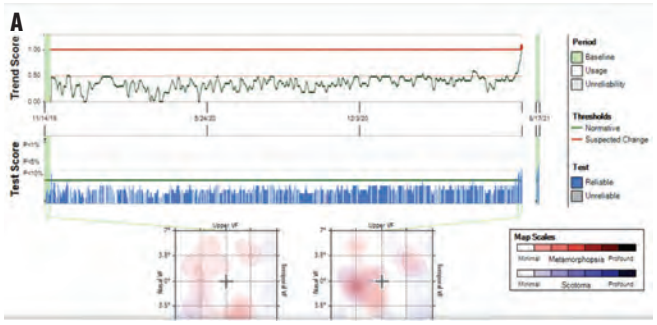


Figure 5. In October 2019, this patient's OCT showed signs of dry AMD in the right (A) and left (B) eyes: extensive drusenoid changes and retinal pigment epitheliopathy.

For the next 6 months, the patient was seen for regular intravitreal anti-VEGF injections in the right eye with little to no change in the left eye, while OCT findings in the right eye steadily improved.



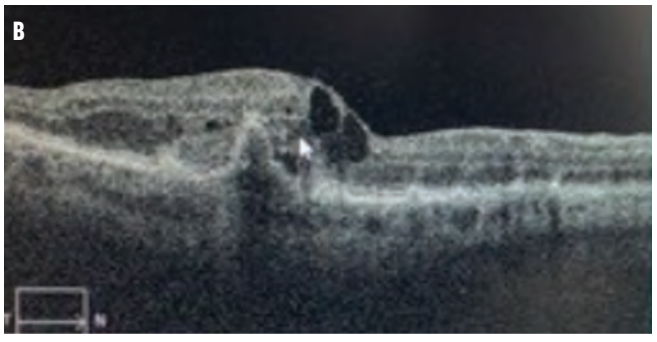


Figure 6. Two months before the patient's scheduled follow-up, the at-home monitoring program alerted the office to changes in her right eye testing (A). In-office examination confirmed extensive drusen, pigment epithelial detachments, and new choroidal neovascularization with intraretinal and subretinal fluid—conversion to wet AMD (B).

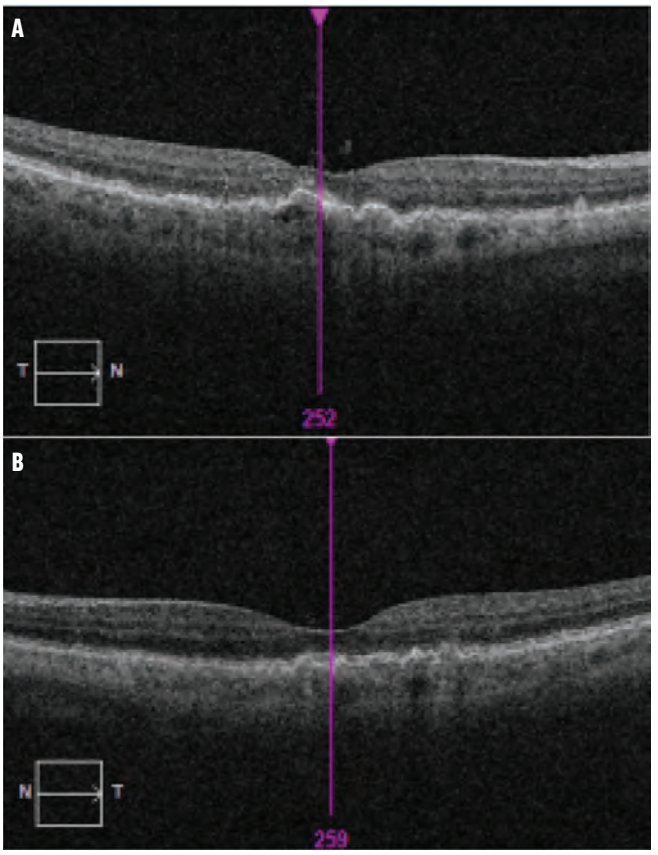
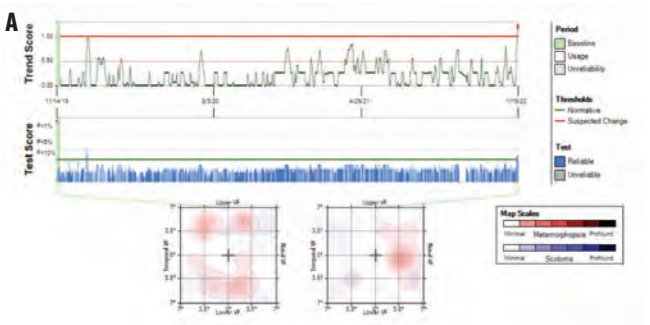


Figure 8. At her last follow-up the patient was stable with improvement seen on OCT imaging in the right (A) and left (B) eyes.



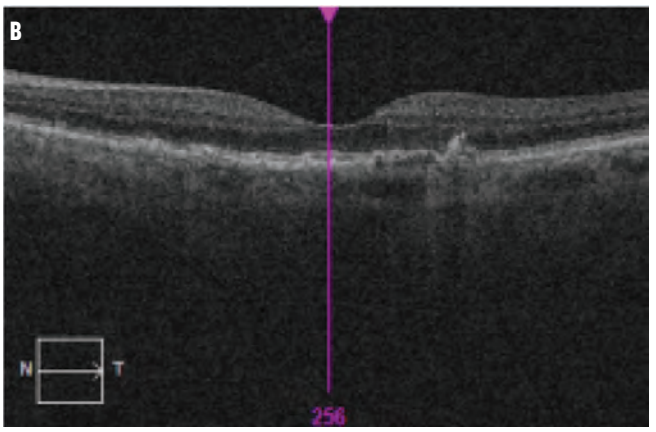


Figure 7. Six months after the right eye converted to wet AMD, at-home monitoring caught changes in the left eye (A), prompting in-office examination and a new diagnosis of wet AMD in the left eye (B).

In January 2022, my office was alerted to aberrations in her at-home testing of the left eye. The patient presented the next day, explaining that her vision had not subjectively changed since last month's visit. Dilated fundus examination did not show significant new abnormalities, but in-office OCT revealed a new, small CNV with very subtle subretinal fluid (Figure 7). Vision had dropped to 20/30 OS. She was diagnosed with conversion to wet AMD with active CNV in the left eye and received an intravitreal injection of an anti-VEGF agent.

At her last follow-up in February 2022, the patient's VA was stable at 20/20 OD and 20/25 OS, and her OCT imaging shows signs of improvement (Figure 8). She is now scheduled for anti-VEGF injections every 4 weeks. ■

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ARTIFICIAL INTELLIGENCE IN AMD IMAGING

Here is a look at what to expect as this tool becomes more ubiquitous in research and the clinic.

BY GIULIA CORRADETTI, MD, AND SRINIVAS R. SADDA, MD


AMD remains a major cause of severe and irreversible vision loss worldwide.[1] As life expectancy continues to increase, so does the prevalence of AMD, with an estimated 288 million people being diagnosed with AMD by 2040.[2,3]

The progress achieved in the treatment of AMD with the introduction of anti-VEGF therapies has greatly improved visual outcomes.[4-6] However, delayed intervention, the unpredictability of recurrent disease, and the need for chronic therapy are all factors that are associated with poor visual outcomes.[7,8]

In addition, no proven therapy is currently available for the prevention or treatment of geographic atrophy (GA).[9] The Age-Related Eye Disease Study demonstrated that micronutrient antioxidant supplements may play a role in reducing the progression of intermediate AMD to wet AMD, but the study also found no apparent benefit in preventing foveal atrophy.[10,11]

Advances in retinal imaging, such as OCT, have dramatically transformed ophthalmic clinical practice and research, allowing high-resolution visualization of the microarchitecture of the retina and choroid. More recently, the development of OCT angiography (OCTA) has allowed the study of the retinal microcirculation and the inner choroid in 3D.[12] Here, we discuss the advances in retinal imaging that have led to the identification of biomarkers for AMD progression that may one day shape how we diagnose, treat, and follow patients with AMD.

THE CHALLENGE

With the increasing interest in earlier interventions to prevent or halt AMD progression, risk stratification is required to effectively design early intervention clinical trials with practical size and feasible duration. Retinal imaging now allows us to identify biomarkers that may predict the development of late-stage AMD. Studies have identified several high-risk biomarkers for AMD, including high central drusen volume, subretinal drusenoid deposits, hyporeflective drusen cores, intraretinal hyperreflective foci, and choriocapillaris flow deficits.[13-15]

The identification of these biomarkers has been facilitated by the availability of both OCT and OCTA, which allow for the detection of subclinical features that may not

AT A GLANCE

- Advances in retinal imaging have led to the identification of biomarkers for AMD progression that may one day shape how we diagnose, treat, and follow patients with AMD.
- Artificial intelligence (AI) algorithms may be able to provide analyses to assist physicians in diagnosing conditions based on specific features extrapolated from large volumes of imaging data.
- Researchers have demonstrated AI's ability to objectively identify, localize, and quantify subretinal fluid and high-risk structural biomarkers on OCT using a fully automated tool.
- AI-based imaging may be particularly useful in the era of personalized medicine, where we may be able to accurately predict outcomes and choose the optimal therapeutic strategies.

AI CAN BE TRAINED TO DETECT SPECIFIC STRUCTURAL FEATURES THAT UNCOVER DISEASE-SPECIFIC PATTERNS, WHICH CAN BE USED BY CLINICIANS TO BETTER UNDERSTAND THE DISEASE AND MAKE APPROPRIATE TREATMENT DECISIONS.

be apparent during a standard ophthalmoscopic examination. Of note, the grading and annotation of these images requires extensive training and may be a challenging and time-consuming process, especially in the context of a busy clinical practice. Even with experienced centralized reading centers, there can be variability between graders due to the subjectivity of the assessments and subtlety of the features characterizing the disease process. Compounding this problem, OCT and OCTA volumes contain a large number of B-scans that must be carefully and qualitatively evaluated and interpreted; the quantitative assessment of biomarkers is even more challenging, frequently requiring analysis with a specialized manufacturer or third-party software.

A PLACE FOR ARTIFICIAL INTELLIGENCE

These clinical challenges present an opportunity for the use of artificial intelligence (AI) algorithms and systems. They may be able to provide analyses to help physicians diagnose conditions based on specific features extrapolated from large volumes of imaging data—all in a short period of time. AI can be trained to detect specific structural features that uncover disease-specific patterns, which can be used by clinicians to better understand the disease and make appropriate treatment decisions.

In the retinal space, there are at least two disease states for which AI algorithms have already come into play: AMD and diabetic retinopathy. In this article, we focus on advances in the AMD space. Several investigators have created advanced AI algorithms designed to annotate color fundus photographs and have achieved performance similar to human graders with regard to the assessment of drusen, pseudodrusen, and GA.[16,17]

Biomarkers for the progression of GA are particularly important because slowing the progression or enlargement of atrophy is considered an FDA-approved clinical endpoint in many ongoing interventional clinical trials. Niu et al developed a model to predict future GA growth based on structural biomarkers on OCT as a potential tool for identifying patients at high risk for rapid progression.[18] Bogunovic et al focused on an earlier stage and studied a deep learning algorithm to predict the risk of progression in eyes with intermediate AMD based on drusen regression on OCT.[19] Other groups have developed AI algorithms to predict whether eyes with intermediate AMD would progress to macular neovascularization or GA.[20]

The activity of neovascular AMD is generally determined by the presence of fluid (subretinal, intraretinal, and subretinal pigment epithelium), which can be accurately identified on OCT. Resolution of retinal fluid is also the key indicator to assess responsiveness to anti-VEGF therapy. Schmidt-Erfurth et al demonstrated AI's ability to objectively identify, localize, and quantify fluid on OCT using a fully automated tool, which could potentially be used for personalized disease management.[21,22] In addition, machine learning approaches have shown the ability to predict BCVA at 1 year based on the initial therapeutic response in eyes with neovascular AMD, highlighting the importance of early treatment and control of disease activity.[23]

Our group has been focused on the development of AI models to automate the detection of structural OCT biomarkers associated with risk for progression of intermediate AMD, showing a performance superior to expert retinal imaging graders.[24]

CLINICAL IMPLICATIONS

Although we may still be in the early days of AI in ophthalmology, imaging studies have already proven these tools to be valuable for detecting specific disease features, offering clinicians the opportunity to screen for disease, prognosticate the disease course, and uncover new insights into the pathophysiology of disease. The ability of AI-based tools to rapidly and accurately process large volumes of data makes it feasible to incorporate them into clinical practice.

AI-based imaging may be particularly useful in the era of personalized medicine, where we may be able to accurately predict outcomes and choose the optimal therapeutic strategies for our patients.

With continued development and training with larger datasets, the performance of AI algorithms will only improve over time. AI's ability to extrapolate useful clinical information from large volumes of imaging data will be of particular importance as our diagnostic technologies get more sophisticated. Thus, we can expect AI to play a significant role in the retina clinic of the future. ■

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(Continued from page 14)

PVR, such as multiple breaks during surgery and redetachments, were included. All patients received oral MTX on the first postoperative day. The study eyes had flat and attached retinas throughout the 6+ month course of MTX.

Al-Khersan et al presented a cost-utility analysis of MTX versus mycophenolate mofetil (MMF) for the treatment of noninfectious uveitis. Costs included medications, lab testing, imaging, clinical visits, and adverse events. Outcome measures included cost and utility of treatment, lifetime quality-adjusted life year gain and cost/quality-adjusted life year ratio. They concluded that MMF had a higher modeled cost due to medication cost. Both MMF and MTX had similar predicted utility gains, and both were cost-effective.

Tabbaa et al presented a multimodal imaging case series of five patients from the same family with autosomal dominant neovascular inflammatory vitreoretinopathy. Genetic testing revealed the pathognomonic *CAPN5* mutation in all five patients, along with a number of variants of unknown significance. Imaging from two patients aged 15 and 40 years highlighted the stages of the disease.

Lin et al evaluated the efficacy of online learning to teach trainees key pathology noted on fundus examination and OCT imaging. They found that most participants repeatedly engaged with the imaging-based multiple-choice quiz modules with measurable performance improvements. They encouraged continued efforts to leverage virtual tools.

Robles-Holmes et al presented the results of a retrospective review of 14 eyes with asymptomatic RDs. More than half (64%) of RDs were found inferotemporally, 86% were posterior to the equator, and 21% presented with a demarcation line. Of asymptomatic RRDs, 31% had prior laser barricade with no progressed RDs during the mean follow-up of 2.76 years. Only two RDs progressed and one required surgery. The authors concluded that close observation, especially for inferior peripheral RDs anterior to the equator and those without large breaks, could be a viable option.

De Carlo et al presented a retrospective chart review of seven eyes that underwent I-125 plaque brachytherapy that developed ocular tumor lysis syndrome (OTLS). The authors concluded that common OTLS associations included large plaque diameter, presence of subretinal fluid, collar-button shape, and high total energy delivered to the eye. They stated that enucleation can be avoided in eyes with OTLS despite poor vision with surgical intervention for hemorrhage, pigment removal, and RD repair. ■

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LET'S TALK ABOUT RETINAL IMAGING ANALYSIS


Deconstructing RGB color channels with broad line fundus imaging technology may one day improve our clinical care.

BY RICARDO LEITÃO GUERRA, MD, MSC, FICO, AND GABRIEL CASTILHO, MD

Some digital ultra-widefield imaging systems are now powered by broad line fundus imaging (BLFI) technology, which is a hybrid of confocal scanning laser ophthalmoscopy and traditional fundus photography. The technology uses line-scanning illumination with light-emitting diodes and an aperture confocal to the illumination, which could help improve image analysis.[1]

RGB CHANNELS

BLFI enables the combination of an ultra-widefield view and a full range of retinal imaging modes to generate images with high dynamic range, contrast, resolution, and natural colors—capturing images that resemble the coloration of the fundus as seen during clinical examination, also known as true color imaging. The tool also allows a single image to be deconstructed into channels to show the individual wavelength views by adjusting the blend function of the software. The blue channel (BC; 435-500 nm) increases the visibility of anterior retinal layers, the green channel (GC; 500-585 nm) permits a view from the sensory retina to the retinal pigment epithelium (RPE), and the red channel (RC; 585-640 nm) and infrared laser diode (785 nm) scans the deeper structures from the RPE to the choroid.[2]

CLINICAL IMPLICATIONS

This imaging tool has the potential to allow clinicians to better distinguish retinal changes specific to certain retinal layers. Retinal alterations that are located in the anterior layers, such as a lamellar hole or a nerve fiber layer defect, are better distinguished in the BC and GC compared with the RC or true color. For example, a lamellar hole would not be distinguishable using the RC and true color imaging, while it would be visible with the BC and GC, with

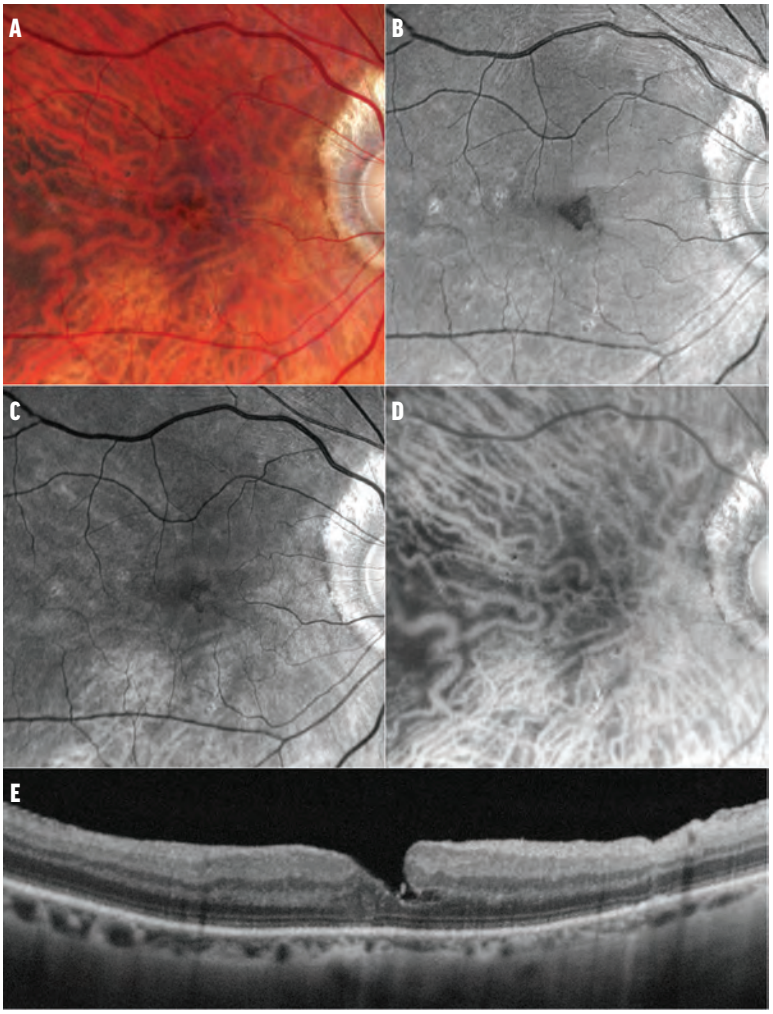

Figure 1. True color imaging shows the macular region without evident signs of alterations (A). The blue channel reveals a trapezoid hypopigmented change in the foveal area (B). The green channel reveals a less evident hypopigmented change in the foveal area, with the retinal vasculature well distinguished (C). The red channel highlights the choroidal vessels, but no changes are seen in the foveal area (D). B-scan spectral-domain OCT imaging (vertically oriented, centered in the fovea) shows details of the lamellar hole (E).

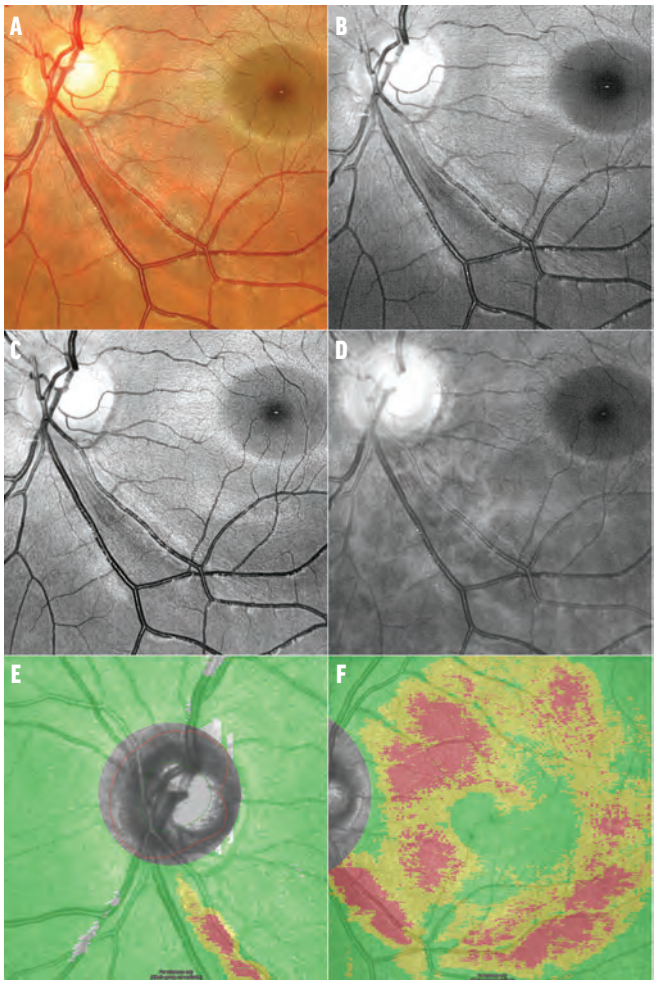

Figure 2. True color imaging shows a nerve fiber layer defect in the inferotemporal arcade (A). The blue channel (B) and green channel (C) show the nerve fiber layer defect; the retinal vasculature is better visualized in the green channel. The defect is still visible in the red channel despite being less noticeable (D). The changes are evident on the spectral-domain OCT quantitative analysis of the retinal nerve fiber layer and ganglion cell layer (E and F).

the lamellar hole being more evident in the BC (Figure 1). A nerve fiber layer defect, such as within the retinal vasculature, is highlighted in the GC due to its deeper penetration, compared with the BC (Figure 2). Although still visible in the RC and true color, the defect is less noticeable, limiting the clinician's ability to characterize the changes.

On the other hand, choroidal nevus are undetectable in the BC and GC (Figure 3). The only visible change is related to drusen, which appear in the BC as light focal dots, correlating with the yellowish foci in the true color image. This pattern is maintained in GC and RC, but contrast is more evident in the GC compared with the other channels.

A choroidal nevus imaged with the RC, reveals a consistent pattern, presenting as a well-defined dark spot, with higher levels of contrast; this allows better identification, measurement, and characterization of the nevus compared with the other color channels, including the true color imaging.

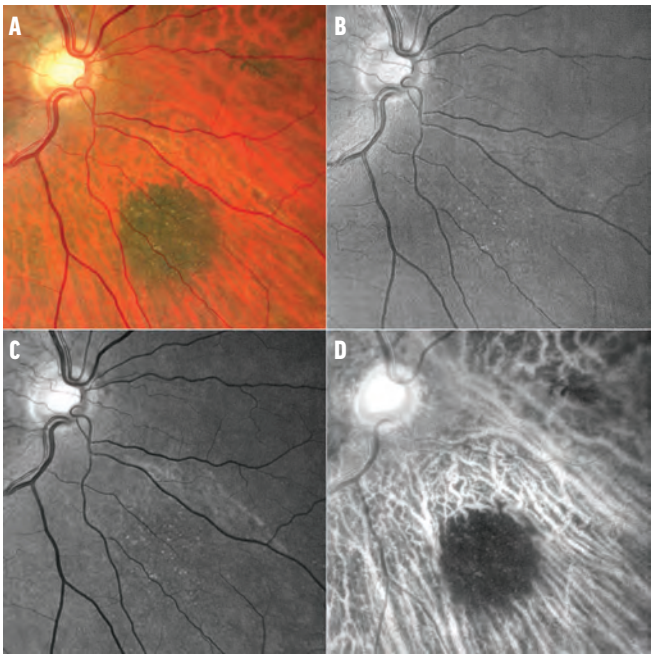

Figure 3. True color imaging shows a dark, flat, and well-defined lesion with drusen in the nasal-inferior quadrant, consistent with a choroidal nevus (A). The choroidal nevus is undetectable in the blue channel, while drusen appear as low-contrast light focal dots (B). The choroidal nevus is also undetectable in the green channel while drusen appear as medium-contrast light focal dots (C). The choroidal nevus appears as a dark, flat, and well-defined lesion in the red channel while drusen appear as low-contrast light focal dots (D).

CONCLUSION

Many other retinal peculiarities can be assessed and characterized using different color channels. Even at relatively close wavelengths, the images exhibit significant distinctions between the color channels. In addition to facilitating the identification of the depth at which a lesion resides, deconstructing the image into color channels allows for a better characterization of the disorders. This improved characterization may provide pieces of information that might be useful during screening by increasing the diagnostic reliability and at follow-up by allowing a more accurate assessment of the lesion. ■

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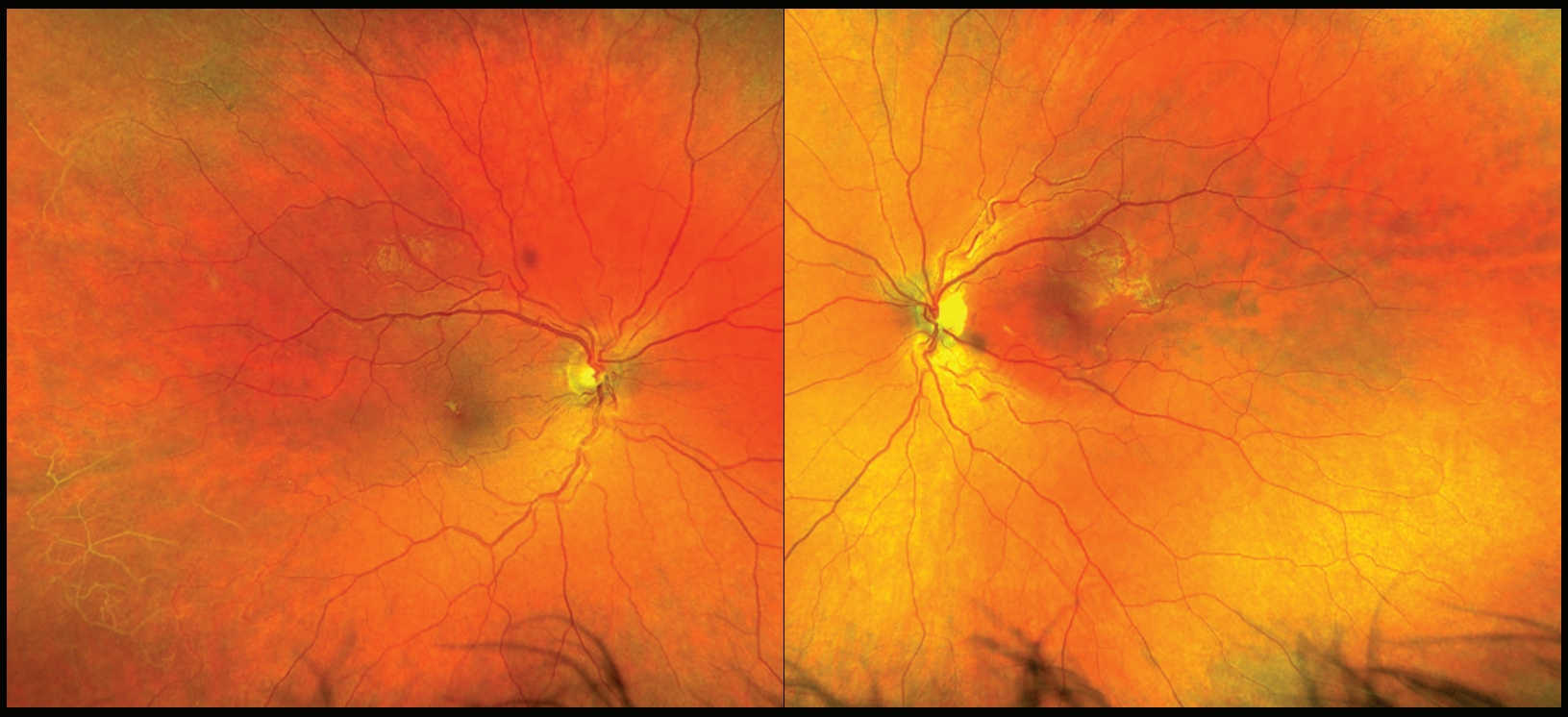

DYSKERATOSIS CONGENITA RETINOPATHY


Understand the ocular signs of a rare genetic condition that poses serious systemic risk.

BY BOONTIP TIPSURIYAPORN, MD, AND YOSHIHIRO YONEKAWA, MD

A 20-year-old woman with a history of dyskeratosis congenita (DC) presented with retinal vascular abnormalities. VA was 20/20 OU, and she was experiencing trichiasis and dry eye symptoms. Fundus examination revealed peripheral nonperfusion with sclerotic vessels in each eye (Main Figure). Widefield fluorescein angiography (FA) demonstrated peripheral nonperfusion, telangiectasias, vascular shunting, and mild vascular leakage in each eye (Figure, next page). The nonperfusion was mild without signs of neovascularization, so close observation was recommended.

DISCUSSION

Dyskeratosis congenita is a rare genetic condition characterized by telomere shortening that can lead to critical systemic sequelae, including bone marrow failure, pulmonary arteriovenous malformations and fibrosis, and gastrointestinal telangiectatic anomalies. Ophthalmic complications include trichiasis, punctual stenosis, exudative vitreoretinopathy, retinal neovascularization, and tractional/exudative retinal detachment.[1-5] Widefield FA is particularly useful for diagnosing and monitoring the associated retinopathy. Nonproliferative vasculopathies may be managed conservatively, but more significant vascular leakage and proliferative neovascular disease would benefit from treatment with laser photocoagulation. Advanced disease with retinal detachment may require surgical intervention. ■

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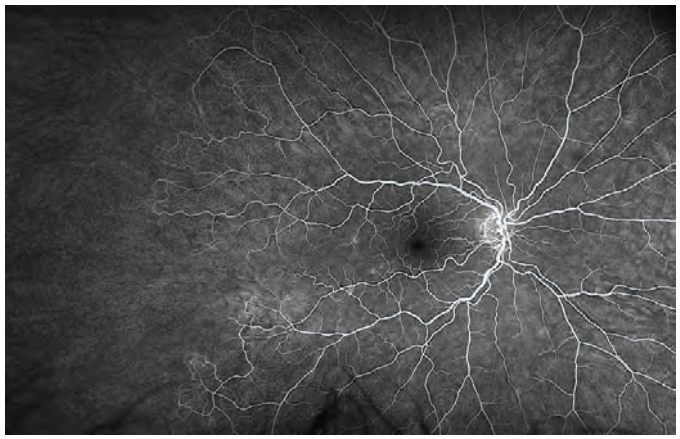

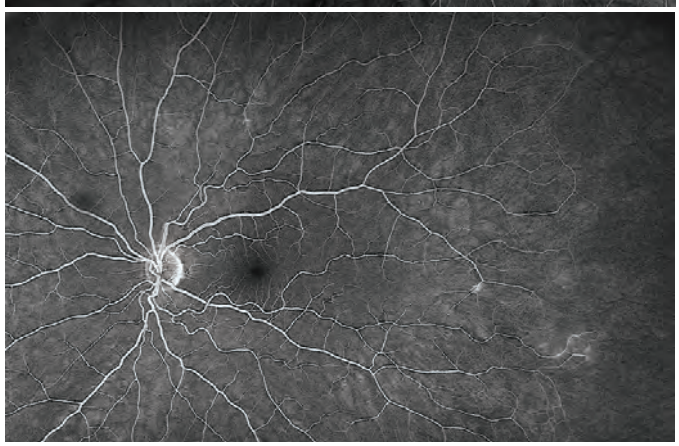

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If you have an image or images you would like to share, email Dr. Nagpal.
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INDEX OF ADVERTISERS

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GREGG T. KOKAME, MD, MMM

What led you to a career as a retina specialist?

My dad was a general surgeon, so I knew I wanted to be a surgeon, but after rotations at David Geffen School of Medicine at UCLA in Los Angeles, I knew that I did not want to be a general surgeon. I was amazed by retinal surgery and the technical ability to do microsurgery with the operating microscope. There was beauty and intricacy in the surgery, as well as the positive effect it had on the lives of patients.

You are the founding partner of a practice with six locations. What are some of the benefits and challenges that come with developing a practice with multiple offices?

I founded Retina Consultants of Hawaii with a vision of creating a world-class retina practice that could allow patients in Hawaii to receive the most advanced retina care here in our island state. By attracting three other top retina specialists, we can now treat patients effectively on three different islands. Patients not living by our main offices in Honolulu and Oahu can be treated on Kauai and Maui without catching a plane for an office visit and treatment—this became especially important with the frequent visits required for intraocular injections. The main challenges have been the transportation and scheduling of our staff to fly to our clinics, the logistics of handling and transporting intravitreal medications, and the volume of patients requiring care at our clinics.

You lecture frequently around the world. What has been the most memorable trip and why?

I have learned so much from my colleagues around the globe and have really enjoyed the friendships I have made. Choosing the *most* memorable trip is difficult as I have lectured at many society meetings and international meetings on six continents. One of the most memorable would have to be the one that included my family. In 2010, there was an international retina meeting in Istanbul, Turkey. At that time, we were still refining the introduction of anti-VEGF treatments, and I presented the first prospective trial of ranibizumab (Lucentis, Genentech/Roche) for a subtype of exudative macular degeneration, polypoidal choroidal vasculopathy. This was an investigator-sponsored trial done only at our site, the Hawaii Macula and Retina Institute. In addition, my family enjoyed the culture and sights of Istanbul and the incredible caves and beauty of Cappadocia—we even stayed in a cave hotel.

How has the pandemic affected your practice in Hawaii?

At the beginning of the pandemic there was a marked effect with the limitation of our practice to emergency patients and those requiring injections, and the limitation of surgery to emergency patients. There was significant concern for our patients, doctors, and staff. There was also the financial burden on our practice; however, we did not lay off any of our staff, and with the help of government support we weathered the initial impact. Now with appropriate precautions our practice and surgical volume are back to normal. However, the marked infectivity of the new COVID-19 variants now makes staffing a problem with multiple unplanned and sudden absences due to infection.

Figure. Dr. Kokame and his family on the slopes of Telluride, Colorado. Although he lives in Hawaii and grew up surfing in its waters, Dr. Kokame's passion is skiing in the snowy mountains.

Your research programs have brought advanced treatments to Hawaii. What professional accomplishment are you most proud of?

My proudest accomplishment is having been awarded the J. Donald M. Gass Medal from the Macula Society. Dr. Gass, the father of medical retina, developed much of our understanding of retinal diseases by his keen observation and putting his findings into a logical yet creative framework. He was also an incredible role model for me with his humble and family-oriented approach to life. I have attempted to model my life after his, and to be awarded the Gass Medal is my most cherished professional accomplishment. ■

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VABYSMO™
faricimab-svoa injection 6 mg

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

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

1 INDICATIONS AND USAGE

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

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

1.2 Diabetic Macular Edema (DME)

4 CONTRAINDICATIONS

4.1 Ocular or Periocular Infections

VABYSMO is contraindicated in patients with ocular or periocular infections.

4.2 Active Intraocular Inflammation

VABYSMO is contraindicated in patients with active intraocular inflammation.

4.3 Hypersensitivity

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

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis and Retinal Detachments

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

5.2 Increase in Intraocular Pressure

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

5.3 Thromboembolic Events

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

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

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

6 ADVERSE REACTIONS

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

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

6.1 Clinical Trial Experience

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

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

Table 1: Common Adverse Reactions (≥ 1%)

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

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

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

6.2 Immunogenicity

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

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

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

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

Data

Animal Data

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

8.2 Lactation

Risk Summary

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

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

8.3 Females and Males of Reproductive Potential

Contraception

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

Infertility

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

8.4 Pediatric Use

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

8.5 Geriatric Use

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

17 PATIENT COUNSELING INFORMATION

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

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

VABYSMO™ [faricimab-svoa]
Manufactured by:
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A Member of the Roche Group
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South San Francisco, CA 94080-4990
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faricimab-svoa injection 6 mg

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INDICATIONS

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

IMPORTANT SAFETY INFORMATION

Contraindications

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

Warnings and Precautions

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

Adverse Reactions

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

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

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

*Dosing Information:

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

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

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

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

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

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