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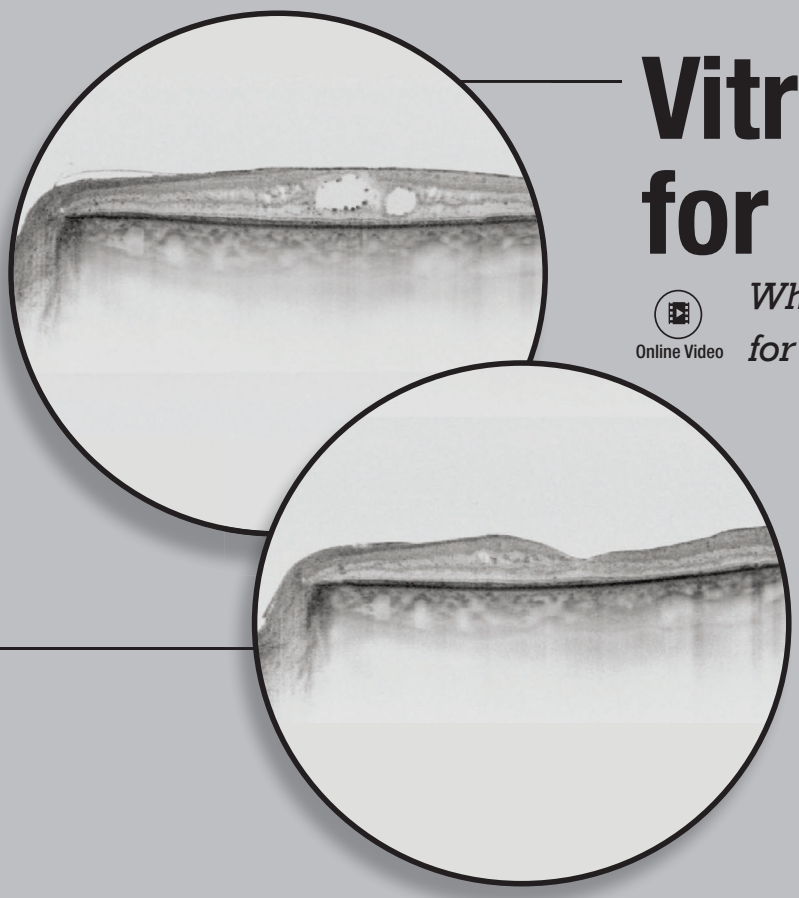


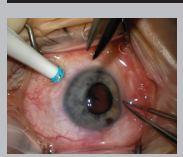
Vitrectomy for DME

Online Video

Why we need to reconsider its role for diabetic macular edema. *Page 20*

Also Inside

Online Video



Pearls for righting aqueous misdirection
Page 19

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

Discover continuous calm in uveitis[1]

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

- Proven to reduce uveitis recurrence at 6 and 12 months[1]*
  At 6 months–18% for YUTIQ and 79% for sham for Study 1 and 22% for YUTIQ and 54% for sham for Study 2 (*P*<.01). At 12 months–28% for YUTIQ and 86% for sham for Study 1 and 33% for YUTIQ and 60% for sham for Study 2.
- Extended median time to first recurrence of uveitis[1,2]
  At 12 months–NE† for YUTIQ/92 days for sham in Study 1; NE for YUTIQ/187 days for sham in Study 2.
- Mean intraocular pressure (IOP) increase was comparable to sham[1,2]
  Study was not sized to detect statistically significant differences in mean IOP.

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

*Study design: The efficacy of YUTIQ was assessed in 2 randomized, multicenter, sham-controlled, double-masked, Phase 3 studies in adult patients (N=282) with non-infectious uveitis affecting the posterior segment of the eye. The primary endpoint in both studies was the proportion of patients who experienced recurrence of uveitis in the study eye within 6 months of follow-up; recurrence was also assessed at 12 months. Recurrence was defined as either deterioration in visual acuity, vitreous haze attributable to non-infectious uveitis, or the need for rescue medications.

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

INDICATIONS AND USAGE

YUTIQ® (fluocinolone acetonide intravitreal implant) 0.18 mg is indicated for the treatment of chronic non-infectious uveitis affecting the posterior segment of the eye.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

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

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

WARNINGS AND PRECAUTIONS

Intravitreal Injection-related Effects: Intravitreal injections, including those with YUTIQ, have been associated with endophthalmitis, eye inflammation, increased or decreased intraocular pressure, and choroidal or retinal detachments. Hypotony has been observed within 24 hours of injection and has resolved within 2 weeks. Patients should be monitored following the intravitreal injection.

Steroid-related Effects: Use of corticosteroids including YUTIQ may produce posterior subcapsular cataracts, increased intraocular pressure and glaucoma. Use of corticosteroids may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses. Corticosteroids are not recommended to be used in patients with a history of ocular herpes simplex because of the potential for reactivation of the viral infection.

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

ADVERSE REACTIONS

In controlled studies, the most common adverse reactions reported were cataract development and increases in intraocular pressure.

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

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

EYEPOINT® PHARMACEUTICALS

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

YUTIQ® (fluocinolone acetonide intravitreal implant) 0.18 mg, for intravitreal injection
Initial U.S. Approval: 1963

BRIEF SUMMARY: Please see package insert for full prescribing information.

1. INDICATIONS AND USAGE. YUTIQ® (fluocinolone acetonide intravitreal implant) 0.18 mg is indicated for the treatment of chronic non-infectious uveitis affecting the posterior segment of the eye.

4. CONTRAINDICATIONS. 4.1. Ocular or Periocular Infections. YUTIQ is contraindicated in patients with active or suspected ocular or periocular infections including most viral disease of the cornea and conjunctiva including active epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections and fungal diseases. **4.2. Hypersensitivity.** YUTIQ is contraindicated in patients with known hypersensitivity to any components of this product.

5. WARNINGS AND PRECAUTIONS. 5.1. Intravitreal Injection-related Effects. Intravitreal injections, including those with YUTIQ, have been associated with endophthalmitis, eye inflammation, increased or decreased intraocular pressure, and choroidal or retinal detachments. Hypotony has been observed within 24 hours of injection and has resolved within 2 weeks. Patients should be monitored following the intravitreal injection *[see Patient Counseling Information (17) in the full prescribing information]*. **5.2. Steroid-related Effects.** Use of corticosteroids including YUTIQ may produce posterior subcapsular cataracts, increased intraocular pressure and glaucoma. Use of corticosteroids may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses. Corticosteroids are not recommended to be used in patients with a history of ocular herpes simplex because of the potential for reactivation of the viral infection. **5.3. Risk of Implant Migration.** Patients in whom the posterior capsule of the lens is absent or has a tear are at risk of implant migration into the anterior chamber.

6. ADVERSE REACTIONS. 6.1. Clinical Studies Experience. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. Adverse reactions associated with ophthalmic steroids including YUTIQ include cataract formation and subsequent cataract surgery, elevated intraocular pressure, which may be associated with optic nerve damage, visual acuity and field defects, secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera. Studies 1 and 2 were multicenter, randomized, sham injection-controlled, masked trials in which patients with non-infectious uveitis affecting the posterior segment of the eye were treated once with either YUTIQ or sham injection, and then received standard care for the duration of the study. Study 3 was a multicenter, randomized, masked trial in which patients with non-infectious uveitis affecting the posterior segment of the eye were all treated once with YUTIQ, administered by one of two different applicators, and then received standard care for the duration of the study. Table 1 summarizes data available from studies 1, 2 and 3 through 12 months for study eyes treated with YUTIQ (n=226) or sham injection (n=94). The most common ocular (study eye) and non-ocular adverse reactions are shown in Table 1 and Table 2.

Table 1: Ocular Adverse Reactions Reported in ≥ 1% of Subject Eyes and Non-Ocular Adverse Reactions Reported in ≥ 2% of Patients

Ocular		
ADVERSE REACTIONS	**YUTIQ (N=226 Eyes) n (%)**	**Sham Injection (N=94 Eyes) n (%)**
Cataract[1]	63/113 (56%)	13/56 (23%)
Visual Acuity Reduced	33 (15%)	11 (12%)
Macular Edema	25 (11%)	33 (35%)
Uveitis	22 (10%)	33 (35%)
Conjunctival Hemorrhage	17 (8%)	5 (5%)
Eye Pain	17 (8%)	12 (13%)
Hypotony Of Eye	16 (7%)	1 (1%)
Anterior Chamber Inflammation	12 (5%)	6 (6%)
Dry Eye	10 (4%)	3 (3%)
Vitreous Opacities	9 (4%)	8 (9%)
Conjunctivitis	9 (4%)	5 (5%)
Posterior Capsule Opacification	8 (4%)	3 (3%)
Ocular Hyperemia	8 (4%)	7 (7%)
Vitreous Haze	7 (3%)	4 (4%)
Foreign Body Sensation In Eyes	7 (3%)	2 (2%)
Vitritis	6 (3%)	8 (9%)
Vitreous Floaters	6 (3%)	5 (5%)
Eye Pruritus	6 (3%)	5 (5%)
Conjunctival Hyperemia	5 (2%)	2 (2%)
Ocular Discomfort	5 (2%)	1 (1%)
Macular Fibrosis	5 (2%)	2 (2%)
Glaucoma	4 (2%)	1 (1%)
Photopsia	4 (2%)	2 (2%)

(continued)

Table 1: Ocular Adverse Reactions Reported in ≥ 1% of Subject Eyes and Non-Ocular Adverse Reactions Reported in ≥ 2% of Patients

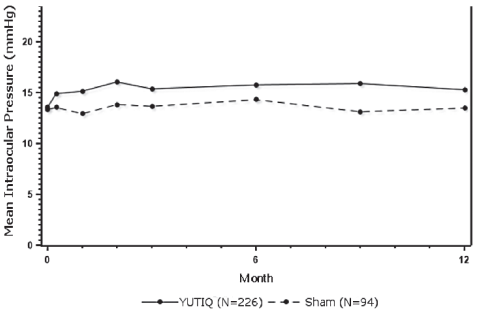
Ocular		
ADVERSE REACTIONS	**YUTIQ (N=226 Eyes) n (%)**	**Sham Injection (N=94 Eyes) n (%)**
Vitreous Hemorrhage	4 (2%)	0
Iridocyclitis	3 (1%)	7 (7%)
Eye Inflammation	3 (1%)	2 (2%)
Choroiditis	3 (1%)	1 (1%)
Eye Irritation	3 (1%)	1 (1%)
Visual Field Defect	3 (1%)	0
Lacrimation Increased	3 (1%)	0
Non-ocular		
ADVERSE REACTIONS	**YUTIQ (N=214 Patients) n (%)**	**Sham Injection (N=94 Patients) n (%)**
Nasopharyngitis	10 (5%)	5 (5%)
Hypertension	6 (3%)	1 (1%)
Arthralgia	5 (2%)	1 (1%)

1. Includes cataract, cataract subcapsular and lenticular opacities in study eyes that were phakic at baseline. 113 of the 226 YUTIQ study eyes were phakic at baseline; 56 of 94 sham-controlled study eyes were phakic at baseline.

Table 2: Summary of Elevated IOP Related Adverse Reactions

ADVERSE REACTIONS	YUTIQ (N=226 Eyes) n (%)	Sham (N=94 Eyes) n (%)
IOP elevation ≥ 10 mmHg from Baseline	50 (22%)	11 (12%)
IOP elevation > 30 mmHg	28 (12%)	3 (3%)
Any IOP-lowering medication	98 (43%)	39 (41%)
Any surgical intervention for elevated IOP	5 (2%)	2 (2%)

Figure 1: Mean IOP During the Studies



8. USE IN SPECIFIC POPULATIONS. 8.1 Pregnancy. Risk Summary. Adequate and well-controlled studies with YUTIQ have not been conducted in pregnant women to inform drug associated risk. Animal reproduction studies have not been conducted with YUTIQ. It is not known whether YUTIQ can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. YUTIQ should be given to a pregnant woman only if the potential benefit justifies the potential risk to the fetus. All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the United States general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. **8.2 Lactation.** Risk Summary. Systemically administered corticosteroids are present in human milk and can suppress growth, interfere with endogenous corticosteroid production. Clinical or nonclinical lactation studies have not been conducted with YUTIQ. It is not known whether intravitreal treatment with YUTIQ could result in sufficient systemic absorption to produce detectable quantities of fluocinolone acetonide in human milk, or affect breastfed infants or milk production. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for YUTIQ and any potential adverse effects on the breastfed child from YUTIQ. **8.4 Pediatric Use.** Safety and effectiveness of YUTIQ in pediatric patients have not been established. **8.5 Geriatric Use.** No overall differences in safety or effectiveness have been observed between elderly and younger patients.

Manufactured by:
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EDITORIAL

By Charles C. Wykoff, MD, PhD

It's later than you think

As society struggles to break out of the COVID-19 pandemic vise-grip, we are all learning to breathe and function again in an open society. While retina clinics worldwide adapted remarkably well to innumerable lockdowns and regulations, our offices continue to adapt to the evolving and regional differences with regard to masking, vaccine and booster documentation, and sick leaves.

What have we learned and what has changed about our profession?

Virtual meetings, infrequent before 2020, are here to stay. The Vit-Buckle Society hosted one of the first 100-percent live virtual meetings in March 2020 and many other societies and conferences adapted to lockdowns by combining prerecorded content with live question-and-answer segments.

Through these two-dimensional meetings, we've learned that while it's possible to maintain established relationships and execute goal-oriented interactions, it's much more challenging to build new relationships or enjoy the spontaneous interactions that so commonly lead to new collaborations and strengthen friendships that occur naturally at in-person meetings.

As such, hybrid meetings may be our new normal. The American Society of Retina Specialists hosted an excellent 2021 meeting in-person and simultaneously live-streamed most of the content, and is doing the same this year. Similarly, ARVO 2022 had both virtual and in-person options for most presentations. More extreme, some meetings such as Angiogenesis, Exudation and Degeneration, appear to have completely transitioned to virtual, with no indication of returning to an in-person format. Such virtual alternatives certainly broaden the reach of the educational activities.

Consistent with adopting virtual meetings, we've more deeply appreciated that portable technology has tremendous potential to impact medical care. Within retina, home-based optical coherence tomography is an obvious evolutionary step forward and is being investigated prospectively.

COVID-19 has changed our practices, too. In this issue, five colleagues share their insights on what we've learned from this pandemic that we can carry forward into future waves and outbreaks (*page* 37).

Maybe the most basic lesson we've been reminded of is to appreciate the time that we have. We never know what tomorrow, both literally and metaphorically, will bring. Enjoy yourself, your family and those around you today, for our days are numbered. It very well may be later than you think.

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.

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Apellis

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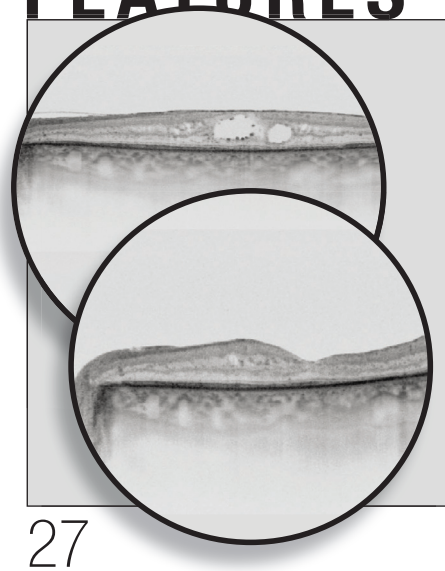
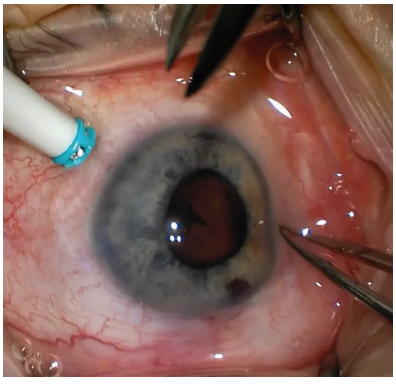
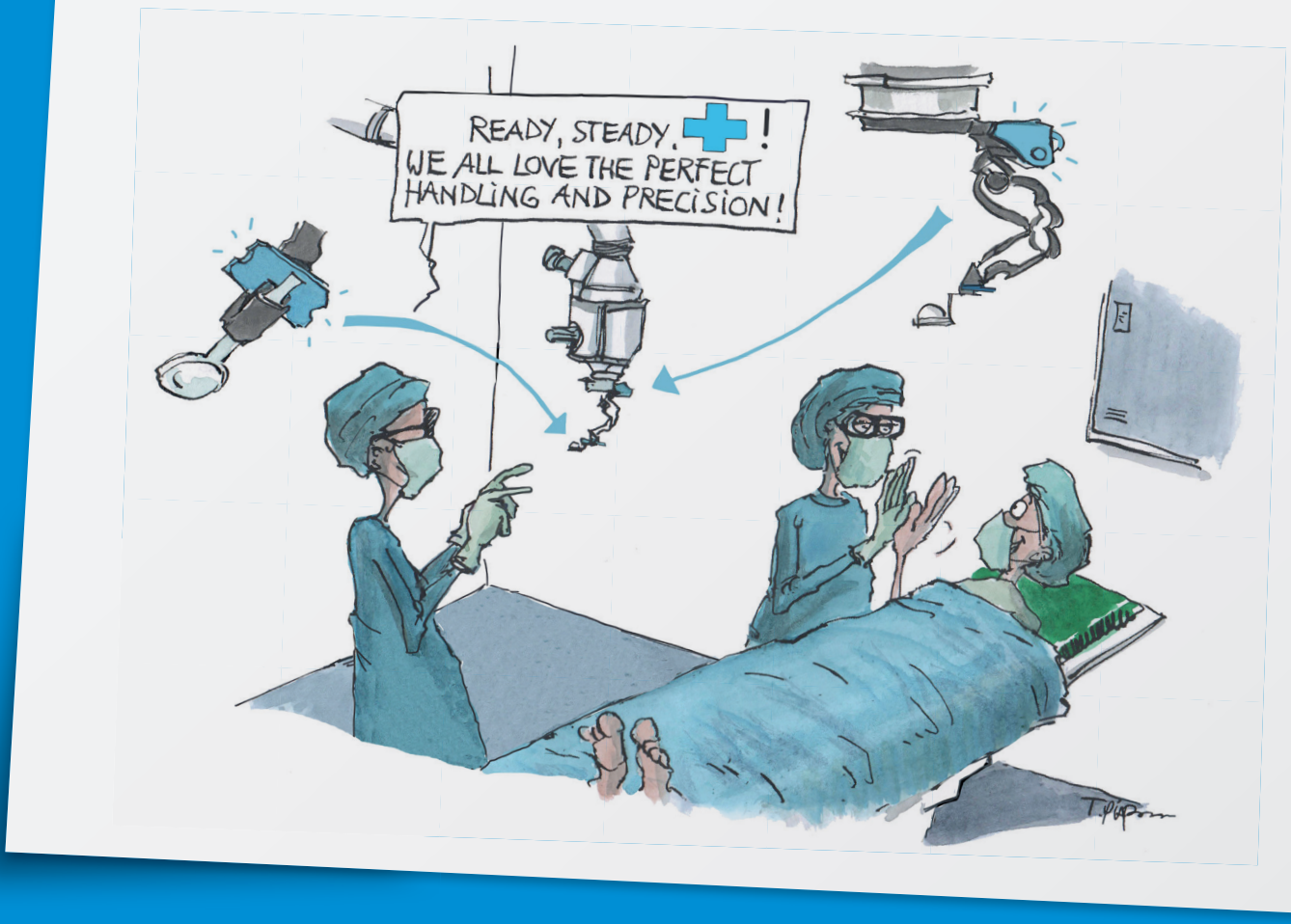
FEATURES



DEPARTMENTS





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OCULUS® SURGICAL

With Byooviz, Biogen takes a leap on pricing first U.S. retina biosimilar

In what is shaping up to be the summer of the biosimilars in retina, two products that reference Lucentis are taking significant steps to enter the U.S. market. Byooviz—pronounced bio-vizz—had its commercial launch July 1, after receiving Food and Drug Administration approval last year. And in August, the FDA is poised to act on an application for CHS-201 that Coherus Biosciences submitted last year.

Byooviz hits the market at $1,130 for a single-use 0.5-mg vial, Jillian Scaife, senior director of marketing access for U.S. biosimilars at Biogen, tells *Retina Specialist*. That's about 40 percent lower than what Global Data reports as the list price of $1,850 for Lucentis (ranibizumab, Genentech/Roche).

Biogen seems to have taken a leap in the pricing for Byooviz. In an interview last year, Peter Downs, an analyst with Market Scope, said that the first biosimilars in other therapeutic areas, such as oncology or immunology, typically come in 10 to 15 percent lower than the reference product. "But by the time you get the third one, it typically comes in at about 60 percent of the reference price," he said. Byooviz, however, is already there, leaving payers and providers wondering where Coherus will go with its pricing if the FDA approves CHS-201.

Byooviz is approved for treatment of neovascular age-related macular degeneration, macular edema following retinal vein occlusion and myopic choroidal neovascularization.

Getting on formularies

Ms. Scaife says Biogen has already engaged payers to put Byooviz on their formularies. "A number of large payers have actually already granted Byooviz parity access to the reference product Lucentis," she says.

The company's marketing team is also reaching out to commercial regional and national payers, including Medicare Advantage and traditional Medicare administrators, to educate them about biosimilars.

While Biogen has commercialized biosimilars in immunology in Europe, Byooviz represents its first foray into biosimilars in the United States. "We will definitely leverage the experience in Europe for our U.S. adoption," she says. That includes a multifaceted provider education program centered on live meetings and monographs.

"And as biosimilars become more widely adopted in clinical practice, we will work closely with third-party investigators to generate real-world evidence on the clinical safety and effectiveness of biosimilars," Ms. Scaife says.

Next up: Coherus

Last year, the FDA set a Biosimilar User Fee action date of August 2 on Coherus' Biologic License Application for CHS-201. Coherus obtained the U.S. license from Bioeq. But that won't be the last word on anti-VEGF biosimilars in the United States. Xbrane Biopharma withdrew the Biologic License Application (BLA) it filed with the FDA for its Lucentis biosimilar candidate, Xlucane, and is contemplating a timeline for resubmission.

Meanwhile, a number of biosimilars of Eylea (aflibercept, Regeneron Pharmaceuticals), which comes off patent next year, are in clinical trials. They include SB15, which Biogen is developing with Samsung Bioepis, with whom it developed Byooviz. The Phase III trial finished up in March.

IN BRIEF

The Food and Drug Administration has approved **Beovu** (brolucizumab, **Novartis**) 6 mg for the treatment of diabetic macular edema. The approval was based on year one data from the Phase III KESTREL and KITE studies, which met their primary endpoint of noninferiority in change in best-corrected visual acuity from baseline vs. aflibercept.

Apellis Pharmaceuticals has submitted a New Drug Application (NDA) with the FDA for intravitreal **pegcetacoplan** for the treatment of geographic atrophy secondary to age-related macular degeneration. Pegcetacoplan is an investigational, targeted complement factor 3 therapy. The NDA submission is based on 12- and 18-month results from the Phase III DERBY and OAKS studies, and 12-month Phase II FILLY study results.

Luxa Biotechnology, a joint venture of **Y2 Solution** and the **Neural Stem Cell Institute**, reports transplantation of the cell product **RPESC-RPE-4W** into the first participant with dry AMD in its Phase I/IIa clinical trial. RPESC-RPE-4W is derived from the retinal pigment epithelium stem cell in the adult human retina. The trial is being conducted at the University of Michigan Kellogg Eye Center, Ann Arbor.

On the lower end of the anti-VEGF price spectrum, Outlook Therapeutics has submitted a BLA to the FDA for Lytenava, an ophthalmic formulation of the widely used Avastin (bevacizumab, Genentech/Roche), which is used off-label to treat AMD, diabetic macular edema and branch retinal vein occlusion. Outlook says it anticipates marketing approval by early 2023.

AAO panel: 'De-adopt' endogenous *Candida* endophthalmitis screening

For decades hospitalists called in ophthalmologists to routinely screen for intraocular infection in patients who contracted *Candida* bloodstream infections. Now, an American Academy of Ophthalmology panel, after reviewing the available evidence, has issued recommendations that "this low-value practice should be de-adopted."[1]

"There just hasn't been a proven benefit to this," Mark P. Breazzano, MD, lead author of the recommendation-writing panel, says. "In medicine we have this sort of cognitive bias or confirmation bias where we want to intervene and thus help people, as we all should, but we need to recognize when the rare chance of helping someone might be outweighed by the potential benefits of modifying treatment." Dr. Breazzano is with Retina Vitreous Surgeons of Central New York, based in Syracuse, and is an assistant professor at SUNY Upstate Medical University.

The panel found that the practice, dating to the 1970s and confirmed as late as 2016 by the Infectious Disease Society of America (IDSA),[2] simply had no medically sound justification. The AAO panel's recommendations fall in line with similar guidance that the Royal College of Ophthalmologists and Intensive Care Society in the United Kingdom issued in 2020.[3] Dr. Breazzano says the U.S. IDSA declined to participate in drafting the new AAO guidelines.

Not the case anymore

Patients with indwelling catheters are prone to *Candida* bloodstream infections. Dr. Breazzano says the concept of routine endophthalmitis screening in these patients dates to a time when antifungal therapies weren't widely available and was based on conflicting clinical definitions. That's not the case anymore.

The AAO panel evaluated a number of case series and systematic reviews—randomized clinical trials and rigorous studies of *Candida* endophthalmitis secondary to fungal infections aren't available—in reaching their consensus, Dr. Breazzano says. The rate of endophthalmitis in these cases was less than 1 percent, he says. "And within that, none have actually been directly confirmed by ocular tissue," he says.

—Richard Mark Kirkner

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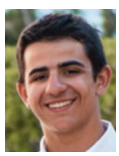
AMD consensus nomenclature explained

An overview of the variants of age-related macular degeneration and their mimickers.

By Tina Felfeli, MD, Michael Grinton, MD, FRCOphth, John Papanikolaou, Parampal S. Grewal, MD, FRCSC, Peng Yan, MD, FRCSC, Dan Weisbrod, MD, FRCSC, and Efrem D. Mandelcorn, MD, FRCSC

Tina Felfeli, MD

Michael Grinton, MD, FRCOphth



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Dan Weisbrod, MD, FRCSC

Efrem D. Mandelcorn, MD, FRCSC

Age-related macular degeneration has been classically categorized as "dry" (non-neovascular or non-exudative) vs. "wet" (neovascular or exudative), but this categorization may be an oversimplification that may not encapsulate the full spectrum and complexity of the disease. Furthermore, the terms *neovascular* and *exudative* may not be fully interchangeable. Here, we'll provide a overview of the variants of AMD and their mimickers with the purpose of guiding management of this multifaceted disease.

The presence of drusen and retinal pigment epithelium changes characterize non-neovascular or nonexudative—dry—AMD in the absence of neovascularization (*Figure 1*). Historically, the Age-related Eye Disease Study classified dry AMD based on examination findings of hard drusen, soft drusen, RPE abnormalities and atrophy.[1]

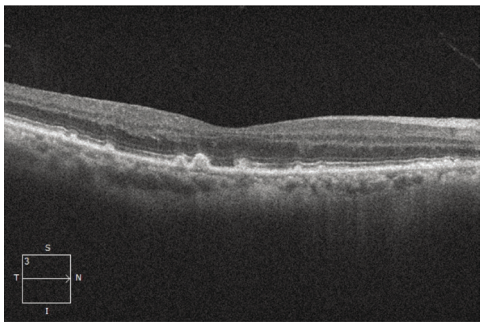

Figure 1. Optical coherence tomography scan showing drusen (accumulation of deposits underneath the retinal pigment epithelium), a sign of dry age-related macular degeneration.

Consensus nomenclature for MNV

Neovascular or exudative—wet—AMD is diagnosed when there is macular neovascularization on multimodal imaging in the setting of drusen and RPE changes. Historically, neovascular AMD was defined as predominantly classic or occult based on angiographic patterns. Recent AMD consensus nomenclature[2] has established use of the term macular neovascularization (MNV) and divided this into types 1, 2 and 3 MNV, primarily based on optical coherence tomography findings. In this classification, type 1 MNV corresponds to occult choroidal neovascularization while type 2 MNV corresponds to a classic CNV. Type 3 MNV corresponds to retinal angiomatous proliferation (RAP).

Characteristics of the three types of MNV in AMD are:

- ***Type 1 MNV*** involves the ingrowth of vessels initially from the choriocapillaris into the sub-RPE space.[2] On fluorescein angiography, type 1 MNV depicts poorly defined regions of fluid leakage

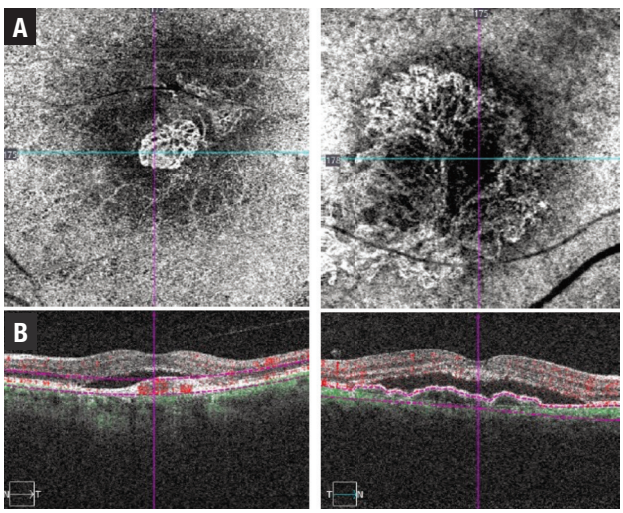

Figure 2. Two examples of type 1 macular neovascular membrane: A) Optical coherence tomography angiography en-face scan; and B) B-scan flow overlay showing subretinal pigment epithelium neovascular membranes.

corresponding to a region of elevated RPE caused by the growth of these vessels.[2] Angiographically, these lesions are typically classified as occult CNV and could present as a fibrovascular pigment epithelial detachment (PED) or late leakage of undetermined origin (*Figure 2*).

- ***Type 2 MNV*** grows from the choroid into the subretinal space. Consequently, hemorrhage or exudation often presents in the subretinal space and may compromise the neurosensory retina more severely.[2] On FA, these lesions are typically classified as predominately classic CNV with a well-demarcated area of hyperfluorescence appearing early, expanding and ultimately obscuring the boundaries of the CNV from leakage (*Figure 3*).
- ***Type 3 MNV***, also known as retinal angiomatous proliferation (RAP), differs from type 1 and 2 lesions as the neovascularization is thought to originate from within the retina itself and is often associated with intraretinal rather than subretinal fluid and hemorrhage. As it progresses, type 3 MNV forms a retinal-retinal anastomosis and invades the subretinal space with the development of a serous PED (*Figure 4*). Finally, a retinal-choroidal anastomosis occurs through the vertex of the PED with the development of CNV. Early type 3 lesions may present as a focal area of hyperfluorescence on FA. As the lesion progresses, a serous PED or CNV may appear on FA.

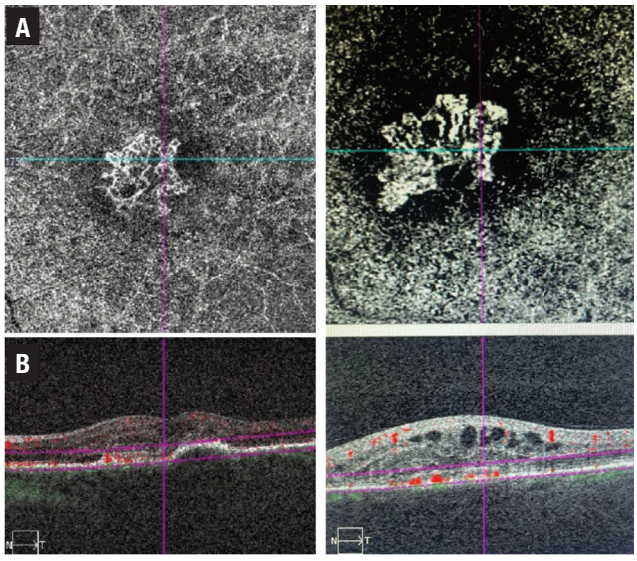

Figure 3. Two examples of type 2 macular neovascular membranes. A) Optical coherence tomography angiography en-face scans; and B) B-scan flow overlays showing subretinal neovascular membranes.

Nonexudative macular neovascularization

In 1973, John Sarks, MD, and colleagues reported a series of patients who

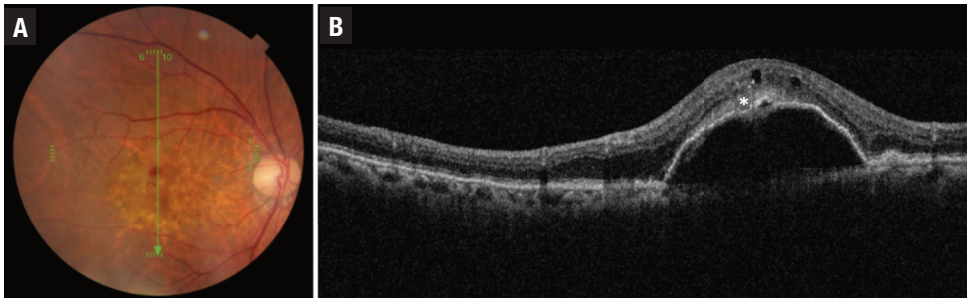

Figure 4. An example of a type 3 macular neovascular membrane. A) Fundus photograph shows intraretinal hemorrhage and pseudodrusen. B) Corresponding optical coherence tomography B-scan shows serous pigment epithelial detachment, intraretinal fluid and subretinal hyperreflective density (asterisk).

Bios

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had no clinical signs of neovascularization, but had type 1 MNV as revealed by histopathological analysis.[3] More recently, with the advent of OCT angiography, many reports of patients with nonexudative, neovascular membranes have been published, suggesting the terms *exudative* and *neovascular* shouldn't be used interchangeably.

The term *neovascular* should refer to the presence of new vessels confirmed on OCTA, while *exudative* simply refers to the presence of fluid or hemorrhage as determined clinically or with OCT imaging (*Figure 5*). With the evolution of OCTA, the prevalence of subclinical nonexudative, neovascular lesions has been reported to range from 6 to 27 percent in fellow eyes of patients with nAMD, and serves as an important predictor of future exudation.[4]

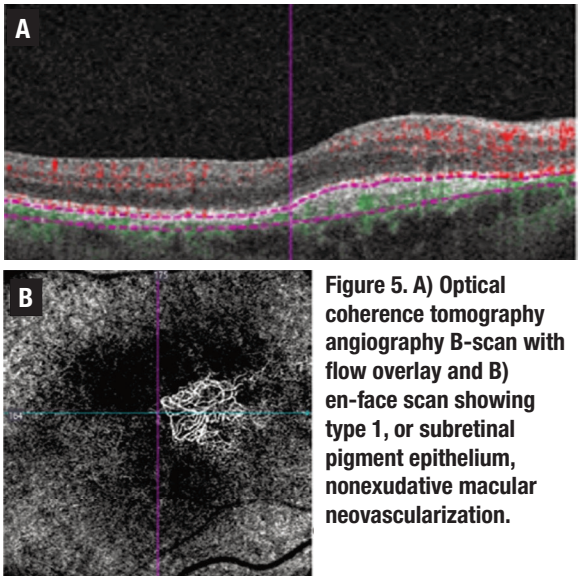


Figure 5. A) Optical coherence tomography angiography B-scan with flow overlay and B) en-face scan showing type 1, or subretinal pigment epithelium, nonexudative macular neovascularization.

The optimal management of patients with nonexudative MNV remains to be established.[5] Some advocate educating these patients about warning symptoms and monitoring them closely for signs of exudation.

PEDs can occur in both non-neovascular and neovascular AMD. Four characteristic types of PEDs exist:

- drusenoid;
- serous;
- fibrovascular; and
- hemorrhagic.

A drusenoid PED is thought to be the result of coalescence of pre-existing soft drusen, whereas a serous PED represents a detachment of the RPE from Bruch's membrane due to the accumulation of fluid.

A vascularized PED occurs when abnormal vessels gain entry to the sub-RPE space through breaks in Bruch's membrane. Signs of a vascularized PED include a notched or shallow irregular border to the PED, which can be associated with fluid, lipid exudate or hemorrhage. A shallow irregular RPE elevation (SIRE) on OCT should raise the suspicion of a vascularized PED or type 1 MNV. In some cases, banding can also be evident on OCT within a fibrovascular PED (*Figure 6*).

An RPE tear is a risk particularly in a vascularized PED, with MNV at the margin of a large PED. When the MNV contracts, which can occur spontaneously or after treatment, the RPE can tear and roll up on itself, leading to an area of geographic atrophy. If this occurs in the center of the macula, the visual prognosis is poor. Sub-RPE hemorrhage, as in a hemorrhagic PED, will appear darker than subretinal hemorrhage.

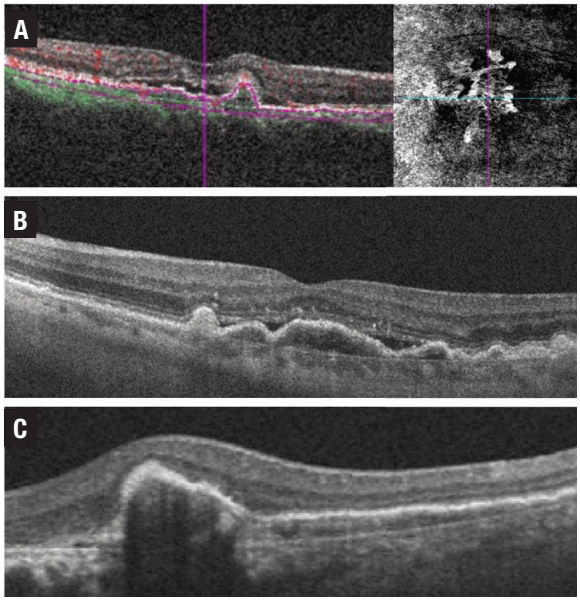


Figure 6. A) Optical coherence tomography angiography B-scan with flow overlay (left) and en-face scan (right) show a vascularized pigment epithelial detachment. B) Shallow irregular retinal pigment epithelium elevation (SIRE). C) Fibrovascular PED with banding.

Acquired vitelliform lesion

AVLs can also develop in AMD and can be mistaken for a drusenoid PED or even MNV. AVLs can be differentiated from drusenoid PEDs as the subretinal material accumulates above the RPE (*Figure 7*). AVLs can also be associated with optically empty spaces under the neurosensory retina, which also shouldn't be mistaken for subretinal fluid from MNV in order to avoid unnecessary treatment. Unlike MNV, AVLs tend to be quite stationary over time. However, they can eventually regress, leading to GA and vision loss.

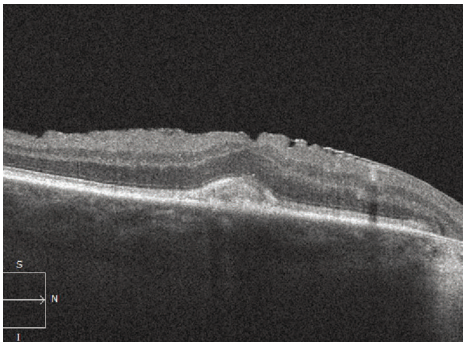


Figure 7. Optical coherence tomography scan shows an acquired vitelliform lesion with accumulation of material above the retinal pigment epithelium (also associated epiretinal membrane).

Fluid mimickers

Active exudation in AMD can present within the retina as intraretinal fluid in the form of cystoid macular edema, under the neurosensory retina in the subretinal space as subretinal fluid or under the RPE, leading to a PED. Vascular endothelial growth factor mediates IRF and SRF in nAMD, so it should respond to treatment with anti-VEGF injections. However, fluid in the setting of AMD can occur in other contexts.

For example, SRF associated with a PED has been well described in the setting of non-neovascular AMD in a few instances, such as a pocket of fluid along the edge of a PED, at the vertex of a PED or under the retina as it drapes over confluent PEDs (*Figure 8*).[6] Unlike active exudate from a neovascular lesion, this fluid can be thought of as a transudate resulting from RPE dysfunction, due to relative ischemia of the RPE, as it is displaced from the underlying choriocapillaris.[6,7] It's important to identify this as nonexudative to avoid unnecessary treatment.

Also, SRF can sometimes be present as a result of RPE dysfunction without MNV in the setting of AMD, as confirmed on multimodal imaging. Some authors have suggested the term "nonexudative detachment of the neurosensory retina" (NED-NR) to describe the presence of SRF when there's no evidence of neovascularization on multimodal imaging.[8]

Patients can often be asymptomatic or minimally symptomatic from dry AMD changes. Care must be taken to not rush into treating these cases. SRF has been shown to not be as detrimental to the health of the overlying retina in cases where it's not progressive, even in the presence of MNV.[9,10] If MNV is excluded on multimodal imaging, these cases can be monitored closely for progressive vision loss or the development of MNV. The SRF tends to be stable and in some cases will resolve over time.

IRF is another location in which fluid in the setting of AMD can occur. IRF typically occurs from intraretinal neovascularization, or intraretinal migration of fluid originating from subretinal or sub-RPE

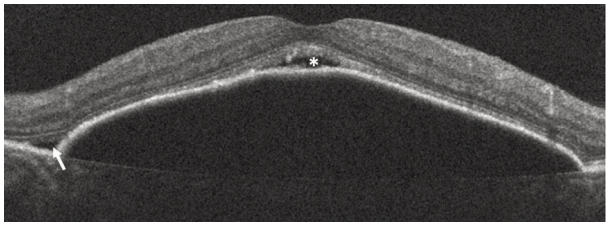


Figure 8. Optical coherence tomography of a large pigment epithelial detachment associated with subretinal fluid at the edge (arrow) and vertex (asterisk) of the PED.

Active exudation can present within the retina as intraretinal fluid in the form of cystoid macular edema, under the neurosensory retina in the subretinal space as subretinal fluid or under the RPE, leading to a PED.

neovascular lesions, with disruption of the outer retinal layers. This contrasts with macular edema in diabetic retinopathy or retinal vein occlusion, in which VEGF-mediated hyperpermeability of endothelial cells leads to IRF.[11]

However, IRF in the setting of AMD shouldn't be mistaken for degenerative intraretinal cystoid lesions (ICLs), which can occur over RPE and outer retinal atrophy (RORA), and doesn't respond to intravitreal anti-VEGF injections.[12] ICLs often appear small and vertically oval in shape on OCT and are thought to be due to degeneration of Muller cells in the retina.

Similarly, outer retinal tubulation can be mistaken for IRF (*Figure 9*). Although outer retinal tubulation occurs in the setting of neovascular AMD, it develops as a result of damage to the underlying retina, is not exudative and generally remains stable over time even in patients receiving anti-VEGF therapy.[13]

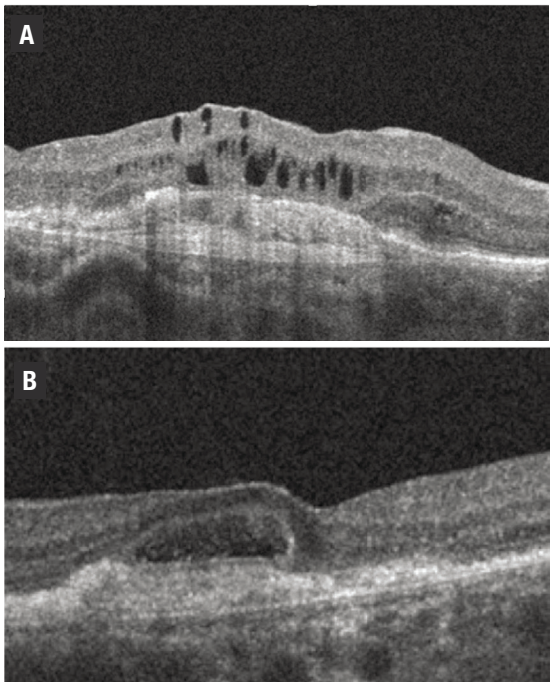


Figure 9. Optical coherence tomography shows: A) degenerative intraretinal cystoid lesions overlying a disciform scar; and B) outer retinal tubulation.

Exudation with IRF is typical in types 2 and 3 MNV. Type 1 MNV typically presents with fluid in the subretinal compartment. However, type 1 MNV with RORA may present with IRF in the absence of SRF (*Figure 10*). This has been described as a result of tight glial connections between the overlying outer retinal tissue and sub-RPE space, with intraretinal exudation through associated defects in the ELM, rather than the more common occurrence of SRF in type 1 lesions.[14]

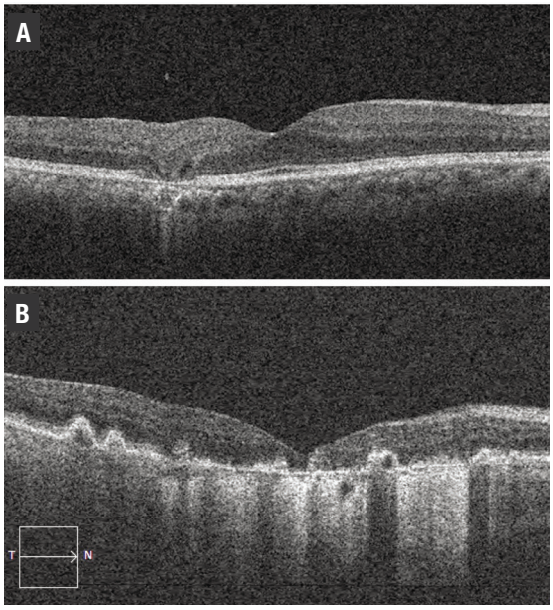


Figure 10. Optical coherence tomography scans of: A) incomplete retinal pigment epithelium and outer retinal atrophy (iRORA); and B) complete RPE and outer retinal atrophy (cRORA).

Fluid: A differential diagnosis

The differential diagnosis of IRF should consider multiple classifications (*Table*).

Exudation with IRF has also been reported in the setting of AMD in the absence of MNV on multimodal imaging. In this exudative form of non-neovascular AMD, IRF may suggest a form of preproliferative type 3 MNV unidentified on multimodal imaging. This has been described as increasingly elevated VEGF levels from a state of chronic retinal ischemia.[15]

These cases can also be monitored for progression if they're asymptomatic and stable. However, if there is progressive accumulation of fluid or vision loss, these patients may respond to intravitreal anti-VEGF therapy despite the absence of MNV on multimodal imaging.

Also included in the differential of fluid is a spectrum of intraretinal alterations that VEGF promotes, including excessive leakage from native retinal vessels, such as in macular telangiectasia, DME, retinal vein occlusions and perifoveal exudative vascular anomalous complex (PEVAC).

Perifoveal exudative vascular anomalous complex

PEVAC is a relatively newly described entity comprised of an isolated large perifoveal aneurysm in the absence of retinal vascular or inflammatory diseases in otherwise healthy individuals (*Figure 11*).[16] The pathogenesis, course and best treatment for the condition isn't certain,[17] but it's an important differential diagnosis to consider in patients with IRF.

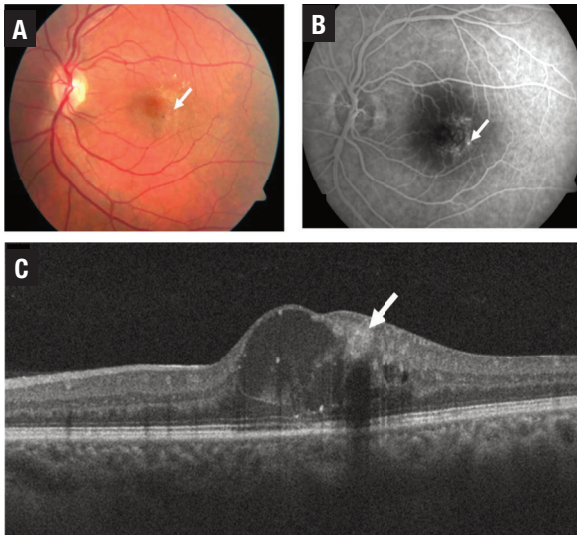


Figure 11. Multimodal imaging of perifoveal exudative vascular anomalous complex (PEVAC) shows: A) an isolated aneurysm (arrow) temporal to the fovea; and B) confirmatory fundus fluorescein angiography. C) Optical coherence tomography shows the aneurysm with a hyperreflective wall and hyporeflective lumen.

Table. Differential diagnoses for intraretinal fluid

Age-related macular degeneration causes	Non-AMD causes

Neovascular AMD
• Type 3 macular neovascularization (MNV)
• Type 2 MNV
• Type 1 MNV
  - Particularly if associated with retinal pigment epithelium and outer retinal atrophy (RORA)
 	
Non-neovascular AMD
• Exudative, non-neovascular AMD
  - Exudation in the absence of MNV
• Neurosensory degeneration
  - Outer retinal tubulation
  - Nonexudative, degenerative cysts
	• Polypoidal choroidal vasculopathy
	• Vitelliform lesions
	• Central serous chorioretinopathy
	• Other causes of MNV (myopia, pachychoroid neovasculopathy, inflammatory, hereditary, neoplastic, traumatic)
	• Retinal vascular disease (diabetic macular edema, retinal vein occlusion, perifoveal exudative vascular anomalous complex/PEVAC)
	• Macular telangiectasia
	• Inflammatory conditions
	• Medications

Polypoidal choroidal vasculopathy

PCV is a vascular disease of the choroid that was first described in the 1990s.[18] PCV lesions contain polypoidal aneurysmal vascular dilations or terminal polyps with or without an associated type 1 branching vascular network (BVN).[19] Clinically, PCV is associated with multiple PEDs, which may be serous or hemorrhagic.

An orange-red lesion may also appear in the choroid, indicating the presence of a polyp. Hard exudates are common, and hemorrhage may be found in all layers of the retina, including occasionally breaking through into the vitreous. Drusen is also conspicuously absent in patients with PCV.

The gold standard for the diagnosis of PCV is indocyanine green angiography. Nonetheless, several studies have also shown that PCV can be diagnosed on enhanced-depth OCT imaging with a high degree of accuracy.[20]

(Continued on page 18)

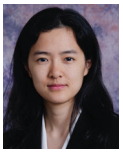
Anticoagulation and a second RVO

Managing retinal vein occlusion in a patient with a history of thrombophilia.

By Deion Sims, Philina Yee, MD, Amy Yuan, MD, and Lisa Olmos De Koo, MD, MBA


Deion Sims


Philina Yee, MD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Dr. Olmos de Koo is an associate professor of ophthalmology and director of the retina fellowship program at the University of Washington in Seattle, where Mr. Sims is a medical student, Dr. Yee is an ophthalmology resident and Dr. Yuan is a retina fellow.

A 71-year-old male with a history of factor V Leiden thrombophilia and on oral anticoagulation therapy, and who had a previous right central retinal vein occlusion in 1999, came to the emergency department with left-sided paracentral vision loss.

He reported cloudiness, color distortion and odd shapes in the left lower side of his vision OS. He denied flashes of light, dark spots, curtains in vision or eye pain. He also denied slurred speech, new focal weakness, numbness or facial drooping. He reported that, upon the advice of his primary-care team and anticoagulation clinic, he had switched from Coumadin (warfarin sodium) to Eliquis (apixaban) two weeks earlier and since then had felt minor dizziness and fatigue.

What we found on exam

On examination, best-corrected visual acuity was stable at 20/25 in the right eye and 20/20 in the left. Intraocular pressures were 19 and 15 mmHg in the right and left eyes, respectively. Both pupils were round, reactive to light and without an afferent pupillary defect. Confrontational fields and extraocular movements were full in both eyes.

The dilated fundus exam of the right eye revealed collaterals and mild pallor of the disc. The macula was noted to have pigmentary changes, focal laser scars and temporal blot heme. These findings were all consistent with the patient's history of CRVO after focal laser treatment in the right eye and unchanged from his visit six months earlier. Color fundus photos and fundus autofluoresence in the left eye (*Figure 1*) demonstrated blot hemorrhages in the superior retina and a tortuous venous system throughout.

Work-up

Optical coherence tomography, fundus photos and fluorescein angiography were performed to document and assess the newly decreased vision in the left eye. OCT of the right eye revealed retinal atrophy and mild paracentral cysts stable from a year ago. OCT of the left showed a normal foveal contour and no intraretinal or subretinal fluid, also stable from a year ago. Fluorescein angiogram demonstrated delayed superior venous filling and slow, late disc leakage (*Figure 2*).

Diagnosis and management

The patient's history of factor V Leiden and remote history of CRVO in the fellow eye, coupled with his report of acute sub-

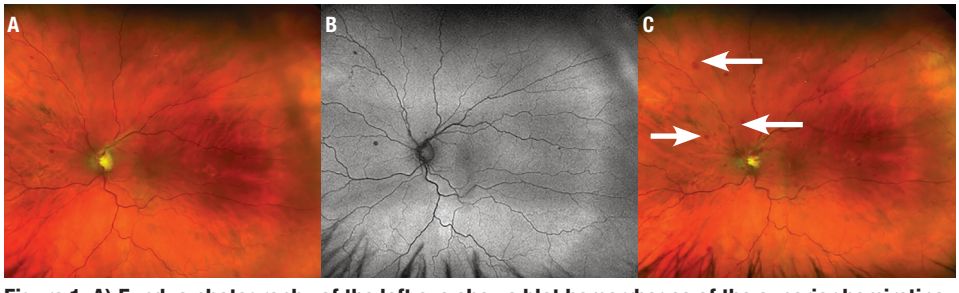

Figure 1. A) Fundus photography of the left eye shows blot hemorrhages of the superior hemiretina as well as a tortuous venous system. B) Fundus autofluorescence of the eye highlights the blot hemorrhages in the superior retina. C) Fundus photography of the left eye two weeks after the initial visit shows increased blot hemorrhages (arrows) now involving the entire retina and a new flame hemorrhage off the optic nerve superotemporally.

jectively decreased paracentral vision with visual acuity of 20/20 in the left eye, plus the presence of intraretinal hemorrhages and delayed superior venous filling on FA, were consistent with a diagnosis of impending hemiretinal vein occlusion.

We paged the patient's primary-care team and anticoagulation clinic and arranged for him to restart his warfarin therapy. We offered the patient topical IOP-lowering therapy with brimonidine twice daily, with the rationale of increasing ocular perfusion pressure. We also followed him closely in the clinic.

Two weeks later, he restarted warfarin and his prothrombrin time (PT) was back within goal at 2.4. VA remained 20/20, but subjectively his vision had worsened and on exam he showed increased blot hemorrhages now spreading to involve the entire retina and a new flame hemorrhage off the optic nerve (*Figure 1C*). OCT remained stable without macular edema. We-added another nonprostaglandin IOP-lowering agent because his IOP stabilized at 14 mmHg.

Three weeks later, and five weeks after his initial presentation, the patient returned with reduced VA of 20/60 and new macular edema on OCT. We treated him with intravitreal bevacizumab.

RVO and anticoagulation

Given the timing of this patient's symptoms after switching from warfarin to apixaban, it's possible that his PT was temporarily subtherapeutic, contributing to the development of RVO. This case demonstrates the importance of closely monitoring patients with a history of thrombophilic disorders, such as factor V Leiden, when switching anticoagulant medication, particularly in those with a previous RVO. It also highlights the challenges in diagnosis and management of impending retinal vein occlusion.

RVO is a leading cause of vascular blindness. Risk factors associated with CRVO include hypertension, open-angle glaucoma and diabetes mellitus.[1] Risk factors for BRVO include hypertension, open-angle glaucoma, cardiovascular disease and high body-mass index.[2] One of the most significant risk factors for developing RVO is an RVO in the contralateral eye. People with BRVO in one eye have a 10 percent risk of developing a BRVO in the contralateral eye within three years.[3] The risk of contralateral involvement in a patient with CRVO increases 1 percent every year and jumps to 7 percent after five years.[3,4]

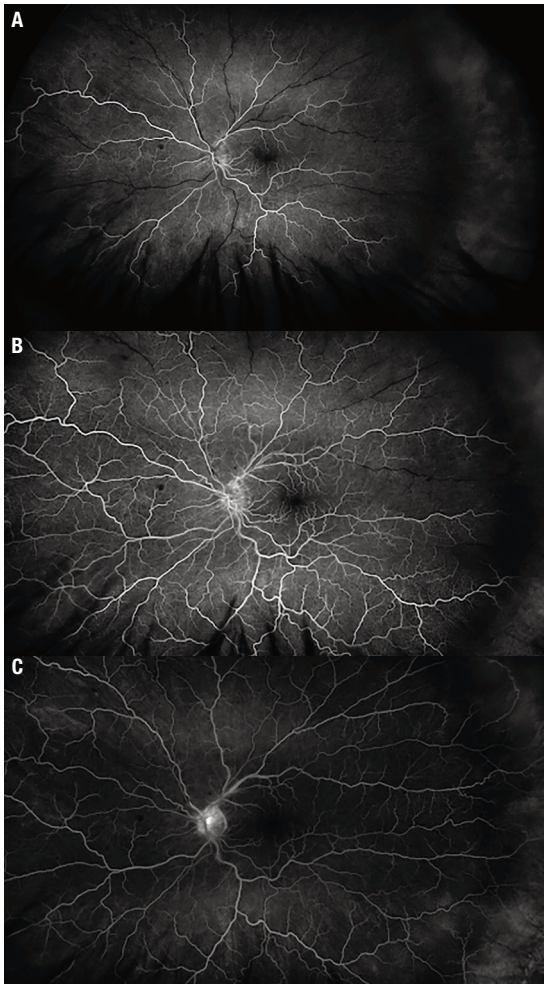

Figure 2. Fluorescein angiogram of the left eye at three different intervals: A) 26 seconds; B) 37 seconds; and C) 3 minutes, 18 seconds. The FA showed delayed superior venous filling and slow, late disc leakage, but no ischemia.

RVO and patient age

When diagnosing RVO in older patients with cardiovascular risk factors, laboratory tests may not be indicated. If the patient is younger, as our patient was in 1999 when he was first diagnosed with CRVO in his right eye, or has none of the typical risk factors, laboratory tests such as complete blood count, fasting serum glucose and thrombophilic screening (factor V Leiden, protein C and S, and antiphospholipid antibodies) may be considered. A carotid duplex may also be helpful.

Currently, there's no treatment available to reverse RVO. Radial optic neurotomy surgery remains controversial in CRVO cases, but would be ruled out when the VA

is relatively preserved.[5] Common complications of RVO are macular edema and neovascularization.

Anti-VEGF injections are now the first-line treatment for macular edema and iris neovascularization.[6]

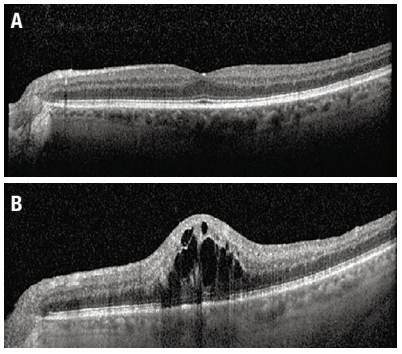

Figure 3. A) Optical coherence tomography at presentation shows no macular edema. B) Five weeks later, OCT shows diffuse central cystic intraretinal fluid.

Triamcinolone has been shown to improve macular edema in CRVO but not BRVO.[7] Patients with RVO should be monitored closely for macular edema or neovascularization during the first six months after diagnosis.

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AMD consensus nomenclature explained

(Continued from page 15)

The three major criteria for diagnosing PCV on OCT are:

- sub-RPE ring-like lesion (i.e., polyp);
- peaked PED; and
- complex RPE elevation on *en face* OCT.[21,22]

Other OCT features include:

- SRF rather than IRF;
- notched PED (a high PED with a low-lying PED indicating the presence of a BVN);
- double-layer sign (separation of the RPE from Bruch's membrane); and
- pachychoroid.

PCV has been described as a variant of a type 1 MNV or it can occur as a standalone disease without signs of drusen and AMD. It's now thought to be part of the pachychoroid spectrum, which includes central serous chorioretinopathy, pachychoroid epitheliopathy, pachychoroid CNV, peripapillary pachychoroid syndrome and focal choroidal excavation.

Bottom line

Given the increase in life expectancy, the prevalence of AMD is predicted to increase substantially. It's important for retina specialists to have an understanding of the classification of this complex disease, including all its subtypes, especially as the future promises new and exciting treatments for both neovascular and non-neovascular AMD as well as advances in imaging and information processing.

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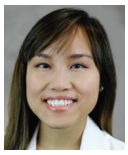
Pearls for righting aqueous misdirection

How to do a pars plana vitrectomy with irido-zonulo-hyaloidectomy when laser and medical therapy fail.

By Grant A. Justin, MD, S. Tammy Hsu, MD, and Lejla Vajzovic, MD

Grant A. Justin, MD



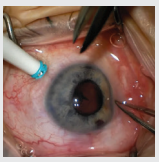
S. Tammy Hsu, MD

Lejla Vajzovic, MD

Aqueous misdirection, also known as malignant glaucoma, is an uncommon type of secondary angle-closure glaucoma that can require vitreosurgical management.[1] The pathophysiology is believed to be secondary to misdirection of aqueous fluid, resulting in hydration of the vitreous body. The vitreous hydration causes anterior rotation of the ciliary body with forward displacement of the iris and lens, and subsequent shallowing of the anterior chamber.

Patients with aqueous misdirection present with a shallow anterior chamber and high intraocular pressure. The differential diagnosis includes pupillary block, choroidal detachment, suprachoroidal hemorrhage or over-filtration from a filtering bleb. To rule out pupillary block, patients must have a patent iridotomy or iridectomy. B-scan ultrasonography and ultrasound biomicroscopy can also aid in evaluating the differential diagnoses.

View the Video



Drs. Justin and Vajzovic perform a pars plana vitrectomy with irido-zonulo-hyaloidectomy in a nanophthalmic patient with aqueous misdirection.
Available at: https://bit.ly/VideoPearl-030

Malignant glaucoma treatments

The initial medical treatment for aqueous misdirection uses cycloplegics and pressure-lowering eyedrops. Acetazolamide and hyperosmotic agents such as mannitol can also be initiated. Medical treatment is successful in about 50 percent of cases.

But when medical treatment doesn't work, a Nd:YAG laser anterior hyaloidotomy can be attempted. However, in treatment-resistant cases, a pars plana vitrectomy with irido-zonulo-hyaloidectomy (PPV-IZH) may be required to reverse the flow of aqueous humor.[1,2] The PPV removes the pathologically hydrated vitreous, and the IZH ensures communication between the anterior chamber and vitreous cavity.

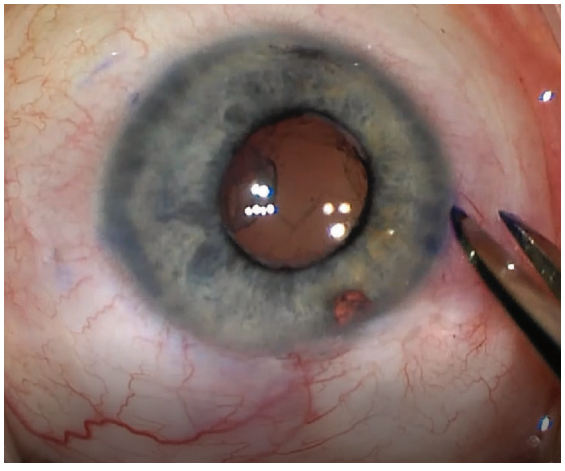


Figure 1. This patient with nanophthalmos and a prior trabeculectomy required placement of ports at 2.5 mm and in a location to avoid the trabeculectomy bleb.

Performing PPV-IZH-PPV

These are the key components of PPV-IZH to consider:

1. Port placement. Many patients with aqueous misdirection will have concurrent medical conditions that require thoughtful port placement (*Figure 1*). Hyperopia is a known risk factor, and patients may be nanophthalmic. As a result, the standard 3-to-4-mm port placement may result in iatrogenic retinal breaks. Transillumination can help to better evaluate the pars plana location. Further, a previous trabeculectomy or a glaucoma drainage device requires careful port placement that accounts for the location of the filtering blebs.

(Continued on page 44)

Bios

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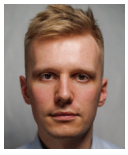
Dr. Hahn has no relevant disclosures.

Does vitrectomy have a place for treatment of DME?

Why we need to reconsider the role of vitrectomy in the management of diabetic macular edema.


Zofia Nawrocka, MD, PhD


Michał Zajac, MD


Jerzy Nawrocki, MD, PhD

By Zofia Nawrocka, MD, PhD, Michał Zajac, MD, and Jerzy Nawrocki, MD, PhD

Bios

Prof. Nawrocka is a vitreoretinal surgeon at the Ophthalmic Clinic Jasne Blonia, Lodz, Poland.

Dr. Zajac is an ophthalmology resident with a focus on retina.

Prof. Nawrocki is a vitreoretinal surgeon and head of the Ophthalmic Clinic Jasne Blonia and inventor of the inverted internal limiting membrane flap technique. He has received 11 Rhett Buckler Awards from the American Society of Retina Specialists for his innovative surgical concepts.

DISCLOSURES: The authors have no financial interest to disclose.

Take-home points

- About 40 percent of patients with diabetes will develop macular edema during their lifetime.
- Early treatment is crucial in obtaining visual success in these patients.
- Vitrectomy with internal limiting membrane peeling results in improvement of anatomy and visual acuity in early onset disease, in eyes with an intact photoreceptor layer and/or with subretinal fluid.
- Recurrences of edema after vitrectomy are rare, but they respond well to anti-VEGF therapy.

Nowadays, the role of vitrectomy in diabetic macular edema needs to be reconsidered. Proper patient selection might improve functional results and offer another choice of treatment for patients who can't always come in for their monthly anti-VEGF injections.

Diabetic retinopathy is the sixth most common cause of blindness in the world. DME, defined as a retinal thickening involving or approaching the center of the macula, represents the most common cause of vision loss in patients affected by diabetes mellitus. One-hundred million people around the world have already been diagnosed with DME secondary to diabetes and the numbers are expected to increase in the coming years.[1]

Glycemic, BP, lipid control crucial

Currently, even with the various DME treatments that exist, most physicians choose anti-VEGF injections as the primary treatment. We must emphasize that regardless of the chosen strategy, controlling glycemia, blood pressure and lipids is always crucial in these patients.

The Diabetes Control and Complications Trial (DCCT) showed that in patients with type 1 diabetes, monitoring of glucose (measurements four times a day) resulted in a decrease in the rate of development of any retinopathy by as much as 76 percent, as well as a 54 percent reduction in the progression of established retinopathy compared to the conventionally treated group (with one time measurement per day). In cases of severe retinopathy, more rigorous glucose control may not be enough to prevent disease progression.[2]

The current treatments for DME include intravitreal pharmacotherapy, vitrectomy and, historically, laser photo-

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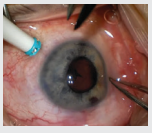

Prof. Nawrocka demonstrates vitrectomy for diabetic macular edema in a treatment-naive patient. Available at https://bit.ly/RetSpecMag-2022-04.

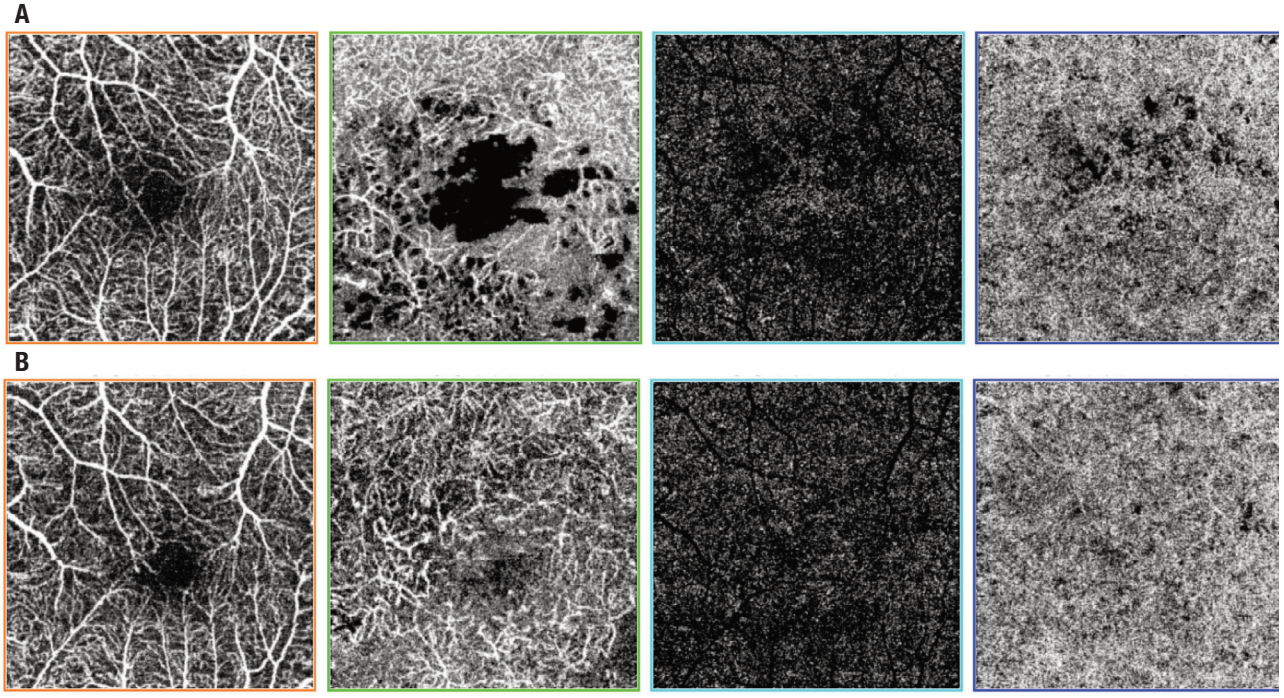

Figure 1. Swept-source optical coherence tomography angiography scans of diabetic macular edema in a 66-year-old man A) preoperatively and B) one year after surgery. The scans depict, from left to right, superficial retinal vessels, deep retinal vessels, avascular zone and choroid, showing that the foveal avascular zone decreased after surgery in the superficial retinal vessels layer.

coagulation of the macula. Intravitreal anti-VEGF injections have emerged as the gold standard for DME treatment. The discovery of the key role of vascular endothelial growth factor in initiating neovascularization changed the therapeutic approach in DME.[3]

Anti-VEGF agents, as we know, cause a significant decrease in central retinal thickness and improve visual acuity by 14 letters on average. Moreover, these drugs decrease the level of DR. Greater efficacy of anti-VEGF injections compared with laser therapy and corticosteroids has been proven. However, the use of laser therapy and corticosteroids seems to be growing slightly, especially as adjunctive therapy in anti-VEGF nonresponders.[5]

Advantages of vitrectomy

Our group has suggested that vitrectomy also might play this role (*Figure 1*).[4] We presented satisfactory results in treatment-naive patients.[4] Not only did anatomy and vision improve, but we also managed to reduce to a minimum the frequency of future anti-VEGF injections. Thus, to achieve good results, proper patient selection seems to be crucial.

The disadvantages of anti-VEGF injections for DME are cost and frequency of administration. Intravitreal injection carries a higher risk of endophthalmitis in patients with diabetes than in patients with neovascular age-related macular edema. Moreover, anti-VEGF agents are teratogenic; thus, patients of child-bearing age must use contraception, and pregnant women can't have them.

Controversy of surgery

The role of surgery in DME still remains controversial. Many studies have reported that anatomy improves, but visual acuity changes only variably.[6,7] However, we must consider that one of the inclusion

criteria for the DRCR Retina Network study was the surgeon's determination that the selected patient had a poor prognosis to respond to further macular laser photocoagulation or had epiretinal membranes.[6] That would suggest that only patients with long-standing macular edema qualified for surgery.

Studies have shown that previous photocoagulation can lead to worse outcomes after anti-VEGF treatment.[2] So, we may extrapolate that laser photocoagulation might also contribute to worse visual outcomes in victrectomized eyes. It's also clear that a long-lasting DME that responds poorly to treatment will result in lower final visual outcomes.

Proper patient selection for surgery is paramount (*Figure 2*). It has been reported that the best results after vitrectomy are obtained in patients with an intact external limiting membrane and ellipsoid zone.[8] A study from Japan reported that patients with subretinal fluid in diffuse macular edema also benefit from surgery.[9]

ILM peeling

Several years ago, we published a study that reported that ILM peeling performed in the setting of complications of proliferative vitrectomy, such as vitreous hemorrhage and tractional retinal detachment, decreases the long-term incidence of macular edema.[10]

We also presented results of vitrectomy in treatment-naive DME patients.[11] The study of 44 patients proved that both anatomical and functional results improve after vitrectomy with ILM peeling. We noted improvement of visual acuity of more than one line in 60 percent of eyes. Only three patients lost VA during the six-month observation period, mainly due to cataract formation (*Video*).

Even if anti-VEGF therapy is usually considered the first-line treatment, we observe initial visual gains three to six months after treatment starts.[12] Similarly, after vitrectomy, improvements are expected within about four months.[13]

Predictors of poor outcome

With multivariate analysis, we identified three factors associated with poor final outcome:

- preoperative presence of ERM;
- duration of diabetes; and
- poor baseline visual acuity.

These data further explain why previous studies failed to show visual improvement after vitrectomy. Because most authors chose patients who were less likely to respond, the results were disappointing.

Recurrences of macular edema after vitrectomy are rare. We observed them in three eyes. In longer observation times (24 to 36 months), about 15 percent of our patients needed additional injections, according to our own unpublished data.

Because the viscosity of the vitreous is 300 to 2,000 times greater than the aqueous, earlier authors hypothesized that vitrectomy might reduce the half-life of anti-VEGF agents, but several studies proved the opposite.[14,15] According to our own observation, these eyes usually respond to anti-VEGF therapy so that they don't need multiple injections.

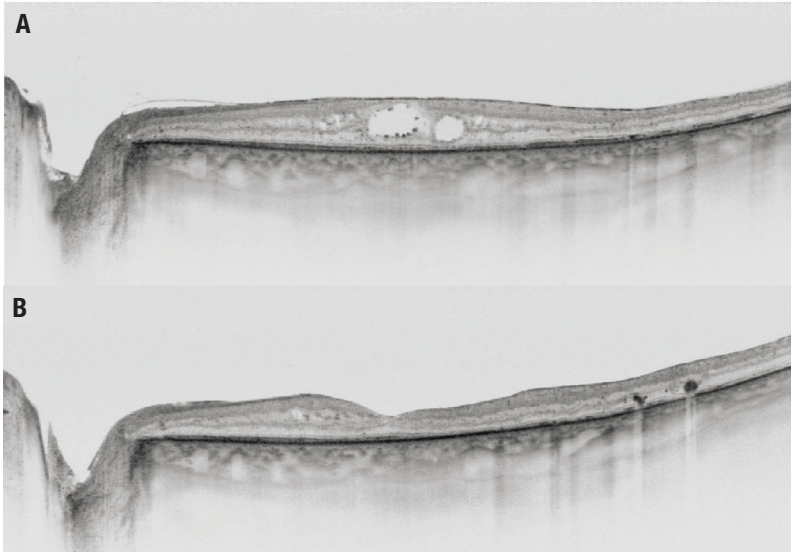

Figure 2. Swept-source optical coherence tomography of diabetic macular edema in a 66-year-old man A) before surgery and B) one year after surgery.

Yuki Morizane, MD, PhD, and colleagues proposed subretinal balanced salt solution injections in the treatment of DME.[16] Subretinal injections are usually recommended in subfoveal hemorrhage in nAMD, but in gene therapy they're advised to be done paracentrally from the fovea. We need further studies to determine whether foveal detachment doesn't cause any serious photoreceptor defects. Currently, we usually perform subretinal injections in DME with good results.[17]

Mechanisms favoring vitrectomy

Several mechanisms have been proposed in which vitrectomy might be helpful in the treatment of DME. Chronic inflammation, hypoxia and traction increase VEGF levels in tissues.[18] The fact that the posterior hyaloid is usually attached in DME might trap VEGF and limit its extraretinal diffusion.[19] The posterior hyaloid is usually thickened in DME and is more difficult to remove than it is during vitrectomies in other macular diseases. Also, the ILM is intraoperatively more fragile. It might not only trap VEGF, but it may also reduce the bioavailability of anti-VEGF agents in the retinal space.

Vitrectomy removes traction as well as glycation products and VEGF. Reducing vitreous viscosity increases the diffusion of molecules through the eye.[20] This results in higher premacular oxygen concentrations and lower intraretinal VEGF concentrations. Vitreoretinal surgery with ILM peeling also induces the glial repairing processes.

Bottom line

Vitrectomy isn't intended to be the first-line treatment for DME, but it should be considered for patients who live far from retinal clinics and aren't able to come in for frequent injections or in patients with financial burdens. Moreover, vitrectomy might be discussed with pregnant women or women planning pregnancy. The obvious indications are the coexistence of traction or epiretinal membranes. Unfortunately, the disease is advanced in these eyes and final results aren't always satisfactory. Good results after vitrectomy are expected in early onset disease with subretinal fluid in patients without severe photoreceptor defects. RS

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Several mechanisms have been proposed in which vitrectomy might be helpful in the treatment of DME. Chronic inflammation, hypoxia and traction increase VEGF levels in tissues.

WHAT COULD SHE SEE THIS YEAR?

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

304 BINGO CARDS

Inspired by a real patient with Wet AMD.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

PROVEN VISUAL OUTCOMES AT YEAR 1 IN THE VIEW STUDIES

Fewer injections with EYLEA Q8 vs ranibizumab Q4

Demonstrated in the largest phase 3 anti-VEGF trials completed to date in Wet AMD (N=2412)[1-3]

Proportion of patients who maintained vision (<15 ETDRS letters lost of BCVA) at Year 1 from baseline[1-3,*]

	Primary Endpoint (Year 1)	
	VIEW 1	VIEW 2
EYLEA Q4	**95%** (12.5 injections†)	**95%** (12.6 injections†)
EYLEA Q8‡	**94%** (7.5 injections†)	**95%** (7.7 injections†)
ranibizumab Q4	**94%** (12.1 injections†)	**95%** (12.7 injections†)

*Last observation carried forward; full analysis set.
†Safety analysis set.
‡Following 3 initial monthly doses.

Vision was maintained at Year 1 with ≈5 fewer injections with EYLEA Q8 vs ranibizumab Q4

EYLEA was clinically equivalent to ranibizumab.

VIEW 1 and VIEW 2 study designs: Two multicenter, double-masked clinical studies in which patients with Wet AMD (N=2412; age range: 49-99 years, with a mean of 76 years) were randomized to receive: 1) EYLEA 2 mg Q8 following 3 initial monthly doses; 2) EYLEA 2 mg Q4; 3) EYLEA 0.5 mg Q4; or 4) ranibizumab 0.5 mg Q4. Protocol-specified visits occurred every 28 (±3) days.[1] In both studies, the primary efficacy endpoint was the proportion of patients with Wet AMD who maintained vision, defined as losing <15 letters of visual acuity at Week 52, compared with baseline.[1]

SEE WHAT EYLEA COULD DO FOR YOUR PATIENTS WITH WET AMD AT HCP.EYLEA.US

anti-VEGF, anti–vascular endothelial growth factor; BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; Q4, every 4 weeks; Q8, every 8 weeks.

ADVERSE REACTIONS

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

INDICATIONS

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

References: 1. EYLEA® (aflibercept) Injection full U.S. Prescribing Information. Regeneron Pharmaceuticals, Inc. August 2019. **2.** Data on file. Regeneron Pharmaceuticals, Inc. **3.** Heier JS, Brown DM, Chong V, et al; for the VIEW 1 and VIEW 2 Study Groups. Intravitreal aflibercept (VEGF Trap-Eye) in wet age-related macular degeneration. *Ophthalmology*. 2012;119(12):2537-2548. doi:10.1016/j.ophtha.2012.09.006

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

03/2021
EYL.21.02.0019

EYLEA® (aflibercept) Injection
For Intravitreal Injection

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

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

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

4 CONTRAINDICATIONS

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

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

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

5 WARNINGS AND PRECAUTIONS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

8 USE IN SPECIFIC POPULATIONS

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

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

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

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

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

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

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

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

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RRD repair: Updates and current perspectives

Several techniques have high success for rhegmagtogenous retinal detachment repair. The choice comes down to patient factors and surgeon judgment.

By Michael J. Huvard, MD

By Michael J. Huvard, MD

Take-home points

- The optimal surgical technique for retinal reattachment remains unknown, but high success rates and comparable visual outcomes have been reported with a variety of techniques. The patient's age or lens status, along with surgeon experience and judgment, help guide individualized treatment approaches.
- A trend has emerged toward vitrectomy alone as the technique of choice for managing primary rhegmatogenous retinal detachment. This coincides with the development of small-gauge vitrectomy platforms.
- Pneumatic retinopexy is an excellent, nonincisional intervention that benefits from stringent patient selection. Barrier laser retinopexy also can be a prudent management option in select patients.
- Traditional metrics of RRD repair include single-surgery and final anatomic success, and best-corrected visual acuity, although growing evidence suggests VA alone is a poor proxy for post-RRD vision and vision-related quality of life.

Rhegmatogenous retinal detachment is a major cause of visual loss and one of the most common pathologies retina specialists repair today. Since Prof. Jules Gonin in 1930 first linked retinal breaks to RRD, the fundamental approach to RD repair has remained the same: find the retinal breaks; treat the retinal breaks; and seal the retinal breaks.[1]

Today, advances in vitreoretinal surgical tools and techniques, particularly microsurgical instrumentation, give retina specialists more tools than ever to treat RRD.

Trends in incisional RRD repair

While the pathogenesis of RRD was recognized in the 1930s, it wasn't until 20 years later that E. Custodis in Germany developed a polyviol explant and Charles Schepens, MD, and colleagues reported using a polyethylene encircling band to achieve retinal reattachment that established scleral buckling as a surgical technique.[2,3]

SB remained the primary technique for RRD repair until Robert Machemer, MD, and colleagues introduced pars plana vitrectomy in the 1970s.[4] At first, PPV was viewed as a higher-risk surgery and reserved for complicated forms of retinal detachment, such as giant retinal tears or diabetic tractional retinal detachments. But the indications for PPV evolved from complex forms of retinal detachment, often as an adjuvant to SB, to the dominant method for RRD repair today.[5] A 2018 survey by the American Society of Retina Specialists showed that SB was used in primary RRD repair in less than 20 percent of cases.[6]

Several reasons exist for the rapid adoption of PPV for RRD repair. One is the development of smaller-gauge instrumentation. Compared to SB, growing data show that PPV results in comparatively less pain, surgically induced trauma and morbidity,

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reduced surgical times and shorter postoperative recovery.[7,8] Also, wide-angle viewing systems have enhanced the surgeon's ability to view vitreoretinal pathology and may improve surgical decision-making.

Aside from RRD repair, the evolution of PPV has been vital in treating a variety of vitreoretinal pathologies, such as full-thickness macular holes, further fueling its adoption.

What the data tell us

As the role of PPV has expanded, much debate has revolved around defining the optimal surgical technique for retinal reattachment. While PPV alone is best for RRD repair in many cases, PPV/SB and primary SB remain widely employed (*Figure 1*).[6] Potential drivers of technique preference are patient age, lens status, presence of a posterior vitreous detachment, extent of the retinal detachment, macular status, location of retinal breaks (below the horizontal meridian), the presence of media opacity (e.g., vitreous hemorrhage) and presence of proliferative vitreoretinopathy.

The most recent large, prospective randomized clinical trial to assess this question was the Scleral Buckling versus Primary Vitrectomy in Rhegmatogenous Retinal Detachment (SPR) study in 2007.[8] This study enrolled more than 500 eyes with medium-complexity RRD—defined as RRD with retinal breaks 1 to 2 clock hours in size—marked vitreous traction, multiple breaks, central extension of the break or superior bullous detachment.[9] The study found that single-surgery anatomic success (SSAS) was the same in phakic eyes treated with PPV (63.8 percent) or SB (63.6 percent), but visual outcomes were superior in the SB group. Pseudophakic or aphakic eyes fared better with PPV than with SB (SSAS of 72 vs. 53.4 percent). No difference in best-corrected visual acuity was found.[9]

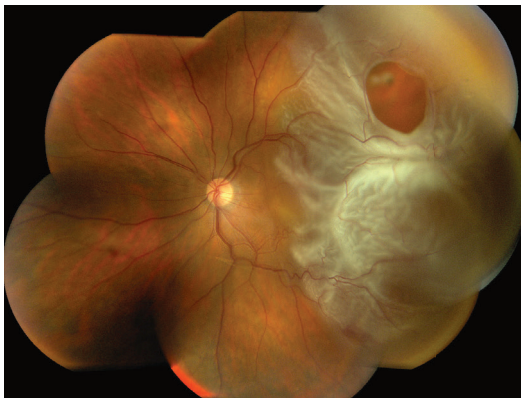

Figure 1. Vitreous fluid flows through a retinal tear to cause a partial retinal detachment involving the macula. The optic nerve and nasal retina are normal and uninvolved. Vitrectomy surgery is indicated to restore vision. (*Courtesy ASRS Retina Image Bank, contributed by Brandon Busbee, MD*).

While the SPR study provided a wealth of data and contributed to our surgical decision-making, its findings may not be generalizable to the current landscape of modern microincisional vitrectomy. The study data were gathered between 1998 and 2003, which predated small-gauge vitrectomy.

In addition, the trial design allowed surgeons to place a supplemental SB in combination with PPV at their discretion. About 50 percent of the cases of primary PPV had a SB placed, which makes it difficult to interpret the true outcomes of PPV vs. PPV/SB or SB. Finally, because the SPR study only considered moderate-complexity cases, non-complex RRD—cases with a single break in a young myopic patient with attached hyaloid, which would overwhelmingly be treated with SB—aren't included.

More recent evidence

Several large, retrospective interventional case series have sought to answer similar questions in the context of modern surgical practices. The Primary Retinal Detachment Outcomes Study (PROS) is a multi-institutional effort that evaluated surgical outcomes in noncomplex RRD repair based on cases performed at five sites in 2015.[10] The distribution of surgical procedures used to treat primary RRD was in line with current trends: 51.7 percent used PPV, 34.8 percent PPV/SB and 13.5 percent primary SB, with a strong preference for performing primary SB in patients younger than 40 years.

The investigators report high rates of SSAS in patients managed with SB (91.2 percent) or PPV/SB (90.2 percent), but notably report a lower SSAS (84.2 percent) in patients managed with PPV alone. Subgroup analysis showed that PPV/SB and SB offered better SSAS than PPV in phakic eyes: 91.2 and 91.7 vs. 83.1 percent.

Pseudophakic eyes similarly fared better

with PPV/SB compared to PPV (92 vs. 84 percent), but mean BCVA wasn't significantly different. Eyes with inferior retinal breaks also had higher SSAS after combined PPV/SB compared to PPV (87.4 vs. 76.8 percent).

These data are similar to a recent report by Jose J. Echegaray, MD, and colleagues that reviewed primary RRD outcomes of 488 eyes from a single institution between 2014 and 2017.[11] They reported SSAS of 81.1 percent with PPV vs. 92.2 percent with PPV/SB for all detachments. A subgroup analysis showed superior SSAS with PPV/SB in phakic patients, but not pseudophakic patients.[11]

Excellent results of PPV alone

However, other large interventional case series have reported SSAS of 90 percent or better with PPV alone.[12] A recent single-institution study by Omar Moinuddin, MD, and colleagues reported primary RRD outcomes of 751 cases from 2011 to 2019, showing high SSAS with PPV, PPV/SB or SB (91.2, 84.3 and 93.8 percent, respectively).[13]

In a subgroup analysis of patients with inferior retinal breaks, they reported a high SSAS (88.9 percent) and final anatomic success (FAS) (96.2 percent) of primary RRD with inferior breaks managed by PPV alone.

Similarly, lens status wasn't found to be significant in predicting SSAS or FAS with comparable outcomes between all surgical modalities. Patients managed with combined PPV/SB or PPV or SB alone demonstrated excellent and comparable BCVA outcomes, suggesting that supplementing PPV with SB didn't improve anatomic or visual outcomes.

Others have also published excellent outcomes of treating RRD with inferior retinal breaks with small-gauge PPV alone.[14] Among the studies previously discussed, many surgeons opted to use PPV/SB (PROS 34.8 percent, Dr. Echegaray 67 percent) rather than primary PPV. This may suggest these surgeons are more comfortable with PPV/SB as they achieved superior results with this approach. Dr. Moinuddin and colleagues, who only utilized PPV/SB in 6.8 percent of their reported cases, opted for PPV alone (89 percent of cases) with excellent and comparable results to PROS and Dr. Echegaray.

The literature for incisional treatment of RRD is extensive even with the lack of high-quality evidence supporting one practice over another. Indeed, a Cochrane review in 2019 found nothing more than "low-certainty" evidence supporting use of PPV over SB for simple RRD.[15] Another meta-analysis of 10 studies from 2003 to 2014 with 1,704 patients concluded that SSAS of PPV/SB was superior to PPV. However, these authors also included patients with complex forms of RRD (e.g., advanced PVR and giant retinal tears) and those in whom 20-gauge instruments were used. Thus, the findings may not be generalizable to modern, small-gauge uncomplicated RRD repair.

In the recent Pneumatic Retinopexy Versus Vitrectomy for the Management of Primary Rhegmatogenous Retinal Detachment Outcomes Randomized Trial (PIVOT), the SSAS of PPV was 93 percent.[16] RRD are heterogenous and hence difficult to compare. Surgeons should opt for retinal reattachment techniques that draw on their training, preferences and experience individualized to each patient to achieve the greatest chance of success.

Nonincisional alternatives

Pneumatic retinopexy (PnR) is an office-based procedure that may be an excellent alternative to incisional repair for non-complex retinal detachments. Most agree the standard criteria that define a good candidate for PnR include an RRD with a single or clustered retinal breaks (usually in the superior clock hours), phakic lens status and the absence of other high-risk pathology such as lattice degeneration. PnR (*Figure 2*) offers a number of potential advantages over incisional techniques, including faster VA recovery and avoiding the operating room and its associated risks.[16]

PIVOT, a 2019 randomized clinical trial,

Pneumatic retinopexy is an office-based procedure that may be an excellent alternative to incisional repair for non-complex retinal detachments.

compared outcomes of PnR vs. PPV for the management of non-complex RRD.[16] The authors reported SSAS of 81 and 93 percent for PnR and PPV, respectively. Their findings underscore that PnR can be an excellent technique with strict patient selection criteria and good surgeon skill.

However, since 2004, PnR procedures have declined and fewer physicians are as comfortable with the technique.[5] To this end, Nicholas Yannuzzi, MD, and colleagues reviewed American Academy of Ophthalmology IRIS Registry outcomes of 9,553 patients who had PnR.[17] They reported an overall SSAS of 68.5 percent, perhaps more in line with real-world results.

One interesting finding from PIVOT was that PnR-treated eyes had better BCVA and less metamorphopsia than PPV-treated eyes. However, a growing body of literature suggests that visual acuity alone is an insufficient proxy for vision and vision-related quality of life after RRD.[18] We need more research to better understand what metrics may best capture vision-related changes after RRD.

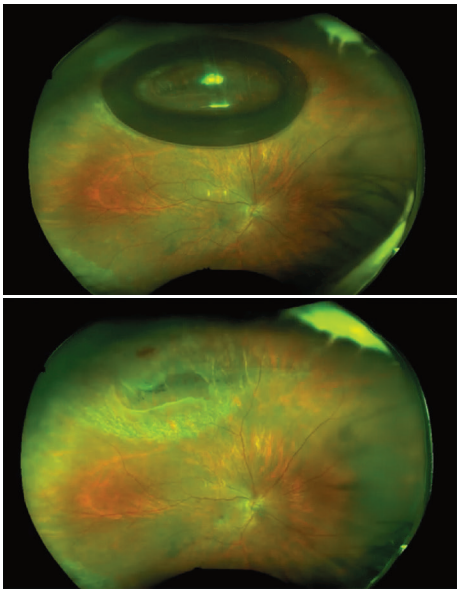

Figure 2. Widefield imaging of a superior macula-off retinal detachment after pneumatic retinopexy shows the retina fully attached, the superior break lasered after 48 hours (top) and the gas bubble fully resorbed. (*Courtesy Efrem D. Mandelcorn, MD, FRCSC*)

Finally, it's prudent to remember that some patients may be excellent candidates for laser demarcation.[19,20] Ideal candidates include those with asymptomatic, peripheral RRDs that spare the macula or who are unable or unwilling to undergo more invasive procedures.

Bottom line

RRD remains a significant cause of visual morbidity and vision loss. With advances in surgical technique and improved instrumentation, SSAS greater than 90 percent is possible with a variety of incisional techniques.

Nonincisional techniques remain an important alternative in select patients. Surgeons should feel confident in selecting a technique reflective of their training; one that works best in their hands. Factors such as patient age or lens status, in combination with surgeon experience and judgment, should help guide individualized treatment recommendations for each patient.

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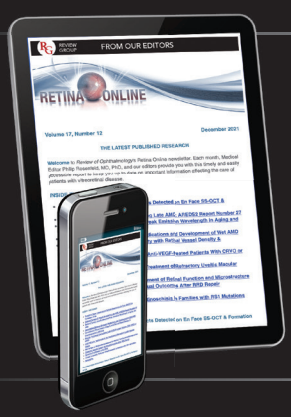

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More durable therapies for nAMD: Where we stand

An update on longer-lasting agents, alternative therapies, novel delivery systems and technology that aims to relieve treatment burden.

Parastou Pakravan, MSc

Jayanth Sridhar, MD

By Parastou Pakravan, MSc, and Jayanth Sridhar, MD

Take-home points

- While anti-VEGF injections have dramatically improved the prognosis of exudative age-related macular degeneration, they pose a significant burden on patients due to the transient effect of treatment and time constraint of monthly clinic visits.
- Longer-lasting agents, alternative therapies and different delivery systems are in development to address the limitations of current anti-VEGF therapies.
- Home-based monitoring and optical coherence tomography may detect disease activity earlier in patients with wet AMD, improving treatment outcomes and allowing providers to use *pro re nata* models with longer-acting injections.
- Gene therapy is still under investigation for the treatment of exudative AMD, but it may provide a possibility for continuous anti-VEGF therapy with one-time treatment.

Bio

Ms. Pakravan is a medical student at the University of Miami Miller School of Medicine.

Dr. Sridhar is an associate professor of clinical ophthalmology at the Bascom Palmer Eye Institute in Miami.

DISCLOSURES: Ms. Pakravan has no disclosures to report.

Dr. Sridhar is a consultant to Alcon, DORC, Genentech/Roche and Regeneron Pharmaceuticals.

It's well known that treatments with anti-VEGF agents pose a significant burden on patients due to the high costs for certain agents, patient anxiety and discomfort, time constraints, the need for frequent clinic visits and the treatments' transient effects.[1] Additionally, real-world studies have reported suboptimal response or failure to maintain a response compared to randomized clinical trials, possibly because adherence to therapy may not be feasible for some patients.[2] It has been well-documented that undertreatment of neovascular age-related macular degeneration may result in progressive vision loss.[2]

Moreover, agents that target the complement cascade in dry AMD are emerging. Two potential drugs now in clinical trials are pegcetacoplan (APL2, Apellis Pharmaceuticals), which targets C3 in the complement cascade, and avacincaptad pegol (Zimura, Iveric Bio), which targets C5.[3,4] Both of these agents are injected monthly per the trial protocol and have shown a reduction in the growth rate of geographic atrophy lesions. Although they have the potential for treating the millions of people suffering vision loss from GA worldwide, the monthly injections for this population may further overwhelm retina providers and practices. This only heightens the urgency to achieve better durability in treatment for wet AMD patients.

To address the limitations the current anti-VEGF treatment paradigm imposes on patients, their families and the healthcare system, longer-lasting agents, alternative therapies and novel delivery systems are in development, which we discuss here.

Seeking greater durability with what we already have

Brolucizumab (Beovu, Novartis) is an anti-VEGF agent the Food and Drug Administration approved in 2019 for the treatment of nAMD.[5] It's concentrat-

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

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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.

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ed to achieve higher molar equivalent doses than other anti-VEGF drugs because of its high solubility and small molecular weight.

The HAWK and HARRIER Phase III clinical trials reported that optical coherence tomography-based anatomical outcomes favored brolucizumab over aflibercept, with 76 percent of brolucizumab participants maintained on q12-week dosing after loading doses up to week 48.[6] However, anecdotal and published reports of postmarket data demonstrated a higher rate of intraocular inflammation, occlusive retinal vasculitis and permanent vision loss associated with intravitreal brolucizumab.[5] These safety signals have deterred many providers from using this agent for their patients.

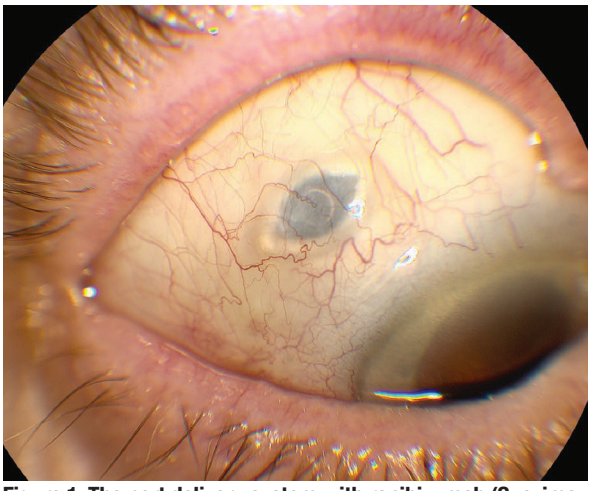

Figure 1. The port delivery system with ranibizumab (Susvimo, Genentech/Roche) as it appears under the healed sclera one month after implantation. (*Courtesy Carl D. Regillo, MD*)

Another novel pathway to treat nAMD involves the role of Tie-2 receptors in vascular permeability. Ang-1 activates Tie-2 receptors and reduces vascular permeability, while Ang-2, a competitive antagonist, increases vascular leakage.

Targeting Tie-2

Another novel pathway involves the role of Tie-2 receptors in vascular permeability. Angiopoietin-1 (Ang-1) is a ligand that activates Tie-2 receptors and reduces vascular permeability, while angiopoietin-2 (Ang-2) is a competitive antagonist that increases vascular leakage.[7]

Intravitreal faricimab (Vabysmo, Genentech/Roche), the newest FDA-approved addition to drugs for nAMD, is a bispecific antibody that targets both VEGF-A and Ang-2.[1] The approved labeling allows administration every one to four months, depending on patient response, after four initial monthly injections.[8]

The Phase III TENAYA and LUCERNE trials demonstrated noninferiority of faricimab with treatment intervals up to 16 weeks compared to aflibercept q8 weeks. More importantly, TENAYA and LUCERNE showed that 45.7 and 44.9 percent of nAMD patients on faricimab, respectively, were extended to dosing every 16 weeks.[8] Notably, 79.7 and 77.8 of patients in TENAYA and LUCERNE, respectively, achieved at least 12-week intervals between injections.

As such, faricimab appears to have the potential to enhance patient quality of life without negative outcomes. However, real-world data regarding the safety of faricimab aren't available yet. Because of the reports of postmarket adverse events with brolucizumab, many clinicians are awaiting more real-world experience before they start treating stable patients with this newest-approved intravitreal agent. [8]

Sustained-release options

Besides newer drugs, clinicians now have the option of sustained-release of long-approved anti-VEGF therapy. The FDA last year approved the port delivery system with ranibizumab (Susvimo, Genentech/Roche) for patients with nAMD (*Figure 1*).[9] The PDS is a surgically implanted device that involves a refillable reservoir accessible via the conjunctiva and extending via the pars plana into the vitreous cavity.

The Phase III ARCHWAY study demonstrated the potential of PDS; the need for refill injection was no more than twice a

year after implantation.[9] They reported that results for PDS with refill frequency of every 24 weeks was both noninferior and equivalent to monthly ranibizumab injections, and 98.4 percent of PDS patients didn't need rescue therapy before the first refill-exchange.[9]

Despite the obvious benefit of less frequent treatments and potentially less clinic visits, the PDS was associated with a higher rate of endophthalmitis (1.6 percent) compared with ranibizumab monthly injections in ARCHWAY.[9] Other reported adverse events from the trial included retinal detachments (5.2 percent), vitreous hemorrhage (2.4 percent), conjunctival erosion (2.4 percent) and conjunctival retraction (2 percent).[9] Again, given its recent approval, real-world data regarding the efficacy and safety of PDS aren't available.

Investigative gene therapies

Gene therapy is a promising opportunity that has been explored most vigorously in ophthalmology in inherited retinal diseases. This process introduces a foreign DNA into host cells via a viral vector. The transfected cells become capable of transcribing the new copy of genes into functional proteins to treat the disease.[2]

The eye represents an ideal target for gene therapy because of its accessibility, the relative ease of measuring structural and functional outcomes and the blood-retina barrier, which prevents a systemic immunogenic response. Gene therapies may provide an avenue for continuous anti-VEGF therapy with only one treatment.

Although the FDA has approved one gene therapy for inherited retinal diseases (Luxturna [voretigene neparvovec-rzyl] Spark Therapeutics) and spinal muscular atrophy, gene therapy for nAMD is still investigative.

RegenxBio is studying a vector, RGX-314, that can express an anti-VEGF antibody fragment similar to ranibizumab.[10] RGX-314 is injected subretinally after completion of pars plana vitrectomy. The Phase IIb/III ATMOSPHERE trial is enrolling patients with nAMD, and has shown promising results so far with no reports of clinically determined immune responses, drug-induced ocular inflammation or postoperative inflammation beyond what's expected after a vitrectomy procedure.[10]

Alternatively, Adverum Biotechnologies is studying gene vectors for nAMD that may not require surgery. ADVM-022 and ADVM-032 are vectors that can express aflibercept and ranibizumab, respectively, using a single in-office intravitreal injection.[11]

These agents are still in clinical trials, but early results have shown greater than an 80-percent reduction in monthly anti-VEGF injection burden, and maintenance of best-corrected visual acuity and central retinal thickness with no reported systemic adverse events.[2,11]

However, last year Adverum suspended its gene therapy clinical trials in diabetic macular edema because of emerging cases of unexpected hypotony 16 to 36 weeks after receiving a high dose of ADVM-022.[12] As such, safety signals are being monitored closely in the nAMD trials of ADVM-022.

An adjunct: Home-based monitoring

Even if these investigative therapies alleviate the treatment burden on patients, their families and the healthcare system, the issue of monitoring between treatments would remain. Patients could theoretically come to a physician's office as infrequently as twice a year with a functional PDS, but they would still need to make an office visit for OCT imaging to monitor their treatment response.

The ForeseeHome (Notal Vision) remote telemonitoring technology has been developed to give physicians the capability to monitor disease activity remotely.[13] ForeseeHome monitors changes in visual function using preferential hyperacuity perimetry to detect signs of scotoma or metamorphopsia suggestive of choroidal

The eye represents an ideal target for gene therapy because of its accessibility, the relative ease of measuring structural and functional outcomes and the blood-retina barrier, which prevents a systemic immunogenic response.

neovascularization.[14] The device informs the retina specialist of vision changes so they can schedule an office appointment to evaluate the patient's disease activity.

Another technology, home-based OCT (*Figure 2*), is an investigative device that captures OCT scans in the patient's home. Data have shown that more than 90 percent of patients were able to obtain analyzable images.[13] The data also suggest the device's high sensitivity in detecting intraretinal and subretinal fluids.

These home devices may have the potential to detect disease activity earlier in patients with nAMD, improve their treatment outcomes and allow providers to use *pro re nata* treatment for more patients.

Bottom line

Although anti-VEGF therapy has become the primary treatment option for patients with wet AMD and has improved their prognosis, the long-term and frequent treatment requirement poses an excessive financial and logistical burden on both patients and their providers. The development of newer drugs with a possibility for less frequent injections or delivery methods with sustained release of anti-VEGF-A could offer the retina community better options to manage patients with nAMD.

Patients may also more widely use home devices to monitor their disease progression and schedule their clinic visits when necessary. These strategies can potentially improve patient compliance and help them stay on top of their AMD treatment, which will ultimately result in enhanced visual outcomes, while easing the treatment burden on them, their providers and the healthcare system. RS

Home-based monitoring may have the potential to detect disease activity earlier in patients with nAMD, improve their treatment outcomes and allow providers to use *pro re nata* treatment for more patients.

Figure 2. A patient self-images with the Home OCT (Notal Vision) investigational home-based optical coherence tomography device.

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Lessons from COVID-19 for the next pandemic

Five retina specialists share what they've learned from the past two years that would serve practices and policy makers well in the next wave or outbreak.

The COVID-19 pandemic has had a severe impact on retina practices, with many still recovering. Here, five retina specialists who've reported at retina meetings on their experiences in the pandemic and their research into pandemic-influenced trends share their thoughts with *Retina Specialist* on what lessons should be carried forward if, or when, another wave or pandemic comes around.

Manage the influence of politics

Abdhish R. Bhavsar, MD, is a partner at Retina Consultants of Minnesota.

I underestimated the influence of politics on medicine. I also learned that managing staff is important, which I didn't quite realize, in the sense that I assumed that everyone would want to wear an N95 mask to protect themselves at the beginning of the pandemic, which we were fortunate to purchase through some creative and nontraditional means, but that wasn't the case.

In my office—and I'm sure this happened many times—an employee was telling patients that she didn't want to wear a mask since she didn't believe in masks and they didn't work. This was at the very beginning of the pandemic when we'd just obtained the N95 masks at a time when no one, not even surgical practices, could get them. We were thinking we wanted to offer the best protection to our staff. The only reason I found out about what this staff member was saying is because one of the patients the employee was talking to was a scientist who told me about it. Otherwise, I would never have known our own staff were spewing stuff to patients that wasn't true or scientifically correct. So, I underestimated that.

These are things that all employers have to watch out for in a medical practice. We have to manage the staff and manage what they tell patients for the safety of all. Even though we may have our rules about how we manage it, we have to make sure that they're doing the same thing.

Educate patients that practices are open

Jesse J. Jung, MD, partner at East Bay Retina Consultants and volunteer faculty at University of California, San Francisco.

We recently presented and published a multicenter collaborative retrospective study through the Young Retina Forum that evaluated the impact the COVID-19 lockdown had on retinal detachment surgeries in the United States, Canada and Mexico.[1]

The study evaluated 261 eyes, of which 169 were treated through the shelter-at-home orders, during which the American Academy of Ophthalmology and the Amer-

We have to manage the staff and manage what they tell patients for the safety of all. Even though we may have our rules about how we manage it, we have to make sure that they're doing the same thing.
—Abdhish R. Bhavsar, MD

ican Society of Retina Specialists recommended nonessential surgeries be put on hold, but operations for organ-threatening or life-threatening emergencies, such as retinal detachment, should still be done. The study also included 92 eyes treated in the three months after the orders were lifted.

We observed that the patients most likely to have a 22-day delay in seeking care during the shelter-at-home orders were about 3.7 years younger than those who didn't delay. Additionally, these eyes were more likely to have proliferative vitreoretinopathy and epiretinal membrane post-surgery. Delay in care leads to more of these complicating factors that can result in less ideal outcomes.

At three months after the initial surgery, the study found that single-surgery anatomic success was 85 percent for patients who had surgery during the shelter-at-home period vs. about 75 percent for patients who delayed care, which wasn't significantly different.

Despite the limitations of the COVID-19 lockdown, vitreoretinal surgeons were still able to care of patients and outcomes were still good, with the final anatomic success still 99 percent. Importantly, this study observed that seeking care for sight-threatening issues, such as retinal detachment, is something that should still be prioritized even in the midst of extreme measures.

In the case of future worsening waves or possible lockdowns, we need to continue to be available and educate our patients about retinal tear/detachment symptoms and that we can successfully take care of them.

In the case of future worsening waves orlockdowns, we need to continue to be available and educate our patients about retinal tear/detachment symptoms and that we can successfully take care of them.

—Jesse J. Jung, MD

Continue the heroism

Paul Hahn, MD, PhD, is a retina specialist at NJ Retina in Teaneck.

In the earliest days of the pandemic, ASRS developed a series of surveys to assess and share the evolving impact of COVID-19 on the retina community.[2] Retina practices saw a drastic early decline in patient volume, both internationally and in the United States; more than 80 percent of responding retina specialists reported a more than 50 percent decline volume in March 2020, the date of the first survey. Recovery was slow through July 2020, the date of the last survey, particularly internationally where 70 percent of respondents still reported seeing less than 75 percent of their pre-COVID volume.

These survey results and other data have indicated that telemedicine wasn't meaningfully adopted by most retina specialists, due to the unique demands of our exam and procedures. Understandably, the survey results indicated significant concern by retina specialists with the vulnerability of the financial health of their practices, but what was more impactful than these financial concerns was the pervasive sense of anxiety, particularly due to the uncertainty of risk to retina specialists. The early days of the pandemic were colored by the COVID-related death of Wenliang Li, MD, the Wuhan ophthalmologist who was one of the first to recognize this disease.

But the ASRS surveys memorialized a consistent and prevalent current of heroic dedication to put patient care first among all else. Our community of retina specialists should be proud of this heroism.

Minimize patient contact

Samuel K. Steven Houston, MD, is a vitreoretinal specialist at Florida Retina Institute in Orlando:

We thought it would be another five, six or seven years from the beginning of COVID that people would seriously start to utilize telemedicine, but COVID provided a significant push for these technologies. The advances in imaging technologies have allowed us to leverage telemedicine to interact with patients.

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ABOUT RICK

Rick Bay served as the publisher of *The Review Group* for more than 20 years.
To those who worked for him, he was a leader whose essence was based in a fierce and boundless loyalty.
To those in the industry and the professions he served, he will be remembered for his unique array of skills and for his dedication to exceeding the expectations of his customers, making many of them fast friends.

(The Rick Bay Foundation for Excellence in Eyecare Education is a nonprofit, tax-exempt organization under section 501(c)(3) of the Internal Revenue Code.)

Optical coherence tomography technology and ultra-widefield imaging allowed me to minimize exposure time with patients. They give me most of the data points I need to make a diagnosis and treatment plan. They also allow patients to have a quicker throughput. We were starting to update the OCT machines in all our offices before the pandemic. Once COVID hit, we were already set up with these imaging technologies.

COVID was the perfect opportunity for us to roll out a hybrid telemedicine model, as we call it. Regular telemedicine for eye care doesn't really work that well. We needed to have the imaging. We set up remote test sites where patients just came in, got their imaging, and then left, so, they would only interact with one staff member. They would either connect with me virtually in the office while they were there for their imaging appointment, or connect with me within a day or two to go over the visit.

One of the limitations that we found early on was that in an older population the technology, such as Zoom or any of the other Webex virtual platforms, was sometimes difficult for them to use. That's when we started the real-time virtual type visit, where patients came in for their imaging and, before they left, they connected with me on the iPad that was in the office. The technician who was there with the patient could troubleshoot any problems if necessary.

One of the limitations that we found early on was that in an older population the technology, such as Zoom, was sometimes difficult for them to use. That's when we started the real-time virtual type of visit.

— Samuel K. Steven Houston, MD

Attain uniform messaging

William E. Smiddy, MD, is professor of ophthalmology and the M. Brenn Green Chair in Ophthalmology at Bascom Palmer Eye Institute at the University of Miami Miller School of Medicine.

In our experience, in addition to the background rate of patients lost to follow-up, around 20 percent of patients who get intravitreal injections had a delay in their treatment that was attributable to the pandemic. Common explanations from patients were that they didn't know we were open or they were afraid to come out and get treatment.

Two things led to this circumstance. Number one is the vulnerability that patients who are on injection-based treatments have to disruptions in their care, such as with COVID-19 or other concurrent medical problems. And number two is we need to have messaging from all levels, whether it's from federal government agencies, news media, state agencies or even the local news, as to what is urgent care, what is emergent care, and what kind of care is still going to be delivered and what kinds of care isn't.

The AAO and ASRS were very clear early on in defining the importance of viewing injection-based therapy as urgent, but that message wasn't universally implemented.

We even had patients who resurfaced, if you will, a year later who thought we were still closed. We never closed. We tried to prioritize and triage the more urgent kinds of patients, such as those who needed surgery or needed injections—patients for whom, if there was an interruption in their care, there was the potential, if not expectation, of a poor prognostic outcome.

Honestly, I was surprised that there wasn't worsening of vision in more people but, indeed, there were many patients who got worse. Although they improved somewhat, many never really got back to their baseline. RS

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Retina Standouts from ARVO 2022

Gene therapy, heads-up surgery, AI and PTI

Four standout abstracts provide new insights into novel treatments and technologies in retina.

By Avni P. Finn, MD, MBA

Avni P. Finn, MD, MBA

Take-home points

- GT005 is an adeno-associated virus-2-based gene therapy that aims to induce the production of complement factor I, suppressing the alternate pathway of the complement system, in hopes of decreasing the chronic inflammatory drive contributing to geographic atrophy progression.
- A guarded light pipe coupled with the NGENUITY visualization system for scleral buckling improves the ability to visualize the peripheral retina, costs less than the chandelier and potentially provides ergonomic and educational advantages.
- Artificial intelligence demonstrated quantitative assessment of fluid in patients with neovascular macular degeneration and may inform more personalized treatment for patients.
- Faricimab dosed via a personalized treatment regimen demonstrated durability with the majority of patients enrolled in Phase III trials achieving dosing every 12 or 16 weeks.

The annual meeting of the Association for Research in Vision and Ophthalmology—ARVO 2022—returned to a live format for the first time since 2019, although some abstracts were presented virtually. More than 11,000 researchers, clinicians and scientists from around the world attended the live meeting in Denver as well as virtual sessions.

Here, we report on four compelling presentations in retina: early results from a Phase I/II trial of a gene therapy that induces complement factor production to target geographic atrophy; a study evaluating a guarded light pipe with a heads-up surgical platform for rhegmatogenous retinal detachment surgery; an analysis of two artificial intelligence algorithms for evaluating retinal fluid in neovascular age-related macular degeneration; and a study of a personalized treatment interval using faricimab for diabetic macular edema.

Nadia K. Waheed, MD, MPH

Subretinal gene therapy for GA secondary to AMD

The FOCUS trial is evaluating GT005 (Gyroscope Therapeutics), an adeno-associated virus (AAV-2) based gene therapy designed to induce complement factor I production, in geographic atrophy.

Previous clinical trials have shown that complement inhibition slows GA growth. The alternate pathway of the complement system provides several different targets for dry age-related macular degeneration. We have data showing that genes encoding low CFI levels are related to an increased risk of AMD. Serologic data confirms this as CFI supplementation suppresses the complement system alternate pathway and reduces the risk of developing AMD.

Bio

Dr. Finn is an assistant professor of clinical ophthalmology and visual sciences at the Vanderbilt Eye Institute in Nashville, Tennessee.

DISCLOSURES: Dr. Finn disclosed relationships with Allergan/AbbVie, Genentech/Roche and Apellis Pharmaceuticals.

By delivering GT005 subretinally, the goal of the FOCUS trial is to allow for long-term CFI expression by creating a biofactory in the eye. This can ultimately downregulate the complement alternate pathway, specifically by sequestering C3b.

Nadia K. Waheed, MD, MPH, an associate professor at Tufts University School of Medicine, Boston, presented results from FOCUS, a Phase I/II open label safety and dose-response trial.[1] So far, the agent has been well tolerated in the first four cohorts.

Retinal pigment epithelial changes had been noted in the high-dose group. However, these changes were restricted to the bleb area without associated significant visual changes. This side effect has been seen in other subretinal gene therapy trials and may be a reason to administer bleb delivery outside the macula.

Dr. Waheed also said the study found no significant associated immune response and no clinically significant inflammation after GT005 delivery. Vitreous levels of CFI increased as expected after delivery and C3 levels decreased. The hope is that this reduces the chronic inflammatory drive contributing to GA progression.

The advantages of subretinal gene therapy for GA are improved transduction to the outer layer cells, lower immune response compared to intravitreal and suprachoroidal approaches, and high expression longevity. The major drawback is that it requires a surgical procedure.

In this vein, a minimally invasive subretinal delivery system, called Orbit, is being designed to deliver subretinal therapy via a suprachoroidal approach. This may improve precision and predictability of delivery and overcome the challenges associated with the traditional surgical-based approach. This delivery system is being tested in cohorts 5 through 7 of the FOCUS study.

Dr. Waheed is chief medical officer of Gyroscope Therapeutics and holds stock in the company. She also disclosed relationships with Nidek, Boehringer Ingelheim, Apellis, Carl Zeiss Meditec, Heidelberg Engineering, Nidek, Optovue, Topcon, Regeneron Pharmaceuticals and OcuDyne.

The advantages of subretinal gene therapy areimproved transduction to the outer-layer cells, a lower immune response than intravitreal and supra-choroidal approaches, and high expression longevity.

John B. Miller, MD

Guarded light pipe in scleral buckling with NGENUITY Platform

Rhegmatogenous retinal detachments are one of the most common surgical diagnoses we as retina specialists treat. We have various techniques to address them, and often scleral buckling is advantageous in young, phakic patients.

John B. Miller, MD, of Massachusetts Eye and Ear Infirmary, highlighted the decline in SB procedures, which may be due in part to difficulties with visualization, limited exposure to SB in training and an increasing reliance on widefield visualization both in the clinic with photography and in the operating room.[2]

Chandelier illumination is one method that addresses some of these challenges, but the illumination and mobility of the chandelier can be limited. Dr. Miller proposed using a guarded light pipe instead, an approach that he said minimizes vitreous movement and dragging.

Guarding the light pipe with a sleeve minimizes its exposure in the vitreous cavity to just the amount necessary to provide adequate illumination. The proposed advantages of combining the guarded light pipe with the three-dimensional heads-up display include improving visualization of the pathology and surgical technique for trainees who may be in the room as well as improving ergonomics for the surgeon. Illumination with the light pipe is used to examine the retina, apply cryotherapy and, in certain cases, drain under direct visualizations. Suturing the sclerotomy the follows this step.

A retrospective case series of eyes

repaired with this technique included 31 eyes done with indirect ophthalmoscopy and 16 eyes with the guarded light pipe. The series showed no statistically significant difference in operative times between the techniques, although the guarded light pipe technique trended toward a shorter time.

Surgical outcomes weren't significantly different between the two study groups. There were no differences in final reattachment rates, visual outcomes, intraoperative complications, reoperation rates or postoperative complications between the two groups. Single-surgery anatomic success was the same at around 87 percent in both groups. One case of vitreous hemorrhage was reported in the guarded light pipe group.

This variation on the traditional SB technique may be advantageous because the light pipe is a familiar tool to vitreoretinal surgeons, costs less than the chandelier, improves the ability to illuminate the peripheral retina and may impart ergonomic and educational benefits.

Dr. Miller is a consultant to Alcon, Allergan/AbbVie, Carl Zeiss, Genentech/Roche and Sunovion.

Tiarnan D.L. Keenan, PhD

Retinal fluid volumes as a biomarker for nAMD

Accurate assessment of fluid dynamics on optical coherence tomography is critical for diagnosis, personalized treatment and visual prognosis. This is important for many diseases, including AMD, diabetic macular edema, retinal vein occlusions and central serous chorioretinopathy.

In our current clinical flow and imaging analysis paradigm, we have limitations. These include the time-consuming nature of quantitative analysis and variability between human graders. In a busy clinical environment, we perform binary assessments of whether fluid is present or absent and have limited ability to perform true comparisons of imaging between visits. Artificial intelligence algorithms have the capability to change this by not only detecting fluid, but by segmenting the fluid and color coding it to make it easier to see. Moreover, these algorithms can quantify the fluid so that it may better inform our management decisions.

Tiarnan D.L. Keenan, PhD, of the division of epidemiology and clinical applications at the National Eye Institute, described the application of two AI algorithms to calculate fluid volume for four different neovascular AMD data sets.[3] They included clinical trial and real-world data sets: the HARBOR data set, Age-Related Eye Disease Study 2 10-year follow-up, and two real-world data sets from Belfast and Tel-Aviv. Fluid volumes in nAMD were quantified including intraretinal fluid compartments, subretinal fluid compartments and pigment epithelial detachments.

The algorithms analyzed more than 20,000 scans from these datasets and made quantitative measures of IRF, SRF and PED volume. This study showed that an AI algorithm can efficiently extract accurate volumes from OCT scans. This type of analysis can have important implications in our clinical practice and research as it may help us to better quantify and follow these imaging biomarkers.

Dr. Keenan has no relevant disclosures.

Caroline R. Baumal, MD

Personalized treatment interval (PTI) dosing of faricimab for DME

Faricimab (Genentech/Roche) provides dual inhibition of angiopoietin-2 and vascular endothelial growth factor and has the potential to extend treatment durability for DME. YOSEMITE and RHINE were two Phase III, randomized controlled trials in patients with center-involving macular edema.

The study showed an AI algorithm can extract accurate volumes from OCT scans, a type of analysis that can have important implications because it may help us to better quantify and follow these imaging biomarkers.

The personalized treatment interval (PTI) was designed to test the durability of faricimab in these patients. Patients were randomized 1:1:1 into three arms: faricimab q8 weeks; PTI faricimab; and aflibercept q8 weeks.[4]

The PTI arm received four monthly injections until they achieved central subfield thickness <325 µm, after which the interval could be extended up to q16 weeks based on CST and visual acuity change. The mean vision gains were comparable between the q8-week and PTI faricimab arms. Anatomic results were also favorable. Visual acuity gains were similar to those in the aflibercept q8-week arm. Reductions in CST favored the faricimab arms.

More patients achieved absence of DME and absence of IRF with faricimab. Seventy-nine percent of patients who achieved q12- or q16-week dosing at week 52 remained on q12-week or more dosing without an interval reduction through week 96. Similarly, 76 percent of patients who achieved q16-week dosing at week 52 remained on that interval through week 96. Only 4.7 percent of patients remained on q8-week dosing and 3.9 percent remained on q4-week dosing.

Caroline R. Baumal, MD, of Tufts Medical Center, concluded that PTI dosing in YOSEMITE and RHINE demonstrated the durability of faricimab in patients with DME. Treat-and-extend-based PTI dosing was able to meet the heterogenous needs of patients with DME.

Most patients in the faricimab PTI arms achieved either q12- or q16-week dosing and these patients were able to maintain this dosing through week 96. The visual acuity gains and anatomic improvements in these patients were similarly maintained over two years.

Dr. Baumal disclosed being a consultant to Genentech/Roche, Novartis, Ora, Gemini, Carl Zeiss Meditec and Regeneron Pharmaceuticals. RS

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Pearls for righting aqueous misdirection

(Continued from page 19)

2. Anterior/core vs. complete PPV. A recent systematic review evaluated anterior/core vitrectomy vs. complete PPV and found a higher rate of relapse in the anterior/core vitrectomy cases.[1] The primary goal of vitrectomy is to disrupt the anterior hyaloid face. However, fluid may continue to fill vitreous cisterns if a complete PPV isn't performed. Also, residual vitreous in the periphery may block the communication the IZH creates, so careful vitreous shave of the vitreous base should be performed underneath the IZH.

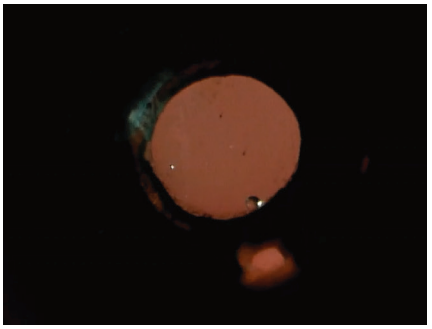

Figure 2. Retroillumination demonstrates no vitreous debris or intraocular lens haptic blocking the irido-zonulo-hyaloidectomy passage.

3. Synechiolysis. If the aqueous misdirection has been present for years, then prolonged irido-trabecular contact can result in significant synechiae, which can cause chronic angle closure. This can also result in patients still needing IOP-lowering drops after the procedure. PPV-IZH should be considered earlier to prevent these complications. Additionally, the release of both posterior synechiae and combination surgery with a glaucoma colleague for goniosynechiolysis may be required.

4. Retroillumination. Frequently, blockage of the IZH opening by residual vitreous, inflammatory membranes or the haptic of an intraocular lens can cause relapse of aqueous misdirection. Retroillumination (*Figure 2*) using the light pipe can evaluate for residual material blocking the IZH. RS

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Surprise! It's the No Surprises Act

How to navigate the regulations when providing care to out-of-network and private-pay patients.

By Suzanne Corcoran

Beginning this year, Congress enacted Title I, known as the No Surprises Act, which falls under the Consolidated Appropriations Act of 2021. This requires that you patients who are paying out-of-pocket a "good-faith estimate" of costs before you provide the services.

You may think, as a vitreoretinal specialist, you wouldn't be affected by this legislation. However, the No Surprises Act (NSA) requirements apply to items and services provided to most individuals enrolled in private or commercial health coverage. They include:[1]

- Employment-based group health plans, both self-insured and fully insured.
- Individual or group health coverage on or outside the federal or state-based exchanges.
- Federal Employee Health Benefit (FEHB) health plans.
- Non-federal governmental plans sponsored by state and local government employers.
- Certain church plans within Internal Revenue Service jurisdiction.
- Student health insurance coverage as defined by Title 45 of the Code of Federal Regulations.[2]

The act doesn't pertain to Medicare (Part B or Part C), Indian Health, Veterans Affairs, TRICARE or other federal plans, including Medicaid since it already has regulatory protections against higher medical bills in place. The majority of commercial plans likely fall under the act.

Where it applies to retina specialists

NSA applies in three categories when a person gets the following covered services:

- Emergency services from an out-of-network (OON) provider or emergency facility.
- OON nonemergency services delivered as part of a visit to an in-network facility.
- OON air ambulance services.

Significantly, the first two points might apply to retina services. As a subspecialist, you'll have referrals from provider networks that you're not part of. You might also provide emergency services in your local hospital even when you're not part of the hospital network. Ambulatory surgery centers are also included in the definition, so consider services you provide in your ASC as eligible. ASCs are also responsible for their own NSA notice. For example, their anesthesia providers might be OON.

Other situations in which the NSA is relevant include when the patient either doesn't have health insurance or does but chooses not to use it, usually because of high copays and/or deductibles.

The art of the good-faith estimate

In any of these scenarios, you as the provider are required to give the patient a good-faith estimate for the services they're seeking. The Centers for Medicare & Medicaid Services instructs patients accordingly:[3]

Providers and facilities must give you:

- *Your good-faith estimate before an item or service is provided, within certain time frames.*
- *An itemized list with specific details and expected charges for items and services related to your care.*
- *Your good-faith estimate in writing (paper or electronic). Note: A provider or facility can discuss the information included in the estimate over the phone or in person if you ask.*
- *Your estimate in a way that's accessible to you.*

Your estimate should be in writing, even if the patient only asks for a verbal explanation. We also recommend that you have the patient sign and date the itemized estimate. It's important you give the patient a copy and save a copy to the patient's file. The arbitrator

Have a question for "Coding Commentary"? Tweet it to us at **@RetSpecMag**

Bio

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will want that if there's a conflict later on.

If you still think the Act doesn't pertain to you, consider these scenarios:

A patient from out of state calls your office on the recommendation of a friend he's visiting. He has HMO insurance and you're out of his network. He's experiencing flashes and an increase in floaters. Your staff member schedules him for an urgent same-day visit. On exam, you find a superior horseshoe tear in his right eye and recommend urgent laser retinopexy in the office.

Question: Does the NSA apply in this encounter?

Answer: Yes. You must give the patient a written good-faith estimate for the exam and any testing (such as extended ophthalmoscopy or optical coherence tomography), as well as the cost of the operation. The exam and testing notice are provided at check-in, before the services. If laser or other surgery is indicated, that good-faith estimate needs to be given before that service.

An established patient returns for her annual diabetic eye exam. She tells the front desk that she has new insurance, and the annual deductible is $2,000, so she wants to pay cash for her visit. You perform a comprehensive eye exam and, because of scattered microaneurysms, also do fundus photography.

Question: Does the NSA apply here?

Answer: Yes. NSA covers any self-pay patient, either because they're uninsured or by preference. You must also give this patient a good-faith estimate for the exam and photos before you provide the services.

A patient can only dispute a bill if the charges are $400 or more than the good-faith estimate, so use great care in providing yourgood-faith estimates.

When disputes arise

Patients can enter the dispute resolution process set up as part of the NSA if the NSA is implicated. CMS defines specific requirements when a patient may dispute a bill for services. They are:[4]

- When the patient is uninsured or self-pay (that is, has insurance but didn't use it to pay for the healthcare item or service).
- The medical items or services were provided on or after January 1, 2022.
- The patient has a good-faith estimate from the provider.
- The patient has a bill dated within the last 120 calendar days (about four months).
- The difference between the good-faith estimate and the bill from any single provider or facility is at least $400.

Note the last point: a patient can only dispute a bill if the charges are $400 or more than the good-faith estimate, so use great care in providing your good-faith estimates.

Remember, you're required to provide an estimate for this class of patients. So, it's not a good idea to just "not give an estimate" to try to thwart the process.

You can find sample fair estimate forms on the CMS website.[5] The NSA doesn't specify a form, but it does require a process that's transparent to the patient. Colleagues may have more user-friendly forms.

The major issue with the NSA doesn't come from your willingness to follow it. The issue will be identifying this small cohort of patients to whom it applies. Be sure your staff members—those in scheduling, check-in and billing, as well as technicians/scribes—are aware of the NSA requirements so you can give patients appropriate estimates. With diligence in your registration process, you can avoid any surprises from the NSA. RS

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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:
Genentech, Inc.
A Member of the Roche Group
1 DNA Way
South San Francisco, CA 94080-4990
U.S. License No.: 1048

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

VABYSMO™
faricimab-svoa injection 6 mg

WHERE 2 WORLDS MEET

The First and Only Dual-Pathway Inhibitor in Retinal Disease[1-5]

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

Image not intended to be a patient portrayal.

Visit VABYSMO-HCP.com

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.

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