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RETINA SPECIALIST

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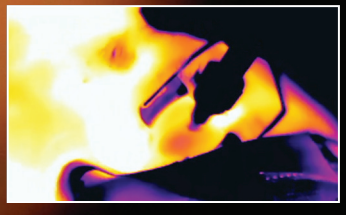
New Insights Into Gene Therapy

Gene Therapy and its potential for DR



A look at early clinical research. With two videos.

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Real-world experience with retinal gene therapy

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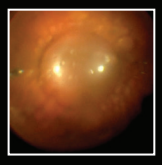
Three Online Videos



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.

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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

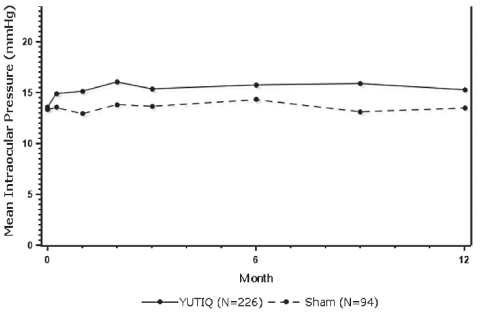
Ocular		
ADVERSE REACTIONS	**YUTIQ (N=226 Eyes) n (%)**	**Sham Injection (N=94 Eyes) n (%)**
Vitreous Hemorrhage	4 (2%)	0
Iridocyclitis	3 (1%)	7 (7%)
Eye Inflammation	3 (1%)	2 (2%)
Choroiditis	3 (1%)	1 (1%)
Eye Irritation	3 (1%)	1 (1%)
Visual Field Defect	3 (1%)	0
Lacrimation Increased	3 (1%)	0
Non-ocular		
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:
EyePoint Pharmaceuticals US, Inc., 480 Pleasant Street, Watertown, MA 02472 USA
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19 Campus Blvd., Suite 101
Newtown Square, PA 19073
Telephone (610) 492-1000
Fax (610) 492-1039

Editorial inquiries (610) 492-1000
Advertising inquiries (610) 492-1011
E-mail retinaspecialist@jobson.com

Jobson Medical Information

EDITORIAL

By Charles C. Wykoff, MD, PhD

Promises and pudding

The failure of KSI-301 to achieve non-inferiority compared to aflibercept in the DAZZLE trial, with a six-letter difference in vision between the arms, hurt (*page 6*). Much hope was built around this anti-VEGF biopolymer conjugate and its inferred ability to dramatically extend intervals between treatments.

While this promise stemmed from sound preclinical models and a Phase Ib trial, the Achilles heel was the absence of a control arm. Nevertheless, KSI-301 showed a signal for meaningful durability, with 59 percent of patients extending to a 20-week interval at year one.

But, neovascular age-related macular degeneration is heterogeneous and some patients need more anti-VEGF treatment than others. Therefore, because the shortest retreatment interval after three loading doses was 12 weeks, it appears that most of the 30 percent of patients on q12-week dosing in DAZZLE probably would've benefited from more frequent dosing.

More difficult to understand is the apparent difference in drying capability between KSI-301 and aflibercept during the loading doses. This deserves further analysis.

Fortunately, KSI-301 still has a path to regulatory approval, so long as the team incorporates learnings from DAZZLE into the ongoing trials in diabetic macular edema and the ongoing pivotal trials are successful.

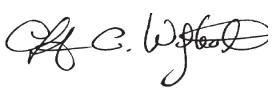
Unquestionably, gene therapy for ophthalmic diseases holds great promise. The approval of voretigene neparvovec-rzyl (VN) for patients with biallelic *RPE65* mutations was a watershed moment in medicine.

Since its 2017 approval, ongoing analyses into previously under-appreciated anatomic sequelae may have implications for other gene therapy programs, report Xuan Cao, MD, and Aaron Nagiel, MD, PhD (*page 22*).

Harnessing gene therapy to create an intraocular, anti-VEGF biofactory to treat exudative retinal diseases is exciting. Early data from the ALTITUDE trial of RGX-314 in diabetic retinopathy seem encouraging, as Dennis Marcus, MD, and colleagues discuss (*page 16*). We must incorporate learnings from challenges related to inflammation, and even hypotony, with other ophthalmic gene therapies in other disease states as we advance these incredible therapeutics.

Even after an agent passes the rigors of regulatory approval and gains market access, meaningful safety events may sometimes only be appreciated with widespread clinical use, as was the case with brolucizumab.

As the proverb goes, *The proof of the pudding is in the eating*. In drug development for retinal diseases, we must ground ourselves in the reality that proof of efficacy and long-term safety can only be determined through well-designed, controlled studies and, ultimately, widespread clinical utilization. I can't wait to try the pudding!



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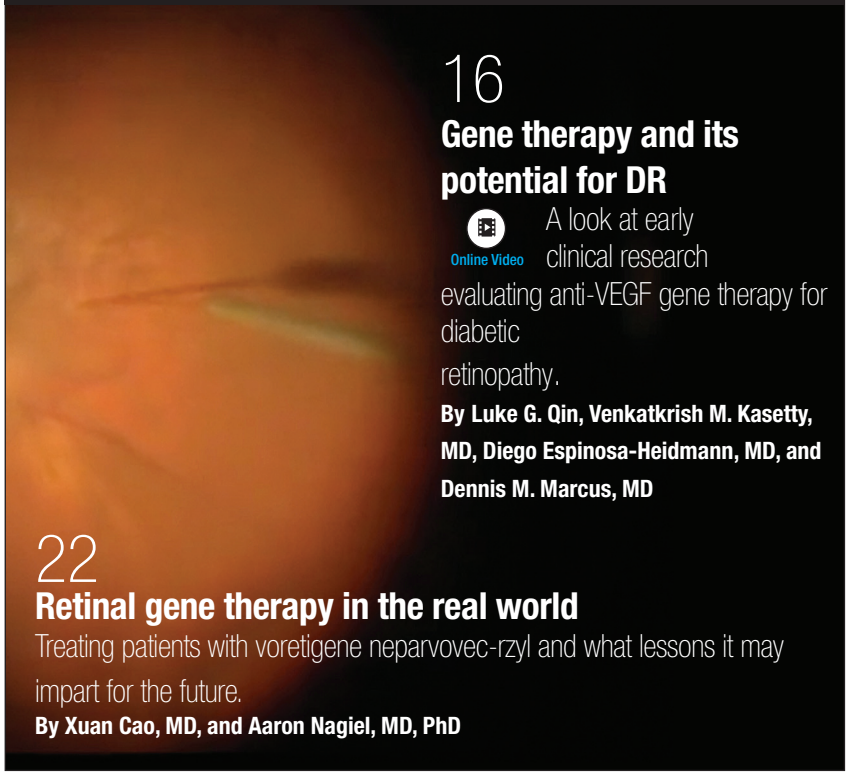
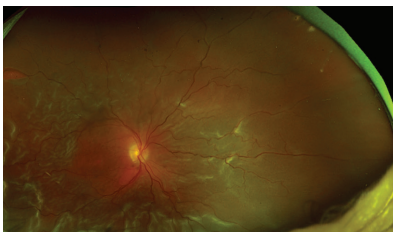
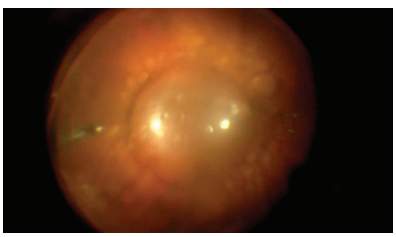
FEATURES

New Insights into Gene Therapy



DEPARTMENTS





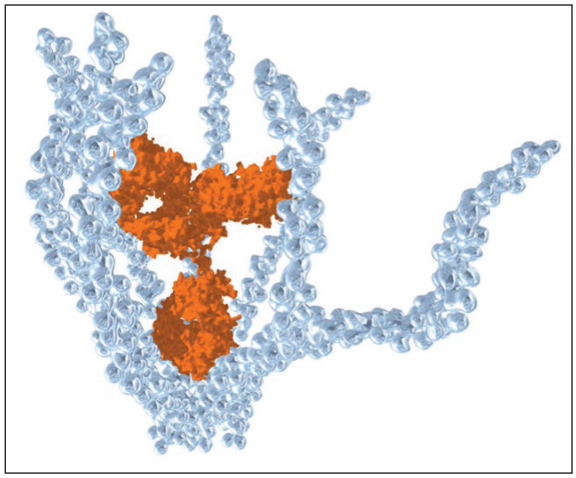
A deeper dive into why DAZZLE results of KSI-301 in nAMD 'disappointed'

While topline data from the Phase IIb/III DAZZLE trial of the investigative anti-VEGF biopolymer conjugate KSI-301 failed to meet its primary endpoint of achieving noninferiority to aflibercept in neovascular age-related macular degeneration, leaders at trial sponsor Kodiak Sciences say they're committed to pursuing the indication as well as other indications for the agent.

Retina specialists, meanwhile, have been parsing the data to make sense of why the 52-week results flopped.

"While we are highly disappointed that DAZZLE did not reach its primary endpoint, we do feel there are valuable insights into the potential for KSI-301 and the value of the ABC (for anti-VEGF biopolymer conjugate) platform more broadly in the treatment of retinal disorders," Kodiak Sciences chief executive officer Victor Perlroth, MD, told securities analysts in a conference call shortly after the results were reported.

Clinicians were likewise caught off guard by the results.



KSI-301 is an anti-VEGF antibody biopolymer conjugate of immunoglobin G1 antibody inert immune effector function (orange cluster) and branched high-molecular weight phosphorycholine polymer (light blue branches). (*Courtesy Kodiak Sciences*)

Stretched too far?

"I was surprised by the results of the IIb/III DAZZLE trial, especially the intraocular inflammation finding," says David Eichenbaum, MD, a DAZZLE investigator and a vitreoretinal surgeon with Retina Vitreous Associates of Florida in the Tampa-St. Petersburg area.

DAZZLE randomized 559 patients to either KSI-301 5 mg or aflibercept 2 mg (Eylea, Regeneron Pharmaceuticals). KSI-301 patients were on a flexible treatment schedule of three, four or five months; the aflibercept group was on a fixed q8-week interval. Both groups received three monthly loading doses.

In previously reported comments, study investigator Carl Regillo, MD, of Wills Eye Hospital, Philadelphia, said that the three-month minimum for KSI-301 injections may have "stretched it too far" for the 30 percent of patients in that arm who could've benefited from more frequent treatments.

Says Dr. Eichenbaum, "The need for a significant minority of KSI-301 patients to receive treatment more often than every three months was less surprising to me, especially in the nAMD disease state under study in DAZZLE."

Dr. Eichenbaum offers an explanation for why some patients in the KSI-301 arm may have needed more frequent dosing.

"The ABC platform is a large biopolymer, and nAMD is a purely subretinal disease," he says. "Perhaps the pharmacokinetics and/or

IN BRIEF

LumiThera, developer of the **Valeda Light Delivery System** photobiomodulation (PBM) treatment for retinal disease, has completed its acquisition of **Diopsys** and its electroretinography technology. LumiThera says the acquisition creates a complementary diagnosis and monitoring platform for its PBM system.

Alimera Sciences reports positive three-year results of the PALADIN study of its **Iluvien** 0.19-mg sustained-release fluocinolone implant in diabetic macular edema. The results, published in *Ophthalmology*, showed a 70.5-percent reduction in treatment frequency.

Belgium-based **ProQR Therapeutics** reports that the pivotal Phase II/III Illuminate trial of **sepofarsen** for the treatment of CEP290-mediated Leber congenital amaurosis 10 didn't meet its primary endpoint of vision improvement at 12 months.

Stealth BioTherapeutics reports the final patient has completed treatment in the ReCLAIM-2 Phase II trial of **elamipretide** for extra-foveal geographic atrophy associated with dry age-related macular degeneration. Topline results are anticipated in the second quarter this year.

bioavailability of the anti-VEGF product had trouble penetrating subretinally; perhaps there's just a proportion of nAMD patients with vascular endothelial growth factor load too great for the suppression offered by KSI-301 at q3 months."

Overall topline results

At one year, the aflibercept arm had best-corrected visual acuity gains averaging 7 letters vs. 1 letter for the KSI-301 arm. As for anatomical outcomes, aflibercept showed average reductions in central subfield thickness of -133.9 µm vs. -91.5 µm with KSI-301.

The KSI-301 arm included three different treatment subgroups: 59.4 percent received q20-week treatment; 10.3 percent q16-week treatment; and 30.3 percent were on a q12-week interval. The q20-week group had an average 52-week BCVA improvement of 6.75 letters. The q12-week group dragged down the overall results, showing about a half-letter loss in BCVA.

Likewise, the q20-week KSI-301 group had anatomical outcomes more in line with the aflibercept group, with an average CST reduction around -100 µm. Again, the q12-week KSI-301 group didn't show CST improvements as robust.

Safety outcomes

With regard to safety, KSI-301 had a 45.8 percent rate of treatment-emergent adverse events (TEAEs) in the treated eye vs. 36.4 percent with aflibercept.

Nine patients in the KSI-301 arm had at least one intraocular inflammation TAEA, a rate of 3.2 percent overall, while there were none in the aflibercept arm. IOI TAEAs included vitritis (3; 1.1 percent) and procedure-related endophthalmitis (1; 0.7 percent).

Dr. Eichenbaum notes that his practice's trial site didn't have any episodes of inflammation. "The aflibercept group performed remarkably well from a safety standpoint, with 0 percent IOI, emphasizing the safety of the well-developed Eylea product," he says.

Ongoing trials

KSI-301 is the subject of five other Phase III trials: DAYLIGHT of monthly dosing in nAMD; BEACON of bimonthly treatment in retinal vein occlusion; GLEAM and GLIMMER of q2-to-q6-month dosing in diabetic macular edema; and GLOW of twice-yearly treatment in nonproliferative diabetic retinopathy. All but GLOW use aflibercept for the comparator: GLOW is using a sham injection.

Dr. Perlroth of Kodiak says topline data from GLEAM, GLIMMER and DAYLIGHT are expected in 2023.

Dr. Eichenbaum notes that RVO and DME "have a purely intraretinal pathophysiology, and perhaps the drug will perform well in a broader population at long intervals in those diseases. The designs for those trials are also more flexible for patients who may need treatment more often."

With regard to safety, he says he's "eager" to see results from DAYLIGHT. "I'm fairly certain that KSI-301 will perform well from an efficacy perspective at high-frequency dosing, and I am hopeful that the IOI rate will be improved, even at more frequent dosing, in this trial," Dr. Eichenbaum says.

Besides serving as an investigator and consultant for Kodiak, Dr. Eichenbaum is also an investigator and consultant for Regeneron Pharmaceuticals.

— Richard Mark Kirkner

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BUSINESS OFFICES
19 CAMPUS BOULEVARD, SUITE 101
NEWTOWN SQUARE, PA 19073
SUBSCRIPTION INQUIRIES (877) 529-1746
(USA ONLY); OUTSIDE USA, CALL (847) 763-9630

BUSINESS STAFF
PUBLISHER
MICHAEL HOSTER
(610) 492-1028 MHOSTER@JOBSON.COM

EXECUTIVE DIRECTOR
JAMES HENNE
(610) 492-1017 JHENNE@JOBSON.COM

REGIONAL SALES MANAGER
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SENIOR CIRCULATION MANAGER
JARED SONNERS
(973) 206-8091 jsonners@mdedge.com

CEO, INFORMATION GROUP SERVICES
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Jobson Medical Information LLC,
395 Hudson Street, 3rd Floor, New York, NY 10014

Five takeaways for PGP in RD surgery

Preoperative gas for pars plana vitrectomy as an adjuvant in retinal detachment surgery can be easy to adopt.

By Miguel Cruz-Pimentel, MD, Tina Felfeli, MD, and Efrem D. Mandelcorn, MD, FRCSC

Miguel Cruz-Pimentel, MD

Tina Felfeli, MD

Efrem D. Mandelcorn, MD, FRCSC

The term "adjuvant therapy," derived from the Latin term *adjuv re*, meaning "to help," was first coined by Paul Carbone and his team at the National Cancer Institute in 1963.[1] The use of preoperative adjuvant treatments in vitreoretinal surgery, such as for the use of anti-VEGF agents one to three days preoperatively in cases of advanced diabetic retinopathy, have been successfully applied.[2]

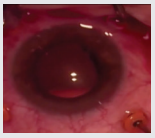
As retina specialists, one of the most common pathologies we face every day is rhegmatogenous retinal detachment. We recently introduced our approach to using preoperative gas for pars plana vitrectomy, or PGP technique, as an adjuvant therapy for PPV[3] in the management of RRDs that are traditionally not considered to be candidates for pneumatic retinopexy.[4] These include RRDs with multiple breaks in more than one quadrant, large breaks extending more than one clock hour and/or inferior breaks requiring PPV. The goal of PGP as an adjunct to PPV for repair of RRDs is to enhance the ease of surgery and improve functional and anatomical success.[3]

Our own experience

Our published case series included 109 eyes that underwent the PGP technique from 2016 to 2020,[3] with a primary anatomical success rate of 95 percent and secondary anatomical success of 100 percent (including those with silicone oil tamponade removed) at last follow-up. Baseline visual acuity improved significantly at the last follow-up and most eyes (65 percent) achieved a final visual acuity of 20/50 or better. We noted preoperatively that PGP reduced the amount of peripheral subretinal fluid by at least 50 percent in bullous detachments.

In this article, we describe the PGP technique and highlight five major advantages and applications of the technique as an adjuvant in retinal detachment surgery.

View the Video



Watch as Drs. Cruz-Pimentel, Felfeli and Mandelcorn demonstrate the preoperative gas technique for pars plana vitrectomy as an adjuvant treatment in retinal detachment surgery. Available at: https://bit.ly/RetSpecMag_2022_04

Surgical technique

The PGP technique is performed starting with an anterior chamber paracentesis under topical anesthesia and sterile technique. Following this, we inject 0.6 mL sulfur hexafluoride (SF6) or 0.3mL perfluoropropane (C3F8) intravitreal gas into the superotemporal quadrant of the pars plana by placing the needle just internal to the scleral wall. We inject the gas away from the detached quadrant for very bullous RRDs to prevent subretinal gas migration.

Following gas injection, we advise patients to maintain a face-down position for four hours "to steamroll"[5] the macular fluid to the periphery, and then in a position to tamponade the retinal break, usually flat on one side or the other. All of our patients underwent PPV within approximately one week following PGP.

Special considerations in the OR

We advise taking special considerations in the operating room. The phakic eye is prepared and draped quickly to decrease any

Ideal candidates for preoperative gas for PPV

- Retinal detachment with multiple large breaks in more than one quadrant and/or inferior breaks.
- RD with macular holes.
- RD with large bullous choroidal detachment.
- Unidentifiable breaks, such as those due to media opacity, including capsular phimosis and vitreous hemorrhage).

Bios

Dr. Felfeli is an ophthalmology resident at the University of Toronto.

Dr. Cruz-Pimentel is a vitreoretinal fellow at the University of Toronto.

Dr. Mandelcorn is an associate professor of ophthalmology at the University of Toronto.

DISCLOSURES: The authors have no relevant financial relationships to disclose.

lens opacification that can develop while the patient is supine. Moreover, gas removal should be done right at the beginning of the surgery.

At the start of PPV, the preoperative gas bubble is removed through the trocar cannula as the blade is retracted through the valve of the superonasal or superotemporal trocar, with the eye tilted to its most superior position, as demonstrated in this video: www.aao.org/1-minute-video/tips-gas-removal-in-phakic-eye-after-pneumatic-ret.

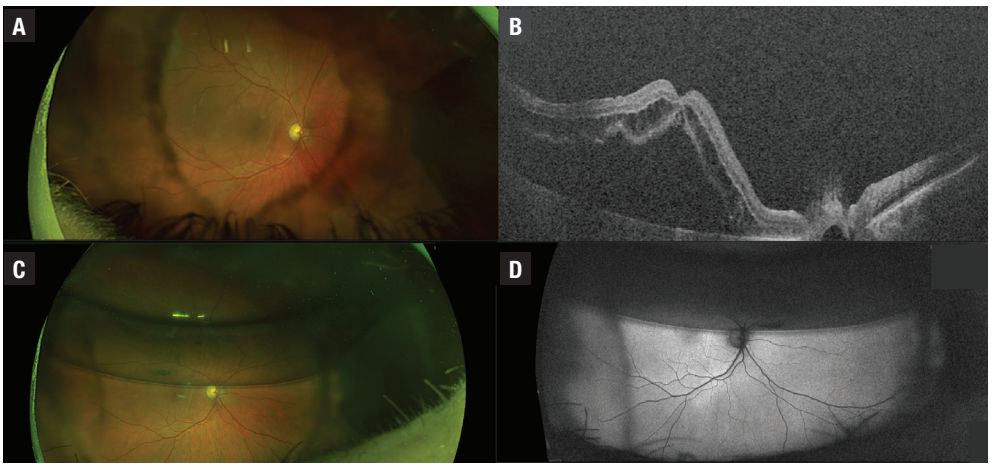


Figure 1. Representative case of a 66-year-old pseudophakic patient with a history of previous tears treated with cryotherapy. The patient had a Soemmering's ring (A), which limited the view of the posterior segment during the examination and a macula-off rhegmatogenous retinal detachment (B). The patient underwent preoperative gas (PGP technique) during pars plana vitrectomy, and inferior holes were found and treated with laser. At two weeks postoperatively, color fundus photos (C) and autofluorescence image (D) demonstrated good anatomical outcomes.

Fluid-air exchange (FAX) using a backflush cannula is then done through the primary break without perfluorocarbon (PFO) liquid-assisted drainage. Retinal breaks are lasered in the attached retina prior to FAX, while breaks in the detached retina are lasered after the FAX. The vitreous cavity air is flushed with either SF6 or C3F8 gas. Patients are advised to maintain a side or face-down position immediately after PPV.

An illustration of the PGP technique and its applications can be found in the accompanying video.

The five major takeaways

1. *PGP protects the macula in both macula-off and macula-on RRDs*

The PGP approach in RRDs with combined inferior and superior breaks promotes reattachment of the macula in most cases. We believe that PGP is essential to ensure timely management of RRDs and faster restoration of central vision. The more rapid reattachment of the macula likely results in a better visual outcome.

Studies have shown that repairing macula-off detachments within three days is critical for preserving vision.[6,7] Presumably, this implies that rapid macular reattachment, especially in situations where operating room access is limited, can give patients the best chance at improved central vision postoperatively. In cases of macula-on detachments, PGP can protect the macula from going macula-off until OR access is available (*Figure 1*).

2. *PGP reduces the amount of subretinal fluid that needs to be drained in vitrectomy*

By making RRDs less bullous and less mobile, PGP allows the surgeon to perform a better shave of the vitreous prior to fluid-fluid exchange or FAX. The reduced amount of residual SRF at the conclusion of surgery can also reduce the amount of posterior migration of SRF into the macula during FAX. Reduced residual SRF can help mitigate the risk of developing retinal folds postoperatively.

A reduction in SRF prior to the PPV also has the benefit of decreasing the need for PFO liquids, with reduced surgical cost and morbidity associated with inadvertently retained PFO—such as postoperative

inflammation, raised intraocular pressure and photoreceptor and retinal pigment epithelium atrophy.[8]

3. PGP reduces the risks associated with choroidal detachments

In patients with associated choroidal detachments, PGP can reduce or eliminate the detachment, which can lessen the risk of redetachment due to underfill when silicone oil is needed as a tamponade. Additionally, PGP can often partially resolve a choroidal detachment, which can diminish the likelihood of placing the trocars or infusion cannula in the suprachoroidal space (*Figure 2*).

4 PGP improves ease of repair for detachments associated with full-thickness macular holes

In cases of retinal detachment with an associated full-thickness macular hole (FTMH), PGP allows for macular (and macular hole) reattachment preoperatively, which can reduce the risk of subretinal injection of tissue-staining agents (indocyanine green or Brilliant Blue). It can also ease the peeling of the internal limiting membrane. In the case illustrated in Figure 3, macular reattachment is achieved with PGP, simplifying the ILM peel around the macular hole intraoperatively.

5 PGP is a timely and simple technique that can easily be incorporated into a retina surgeon's practice

PGP is an office-based technique that's a timely intervention in situations where the OR can't be accessed immediately due to availability of resources. Moreover, PGP is easy for surgeons to incorporate into their practice, even if they have minimal experience with pneumatic retinopexy. For surgeons who often choose PPV as their primary RRD repair modality, PGP is an excellent option. PGP takes advantage of both the high anatomical success rates of PPV for RRD and the high functional success rates of pneumatic retinopexy. The PGP technique nicely marries these two options by optimizing both.

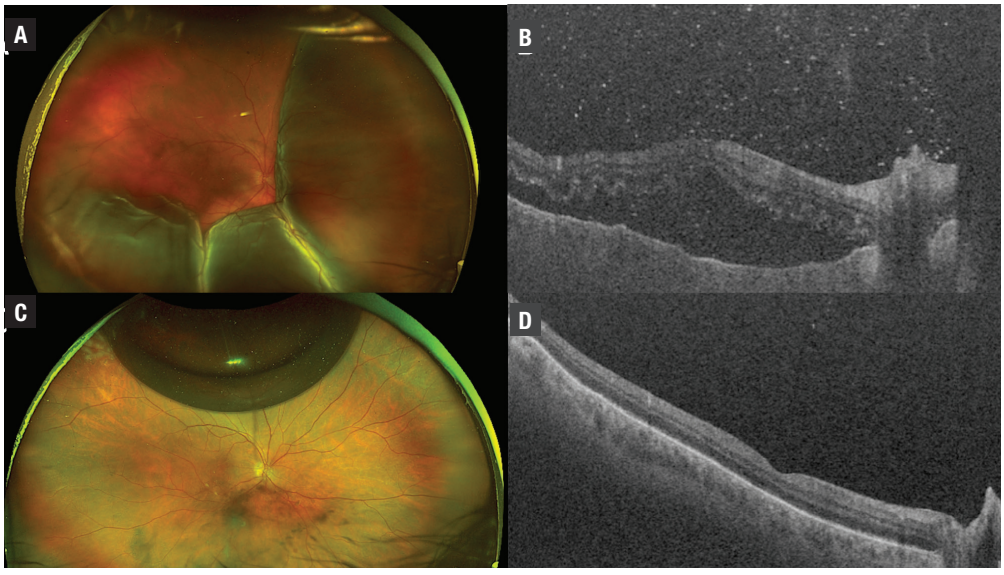


Figure 2. Representative case of a 65-year-old patient with a macula-off rhegmatogenous retinal detachment with an associated choroidal serous detachment and posterior vitreous detachment grade A with superior and inferior breaks (A and B). On day four following preoperative gas, the choroidal detachments resolved and the macula reattached with persistent fluid inferiorly due to inferior breaks and good laser barricade around the superior break (C and D). The patient underwent pars plana vitrectomy on day five following the initial presentation.

Bottom line

Overall, the PGP technique may provide good anatomic and functional outcomes in cases in which pneumatic retinopexy isn't suitable, including multiple large breaks in more than one quadrant, and/or inferior breaks, retinal detachments with associated macular holes, presence of large bullous choroidal detachments, unidentifiable breaks and media opacity due to vitreous hemorrhage.

The PGP technique with PPV for rheg-

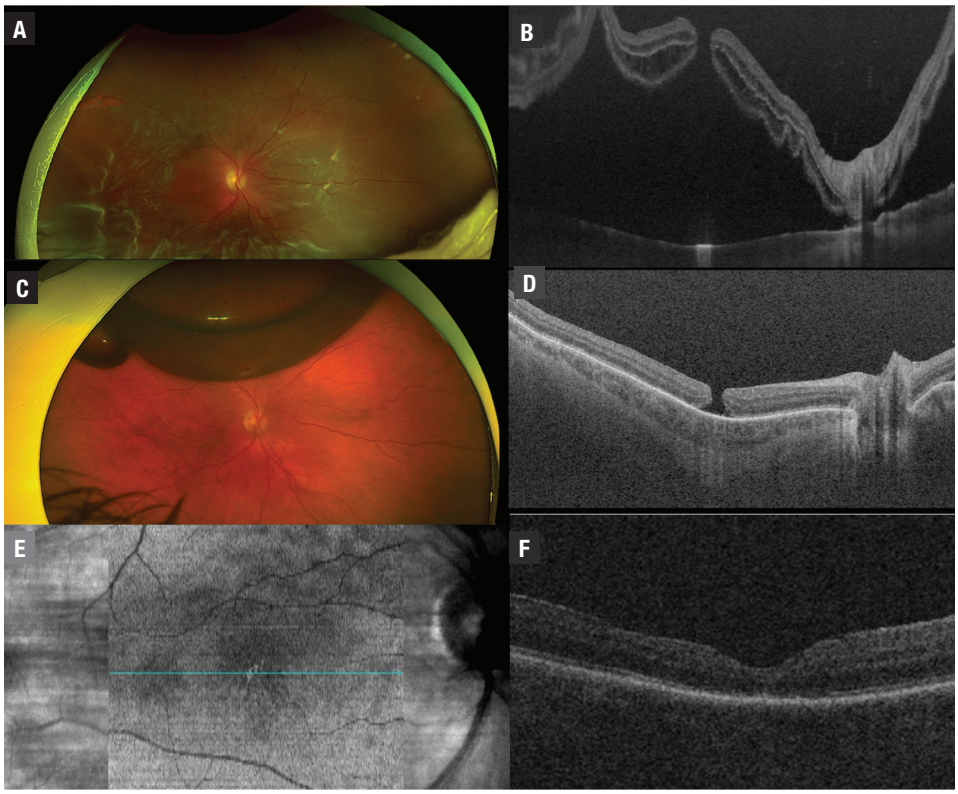


Figure 3. Representative case of a 62-year-old patient with congenital deafness who presented with a rhegmatogenous retinal detachment with several breaks in the temporal quadrant and a full-thickness macular hole in the right eye (A and B). The preoperative gas (PGP technique) with pars plana vitrectomy technique was used, followed by laser retinopexy at 48 hours (C and D). The patient also underwent PPV with internal limiting membrane peel within one week. Postoperatively, this complex case had a good anatomical outcome (E and F).

matogenous retinal detachments can easily be incorporated into the retina specialist's routine surgical practice, based on the advantages that we've outlined here.

Surgeons from the United Kingdom, Max Davidson and Aman Chandra, who have successfully adapted this technique, have found that implementing PGP marries the anatomical and functional benefits of pneumatic retinopexy and PPV, achieving good results in both simple and complicated RRDs.[9] RS

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In patients with associated choroidal detachments, PGP can reduce or eliminate the choroidal detachment, which can lessen the risk of redetachment due to underfill when silicone oil is needed as a tamponade.

WHAT COULD SHE SEE THIS YEAR?

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

Inspired by a real patient with DME.

375 MATH TESTS

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.

REGENERON

777 Old Saw Mill River Road, Tarrytown, NY 10591

EYLEA ACHIEVED RAPID, SUSTAINED OUTCOMES IN DME

Demonstrated efficacy outcomes in VISTA and VIVID, phase 3 anti-VEGF trials in DME (N=862)[1]

Mean change in BCVA (ETDRS letters) at Year 1 from baseline[1-5,*]

	Initial Gains (Month 5)		Primary Endpoint (Year 1)		Prespecified Exploratory Endpoint (Year 3)	
	VISTA	VIVID	VISTA	VIVID	VISTA	VIVID
EYLEA Q4	+10.3 (n=154)	+9.3 (n=136)	+12.5 (n=154)	+10.5 (n=136)	+10.4 (n=154)	+10.3 (n=136)
EYLEA Q8†	+9.9 (n=151)	+9.3 (n=135)	+10.7 (n=151)	+10.7 (n=135)	+10.5 (n=151)	+11.7 (n=135)
Control	+1.8 (n=154)	+1.8 (n=132)	+0.2 (n=154)	+1.2 (n=132)	+1.4 (n=154)	+1.6 (n=132)

P<0.01 vs control at Year 1.

The analyses of these exploratory endpoints were not multiplicity protected and are descriptive only.

Year 2 data was consistent with results seen in Year 1.[5]

VISTA and VIVID study designs: Two randomized, multicenter, double-masked, controlled clinical studies in which patients with DME (N=862; age range: 23-87 years, with a mean of 63 years) were randomized and received: 1) EYLEA 2 mg Q8 following 5 initial monthly doses; 2) EYLEA 2 mg Q4; or 3) macular laser photocoagulation (control) at baseline and then as needed. From Week 100, laser control patients who had not received EYLEA rescue treatment received EYLEA as needed per re-treatment criteria. Protocol-specified visits occurred every 28 (±7) days.[1]

In both clinical studies, the primary efficacy endpoint was the mean change from baseline in BCVA at Week 52, as measured by ETDRS letter score.[1]

*Last observation carried forward; full analysis set.
†Following 5 initial monthly doses.

SEE WHAT EYLEA COULD DO FOR YOUR PATIENTS WITH DME 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.** Korobelnik JF, Do DV, Schmidt-Erfurth U, et al. Intravitreal aflibercept for diabetic macular edema. *Ophthalmology.* 2014;121(11):2247-2254. doi:10.1016/j.ophtha.2014.05.006 **3.** Brown DM, Schmidt-Erfurth U, Do DV, et al. Intravitreal aflibercept for diabetic macular edema: 100-week results from the VISTA and VIVID studies. *Ophthalmology.* 2015;122(10):2044-2052. doi:10.1016/j.ophtha.2015.06.017 **4.** Data on file. Regeneron Pharmaceuticals, Inc. **5.** Heier JS, Korobelnik JF, Brown DM, et al. Intravitreal aflibercept for diabetic macular edema: 148-week results from the VISTA and VIVID studies. *Ophthalmology.* 2016;123(11):2376-2385. doi:10.1016/j.ophtha.2016.07.032

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

04/2021
EYL.21.03.0211

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

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

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

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

4 CONTRAINDICATIONS

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

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

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

5 WARNINGS AND PRECAUTIONS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

8 USE IN SPECIFIC POPULATIONS

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

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

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

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

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

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

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

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

REGENERON

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

Issue Date: 08/2019
Initial U.S. Approval: 2011

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

EYL.20.09.0052

Department Editor ***Paul Hahn, MD, PhD***

Removing retained PFO/SO mixture

This technique uses an 18-gauge angiocatheter to remove fluid left behind after surgery for complex retinal detachments.

By Sandra Hoyek, MD, Dan Gong, MD, and Nimesh A. Patel, MD

Sandra Hoyek, MD

Dan Gong, MD

Nimesh A. Patel, MD

Perfluoro-n-octane is an important intraoperative aid in repairing complex retinal detachments, particularly in cases with giant retinal tears and proliferative vitreoretinopathy.[1]

While perfluoro-n-octane (PFO) is typically removed entirely during fluid air exchange (FAX), there may be inadvertent liquid retention. This substance can dissolve in a silicone oil (SO) tamponade, forming a transparent, high viscosity material, referred to as "sticky silicone oil."[2]

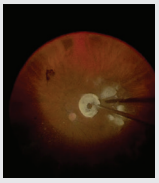
Because PFO is toxic to photoreceptors and causes visual field disturbances, prompt removal is often necessary. However, due to the density and viscosity of the substance, a unique collection forms posteriorly, which can't be aspirated by conventional methods (*Video*).

Surgical technique

We use a three-port pars plana approach. We remove the silicone oil that isn't mixed with PFO via viscous fluid extraction through the vitrectomy port in standard fashion. Then we perform a superotemporal localized conjunctival peritomy and use a 20-gauge microvitreoretinal blade to make a sclerotomy 3.5 to 4 mm posterior to the limbus, which is slightly enlarged to accommodate an 18-gauge instrument.

View the Video

Watch as Drs. Gong and Patel use an 18-gauge angiocatheter to remove a viscous PFO-silicone oil mixture. Available at: https://bit.ly/VideoPearl_028

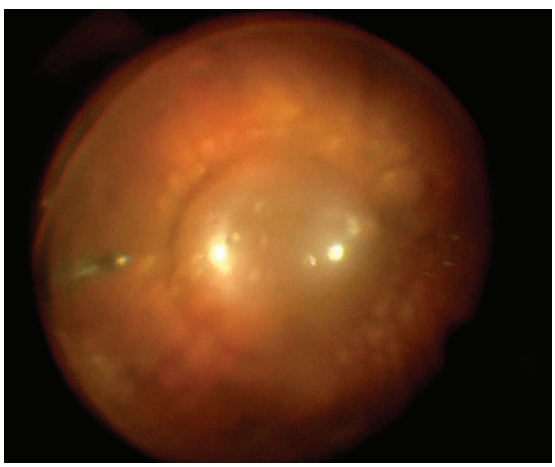


The next step is to connect an 18-gauge angiocatheter directly to the viscous fluid control extractor. The catheter, inserted into the newly created sclerotomy, can be advanced posteriorly until the tip is immersed in the remaining PFO/SO mixture. Active foot pedal-controlled aspiration is then initiated with simultaneous infusion of balanced salt solution to remove the target material.

Surgical pearls

Here are three pearls for using the angiocatheter to remove retained PFO/SO:

- The 18-gauge catheter can often be found in the operating room's anesthesia cart.
- Due to its size, the 18-gauge catheter may aspirate more fluid than is being infused and lead to a transient decrease in eye pressure. Therefore, keep a low and constant suction and ensure that the catheter tip is in the viscous mixture rather than in BSS.
- If there's difficulty inserting the angiocatheter, the tip may be beveled 45 degrees to facilitate entry.



Dense and viscous silicone oil and perfluoro-n-octane mixture on the posterior retina surface.

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Bios

Dr. Hoyek is a postdoctoral research fellow in ophthalmology at Massachusetts Eye and Ear Infirmary and Harvard Medical School, Boston.

Dr. Gong is an instructor of ophthalmology at Mass Eye and Ear and Harvard Medical School.

Dr. Patel is also an instructor of ophthalmology at Mass Eye and Ear and Harvard Medical School, as well as director of pediatric retina at Boston Children's Hospital.

Dr. Hahn is a partner at New Jersey Retina in Teaneck.

DISCLOSURES: Drs. Hoyek, Gong and Patel have no relevant relationships to disclose.

Dr. Hahn is a consultant to DORC.

New Insights into Gene Therapy

Gene therapy and its potential for DR

A look at early clinical research evaluating anti-VEGF gene therapy for diabetic retinopathy.


Luke G. Qin


Venkatkrish M. Kasetty, MD


Diego Espinosa-Heidmann, MD


Dennis M. Marcus, MD

By Luke G. Qin, Venkatkrish M. Kasetty, MD, Diego Espinosa-Heidmann, MD, and Dennis M. Marcus, MD

Take-home points

- Persistent and frequent intravitreal anti-VEGF injections are required to optimize visual acuity outcomes for patients with retinal vascular disease, but they result in significant treatment burden.
- Patient noncompliance is a major factor contributing to suboptimal visual outcomes for eyes with diabetic retinopathy.
- Gene therapy offers a potential one-time treatment allowing for the endogenous expression of anti-VEGF, which has the potential to significantly reduce treatment burden.
- Early clinical research evaluating anti-VEGF gene therapy for diabetic retinopathy provides excitement and promises to address and reduce treatment burden, although further study is needed to ensure safety and validate efficacy.

Diabetic retinopathy remains the leading cause of vision loss in developed countries with vision-threatening complications, including diabetic macular edema, vitreous hemorrhage or tractional retinal detachment. Anti-VEGF injections have been established as the primary treatment for DME and an alternative or adjunct to panretinal photocoagulation for proliferative DR.[1-5]

Challenge of anti-VEGF therapy

While intravitreal anti-VEGF treatment has been shown to be effective, it results in a significant injection burden, with patient compliance a significant barrier to optimal outcomes for proliferative DR and even as a first-line therapy for DME.[6-8] For PDR, PRP is most frequently done because clinicians often don't consider anti-VEGF monotherapy due to the compliance, cost and treatment burden issues.

Recent PANORAMA and DRCR Retina Network Protocol W data establish the role of intravitreal aflibercept (Eylea, Regeneron Pharmaceuticals) in the improvement in scores in the Diabetic Retinopathy Se-

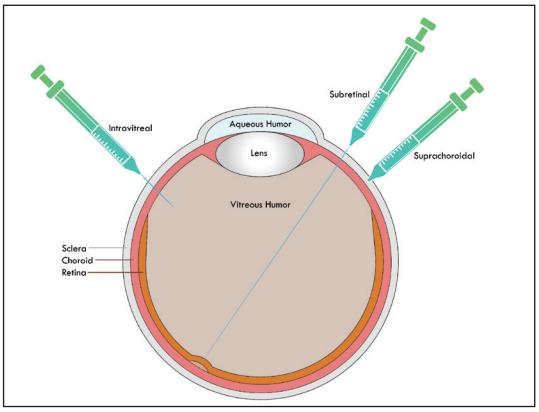
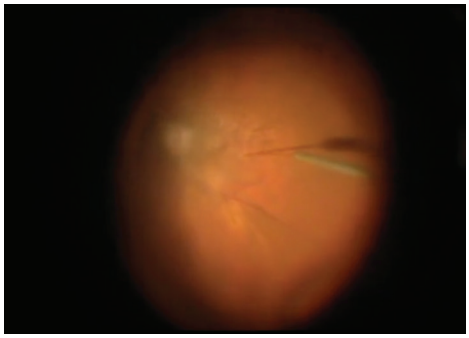


Figure 1. This illustration demonstrates the three delivery routes for retinal gene therapies: intravitreal injection; subretinal placement involving bleb formation; and suprachoroidal delivery.



Video 1. Allen Ho, MD, of Wills Eye Hospital, Philadelphia, demonstrates administration of subretinal RGX-314 in a patient with neovascular age-related macular degeneration. Available at: bit.ly/RetSpecMag_2022_01.(*Courtesy Allen Ho, MD*)

verity Scale and reduction of vision-threatening complications—that is, DME and PDR—in eyes with severe non-proliferative DR.[9] The retina community has also been reluctant to readily adopt anti-VEGF therapy for severe NPDR without DME as persistent/frequent injections are necessary for eyes that can be otherwise observed.

Gene therapy, allowing for the endogenous expression of anti-VEGF, has the potential to be an alternative to PRP in the treatment of PDR and to reduce injection burden in DME or in severe NPDR or PDR, as well as preventing vision-threatening complications while avoiding PRP-induced visual field loss and nyctalopia.

Gene therapy for retinal pathology

The retina remains a unique target for gene therapy. In 2017, voretigene neparvovec-rzyl (Luxturna, Spark Therapeutics/Roche) emerged as the first Food and Drug Administration-approved retinal gene therapy targeting the *RPE65* mutation for retinal degeneration.[10] This drug is delivered via subretinal injections of an adeno-associated virus (AAV) vector carrying a functioning copy of the *RPE65* gene. Three-to-four-year follow-up data demonstrated sustained improvements in visual navigation, light sensitivity and visual field with a good safety profile.[11]

Gene therapy has also been explored for choroideremia and X-linked retinoschisis, with promising data employing subretinal vector administration.[12,13]

Gene therapy for DR and DME aims to provide an endogenous supply of anti-VEGF that prevents disease progression (to DME, high-risk PDR and vitreous hemorrhages), reduces the number of supplemental anti-VEGF injections and alleviates treatment burden on patients.

Adverum's preclinical assessments have demonstrated the potential of anti-VEGF gene therapy in providing safe and effective long-term treatment for DME and neovascular age-related macular degeneration.[14] RegenxBio and Adverum are currently exploring the delivery of anti-VEGF gene fragments using AAV vectors to induce the endogenous production of anti-VEGF.

Delivery mechanisms

Investigators are studying these three gene therapy delivery routes (*Figure 1*).

- ***Subretinal space.*** This has been the most widely evaluated route because it targets the retinal pigment epithelium and photoreceptors more so than other mechanisms, and it has the potential for safer immunologic outcomes compared to intravitreal delivery.[15] However, subretinal approaches require surgical intervention with vitrectomy and come with the inherent drawbacks of adaptation, invasiveness, complications and cost.
- ***Intravitreal gene therapy.*** This in-office procedure is ideal because retina specialists are most familiar with it. Challenges, however, with intravitreal gene therapy include less targeted pharmacokinetic and drug delivery and reduced immune privilege.
- ***Suprachoroidal space.*** Defined as the potential space between the sclera and choroid, with a thickness of only 35 µm, it allows for an in-office administration of drug to the choroid, RPE and the neurosensory retina while bypassing the need for internal limiting membrane penetration

Bios

Mr. Qin is a medical student at the Medical College of Georgia, Augusta University, Augusta.

Dr. Kasetty is a second-year ophthalmology resident at Henry Ford Hospital in Detroit.

Dr. Marcus is a vitreoretinal surgeon and managing physician at Southeast Retina Center, director of clinical research at Eye Health America, and professor of clinical ophthalmology, Medical College of Georgia, Augusta University.

Dr. Espinosa-Heidmann is a vitreoretinal surgeon, associate professor and retina fellowship director at the department of ophthalmology at the Medical College of Georgia, Augusta University.

DISCLOSURES: Mr. Qin, Dr. Kasetty and **Dr. Espinosa-Heidmann** have no disclosures.

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required after intravitreal drug delivery.[16]

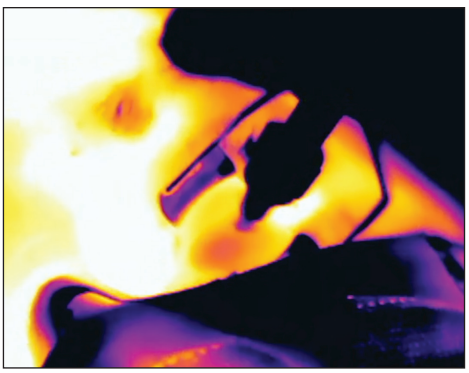
Suprachoroidal delivery is already employed in other pathologies. Suprachoroidal triamcinolone acetonide (Xipere, Clearside Biomedical) was approved by the FDA for uveitis-related macular edema.[17] Additionally, suprachoroidal injections may provide greater drug bioavailability to the posterior pole with more diffuse gene expression.[18] Suprachoroidal gene delivery may portend greater localized immune response compared to subretinal delivery, but likely results in less systemic humoral response compared to intravitreal delivery.[19]

Suprachoroidal delivery is already employed in other pathologies. Additionally, suprachoroidal injections may provide greater drug bioavailability to the posterior pole with more diffuse gene expression.

Investigative gene therapies for diabetic retinal disease

• ***RGX-314 (RegenxBio).*** This candidate utilizes an AAV8 vector with a gene encoding an anti-VEGF antibody fragment. Phase I/IIa data evaluating the subretinal administration of RGX-314 in the treatment of nAMD has shown stable visual acuity, decreased central subfield thickness and reduced treatment burden compared with anti-VEGF injections (*Video 1, page 17*).[20,21]

Early Phase II results from the ALTITUDE trial (NCT04567550) evaluating suprachoroidal RGX-314 for DR without center-involved DME demonstrated improvement in DRSS level, minimal adverse effects and no cases of endophthalmitis or intraocular inflammation. No prophylactic topical, periocular or systemic steroids were administered (*Video 2*).[22] Six-month data revealed that three of 15 treated eyes demonstrated one-step improvement in DRSS and seven eyes had more than a two-step improvement (*Figure 2*).



Video 2. In this video, Dennis Marcus, MD, administers suprachoroidal RGX-314 in a patient with diabetic macular edema. Available at: https://bit.ly/RetSpecMag_2022_02.

Greater-than-two-step DRSS improvement was observed in three of seven severe NPDR eyes and in two of eight PDR eyes, and increased to four of even and three of eight eyes, respectively, at six months. At six months, two-step improvement rates after suprachoroidal RGX-314 were comparable to those seen in severe NPDR eyes in the RIDE/RISE and PANORAMA trials.[23,24]

Suprachoroidal delivery of RGX-314 for nAMD is also being studied in the AAVIATE trial (NCT04514653). Early Phase II data is promising and has shown stable visual acuity, CST and a reduced treatment burden over six months compared to a ranibizumab control group.[25]

• ***ADVM-022 (Adverum).*** Similar to RGX314, ADVM-022 (AAV.7m8-aflibercept) aims to reduce the treatment burden of DME through endogenous anti-VEGF production. The INFINITY trial (NTC04418427) is evaluating the safety and efficacy of intravitreal ADVM-022 in patients with DME. While the initial results were promising, patients in the high-genomic load group experienced significant intraocular inflammation, with three eyes developing hypotony that required surgical intervention.[26]

Study enrollment was terminated to further evaluate the safety profile. The etiology of this inflammation hasn't been determined, although inadequate anti-inflammatory prophylaxis for high-dose treatment, comorbidities in affected patients, and diabetic- and vascular-related complications leading to the breakdown of the blood-retina barrier have been proposed.[27,28]

However, the low-dose treatment was

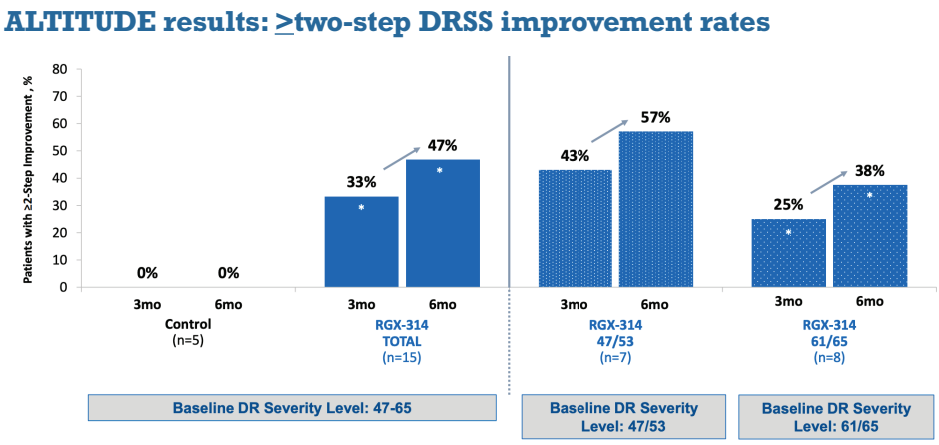


Figure 2. Six-month data from the ALTITUDE trial demonstrated that the number of patients in Cohort 1 who had greater than two-step improvements in Diabetic Retinopathy Severity Scale score after treatment with RGX-314 increased from three to six months. (*Courtesy RegnexBio*)

well tolerated with no complications, mild-to-moderate inflammation and no cases of hypotony. Despite these complications, both high and low-dose ADVM-022 showed a greater probability of remaining free of rescue anti-VEGF injections over a 40-week period compared to the aflibercept controls (*Figure 3*).

Intravitreal ADVM-022 for nAMD also may be promising. Two-year OPTIC data (NCT03748784) demonstrated an 80-percent reduction of annualized injection frequency over two years, while maintaining a stable to improved CST and stable visual acuity of low dose intravitreal ADVM-022 compared to aflibercept control.[29,30]

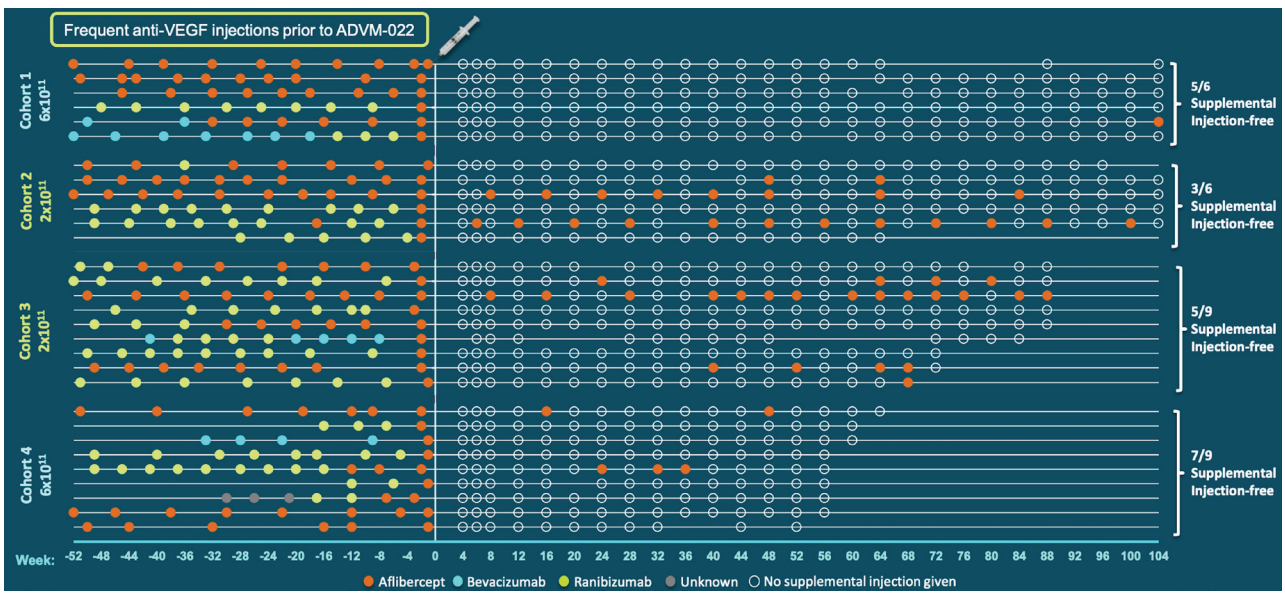


Figure 3. This chart shows that the majority of patients treated with ADVM-022 didn't require supplemental anti-VEGF treatment. The white line indicates treatment with ADVM-022, with the plot to the left indicating pretreatment anti-VEGF injections, and the plot to the right indicating posttreatment injections. The far left column shows the size of the dose in vector genomes per eye given in each cohort. (*Courtesy Adverum*)

Bottom line

Anti-VEGF gene therapy for DR with and without DME remains a potential exciting "one-and-done" approach in a patient population known for noncompliance. Early data with anti-VEGF gene therapy for DR and nAMD show stable visual acuities and reduced treatment burden. Regression of DR in some eyes indicates objective anatomic improvement using office-based suprachoroidal injection.

These encouraging short-term studies must be balanced by the potential of gene therapy-induced inflammation and autoimmune response and other potential safety concerns, as evidenced already in the INFINITY trial for DME with intravitreal ADVM-022. Further study of optimal techniques and delivery approaches as well as vector type will further elucidate the promise of anti-VEGF gene therapy for our diabetic patients. RS

These encouraging short-term studies must be balanced by the potential of gene therapy-induced inflammation, autoimmune response and other potential safety concerns.

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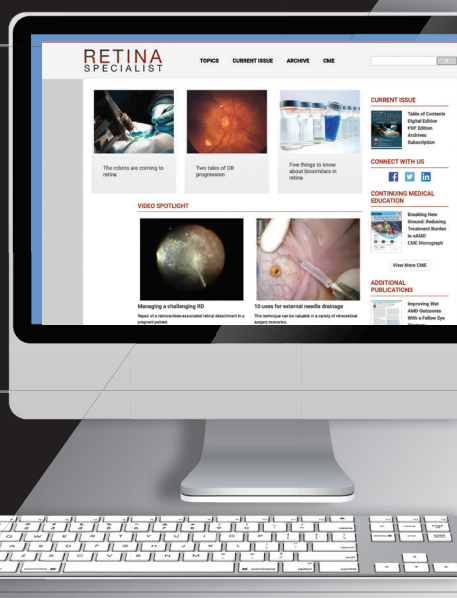
Each month, Medical Editor Philip Rosenfeld, MD, PhD, and our editors provide you with this timely and easily accessible report to keep you up to date on important information affecting the care of patients with vitreoretinal disease.



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New Insights into Gene Therapy

Retinal gene therapy in the real world

Treating patients with voretigene neparvovec-rzyl and what lessons it may impart for the future.

Xuan Cao, MD

Aaron Nagiel, MD, PhD

By Xuan Cao, MD, and Aaron Nagiel, MD, PhD

Take-home points

- Early real-world experience with voretigene neparvovec-rzyl (Luxturna) has demonstrated a comparable safety profile similar to the data from clinical trials.
- Perifoveal chorioretinal atrophy is a treatment-emergent adverse event that wasn't previously reported during clinical trials and requires further investigation.
- Fine-tuning the surgical delivery techniques could have significant applications for new retinal gene therapies in the pipeline.
- Gene therapy holds promise not only for inherited retinal disease, but also for neovascular age-related macular degeneration and diabetic retinopathy, which carry significant societal burden.

Bio

Dr. Cao is an ophthalmology resident at Los Angeles County and University of Southern California Medical Center/USC Roski Eye Institute, Los Angeles.

Dr. Nagiel is an assistant professor of ophthalmology at Children's Hospital Los Angeles, which is affiliated with the USC Roski Eye Institute.

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Dr. Nagiel is a consultant for Allergan/AbbVie, Biogen, Novartis and RegenxBio.

Voretigene neparvovec-ryzl represents the first Food and Drug Administration-approved gene therapy of its kind for the treatment of *RPE65*-mediated retinal dystrophy.[1] This treatment is now being delivered at 10 designated ocular gene therapy treatment centers across the United States.

As with any newly approved therapy, the first few years of real-world use can provide significant insight into how well the treatment performs along with any treatment-related side effects that may not have revealed in the controlled clinical trial environment. Our group last year presented the eagerly awaited interim one-year analysis of the post-authorization safety study (PASS) at the Retina Society in Chicago, allowing us a peek into how early experiences with voretigene neparvovec-rzyl (VN, Luxturna, Spark Therapeutics) holds up against clinical trial data.[2]

Here we discuss those findings along with our center's experience, and its potential implications for the future of retinal gene therapy.

PASS one-year interim analysis

This study represents a subset (37 of the 88 total patients) who received VN between March 2018 and April 2019 across the 10 designated U.S. treatment centers. It's important to recognize that this interim analysis represents only a subset of the total study population.

The majority of treatment-emergent adverse events (TEAEs) were mild in nature and similar to those found at year 1 in the Phase III clinical trial. Serious TEAEs included one case of foveal degeneration and two cases of rhegmatogenous retinal detachment, all of which were determined to be related to the administration procedure itself.

Also reported were several cases of chorioretinal atrophy (*Figure 1*), a TEAE

that wasn't previously recognized during the clinical trials, having been first described by William S. Gange, MD, and colleagues.[3]

Altogether, these safety data were generally consistent with the known clinical safety profile of VN and didn't identify any unacceptable barriers to its continued use. The one- and five-year follow-up data across the full cohort are highly anticipated to further monitor the safety and efficacy of VN from a larger overall patient population.

Surgical delivery techniques

Many of the designated ocular gene therapy centers initially delivered the vector according to the recommendations of the Luxturna surgical manual. This entailed the use of connection tubing that allowed a skilled assistant to inject the vector while the primary surgeon positioned the subretinal cannula.

However, this approach has its downsides, including that the primary surgeon can't have full hand-eye-foot pedal control of the injection. Also, it requires a trained assistant who may not always be available.

As a result, many treatment centers have pivoted toward foot-pedal control via the silicone oil injection setup using the MicroDose Injection Kit (MedOne Surgical). Before loading the vector into the syringe, it's essential to mobilize the syringe's stopper using the inject/extract functions.

Once the vector is loaded with the subretinal cannula attached, we then deliver the subretinal bleb at an intraocular pressure of 10 mmHg and maximum injection pressure of 10 to 16 PSI. This allows for some play in the pedal, since the max pressure level is typically not necessary to achieve slow, steady bleb propagation.

Another important adjunct is the use of intraoperative ocular coherence tomography guidance to precisely determine the location and extent of the bleb, including the ability to monitor for fovea detachment during delivery (*Figure 2, page 29*).

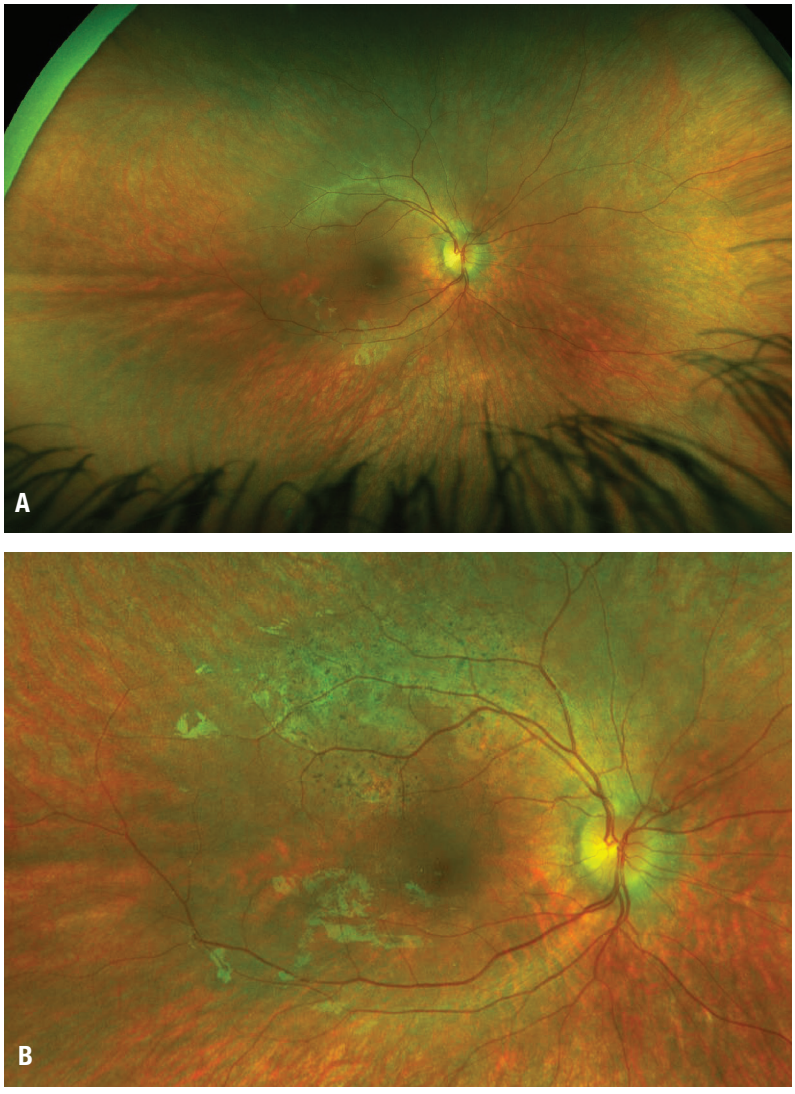

Figure 1. Perifoveal atrophy in the right eye of a 6-year-old boy treated with voretigene neparvovec-rzyl at (A) baseline and (B) one year postoperatively.

Chorioretinal atrophy

The one-year interim analysis also showed that a minority of patients undergoing treatment with VN developed chorioretinal atrophy due to etiologies that aren't entirely understood at this time. A 2022 multicenter retrospective analysis by Dr. Gange and colleagues

found a total of 18 eyes from 10 patients who underwent treatment with VN who developed progressive chorioretinal atrophy at four treatment centers across the United States.[3]

In this study, patients were identified as having chorioretinal atrophy if they met two conditions: if the areas of atrophy weren't considered directly related to the subretinal cannula touchdown site; and if the atrophic areas displayed progressive enlargement over time. Eight of the 10 patients developed bilateral atrophy. The areas of atrophy were noted to be within and outside of the bleb in 10 eyes (55.5 percent), exclusively within the bleb area in seven eyes (39 percent), and exclusively outside of the bleb in one eye (5.5 percent).

While there was no statistically significant change in visual acuity, patients did show consistent improvements in full-field stimulus threshold testing and Goldmann visual fields, with a subset demonstrating paracentral scotomas related to the atrophic changes. Studies are ongoing to identify ocular factors, surgical delivery techniques and vector-related factors that may contribute or predispose to the development of chorioretinal atrophy in patients undergoing treatment with VN.

Studies are ongoing to identify ocular factors, surgical delivery techniques and vector-related factors that may contribute or predispose to the development of chorioretinal atrophy in patients undergoing treatment with VN.

Emerging retinal gene therapies

The early real-world success of subretinal VN delivery is encouraging as a number of other gene therapies for inherited retinal diseases continue to make their way through the pipeline. MeiraGTx/Janssen's ongoing gene therapy trials for RPGR have also shown encouraging data that the therapy is well-tolerated and can lead to significant improvements in vision for those with X-linked retinitis pigmentosa.[4] Similarly, Applied Genetic Technology Corp.'s trials for RPGR are continuing based on promising results from earlier Phase I/II trials.[5]

Active pivotal gene therapy studies for *CNGA3* and *CNGB3*-linked achromatopsia hold promise to improve visual acuity and contrast sensitivity in treated patients.[6,7] Several other subretinal gene therapy trials are under way or being planned, so the next few years will be an exciting time.[8,9]

Gene therapy beyond IRD

The promise of retinal gene therapy extends beyond the realm of treating inherited retinal diseases. RGX-314 (RegenxBio) is being developed as a subretinal gene therapy targeting vascular endothelial growth factor by delivering a gene encoding a therapeutic anti-VEGF Fab protein.

After it's injected into the subretinal space, RGX-314 is designed to produce continuous anti-VEGF therapy. Two pivotal trials are under way comparing outcomes in patients receiving two dosages of RGX-314 with those receiving ranibizumab (ATMOSPHERE, NCT04704921)[9,10] and aflibercept (ASCENT, no NCT number listed) in neovascular age-related macular degeneration.[10,11]

RegenxBio is also testing a similar vector for suprachoroidal delivery in the AAVIATE[11] (NCT04514653) and ALTITUDE (NCT04567550)[12] trials in nAMD and diabetic macular edema, respectively.[11] This suprachoroidal approach has definite advantages for therapeutics, functioning as a "biofactory" by avoiding the need for vitrectomy.

Finally, another gene therapy approach is via direct intravitreal injection. ADVM-022 (Adverum) is an adeno-associated virus (AAV) vector designed to generate aflibercept. It's being tested in the OPTIC (NCT03748784) and INFINITY (NTC04418427) trials for nAMD and DME, respectively.[13] This approach is promising, but questions arose after one subject with DME developed panuveitis, vision loss and hypotony.[14]

If approved at some point in the fu-

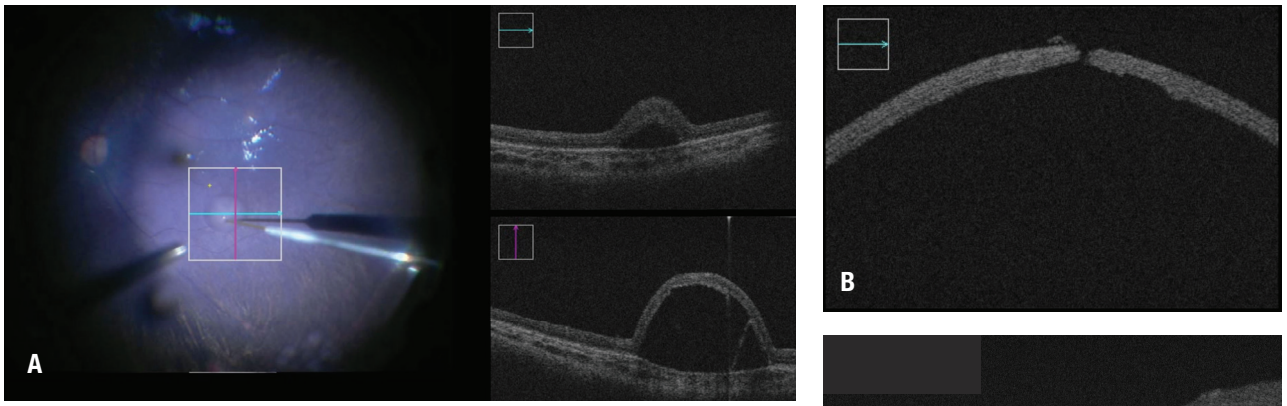

Figure 2. Subretinal delivery of voretigene neparvovec-rzyl into the right eye of a 22-month-old girl. A) Bleb creation using intraoperative optical coherence tomography guidance. B) OCT cross-sectional view of the retinotomy site. C) Intraoperative monitoring of foveal detachment.

ture, these therapies could significantly reduce treatment burden for a variety of VEGF-mediated ischemic retinopathies, including nAMD, retinal vein occlusion and diabetic retinopathy.

Bottom line

Real-world data for VN thus far has been encouraging and has shown a safety profile largely comparable to results found in clinical trials. Most treatment-related adverse events were transient, mild and responsive to treatment. The age of gene therapy for retinal diseases is here, and its promise extends beyond just inherited retinal disease to common eye diseases with significant societal burden.

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Pearls for implanting and refilling PDS

Implanting Susvimo isn't difficult, but it's unique. Tips from patient selection to managing potential complications and refills.


Samir N. Patel, MD


Michael A. Klufas, MD

By Samir N. Patel, MD, and Michael A. Klufas, MD

Take-home points

- Ideal candidates for the port delivery system with ranibizumab include patients with a strong motivation to not have repeated intravitreal injections or those who are being undertreated.
- PDS implantation isn't a difficult procedure, but it has some important nuances and it's distinct from a vitreoretinal surgeon's traditional skill set.
- It's important to establish patient expectations of likely frequent follow-up in the first six months after surgery.
- PDS refill exchanges are different from traditional intravitreal injections and require slight modifications to the typical technique for intravitreal injections.

Last year, the Food and Drug Administration approved the port-delivery system with ranibizumab, now called Susvimo (ranibizumab injection, Genentech/Roche) 100 mg/mL, for intravitreal use via ocular implant for the treatment of neovascular age-related macular degeneration that responded to at least two anti-VEGF injections, regardless of anti-VEGF agent.

PDS is an innovative technology that aims to reduce treatment burden for both the patient and clinician. Direct-to-patient advertising and local news stories on the FDA approval of PDS have increased awareness of it, and more patients are inquiring about it. In this article, we discuss pearls for implementing PDS in your practice.

Who's a good candidate for PDS?

Two populations of patients may be worthwhile for further discussions about PDS:

• ***Patients with a strong motivation to not have frequent injections or those who don't like the injection procedure regardless of interval***. This can be different from the patient's and doctor's perspective. For instance, a patient getting injections every eight weeks may feel like their day is "shot" afterwards and they would be willing to undergo PDS placement to have a procedure only twice a year.

• ***Patients who get injections every four to six weeks but aren't totally compliant.*** Their noncompliance may be due to medical or social factors. From a physician and patient perspective, they may have better control of exudation on optical coherence tomography and better objective (or sub-

Bio

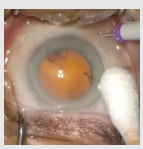
Drs. Patel and **Dr. Klufas** are with Wills Eye Hospital, Mid Atlantic Retina, Philadelphia.

DISCLOSURES:

Dr. Patel has no relevant relationships to disclose.

Dr. Klufas reports relationships with Genentech/Roche, Regeneron Pharmaceuticals, Allergan/AbbVie and RegenexBio.

View the Video



Watch as Carl Regillo, MD, of Wills Eye Hospital, Mid Atlantic Retina, Philadelphia, implants the port delivery system with ranibizumab (Susvimo, Genentech/Roche). Available at: bit.ly/RetSpecMag_202203

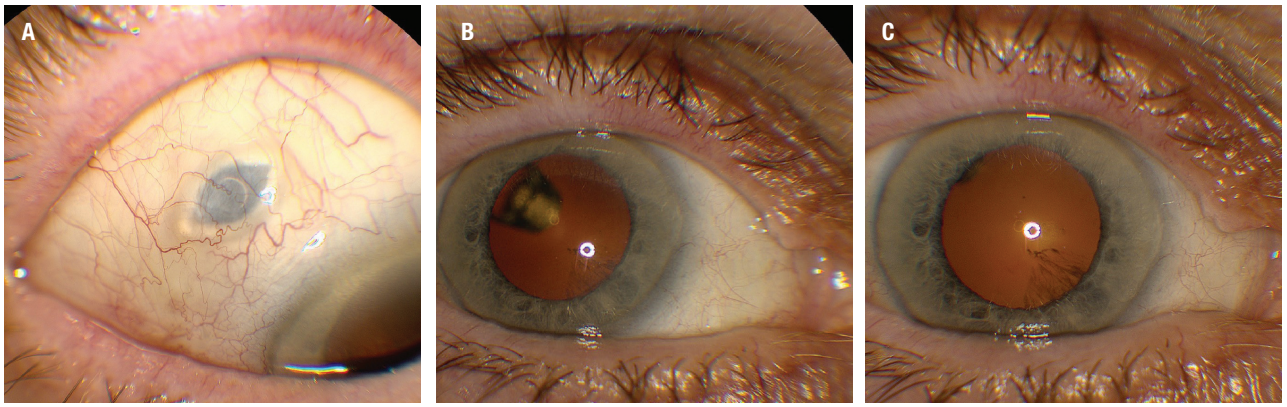


Figure 1. External photographs of the port delivery system with ranibizumab implant (Susvimo) one month after insertion. A) The implant as it appears under the healed sclera. B) A view of the implant through the dilated pupil with the eye fixated temporally. C) A view through the pupil fixated centrally. (*Courtesy Carl D. Regillo, MD*)

jective) vision with more frequent therapy. Essentially, these are patients that we as physicians know do better with monthly therapy but, in reality, only get 10 or fewer injections in a typical 12-month period, as several real-world studies have shown.

Additional clinical characteristics to consider for ideal candidates

What's more, aside from the treatment interval, you should consider additional clinical characteristics to determine if PDS is an acceptable alternative to traditional intravitreal injections. Ideal candidates have a few key characteristics that include:

- an appropriate age; the chance that a single implant will last the patient's remaining lifetime is greater the older a patient is, although we don't have firm data supporting this;
- a mobile conjunctiva that doesn't appear thin in the superotemporal quadrant;
- no history of conjunctival incision; and
- a low chance of requiring an additional conjunctival incisional procedure, such as a glaucoma filtering procedure, in the next five to 10 years.

Informed consent, black-box warning

Additionally, the patient should be able to undergo the informed consent process and understand the need for perioperative visits as well as the risks, benefits and alternatives to the current standard of care—i.e., continued intravitreal injections.

We should describe the black-box warning regarding an increased risk of endophthalmitis vs. monthly intravitreal injections to patients. Indeed, in the Archway trial, the risk of endophthalmitis was 1.6 percent (4/248), and all cases occurred more than one month after the initial surgery (days 57, 59, 161 and 282).[1]

As with any novel surgical device, our understanding of the potential long-term complications of PDS will evolve. We should discuss with patients specific risks such as implant dislocation and conjunctival erosion.

Potential red flags

Potential red flags for PDS implantation may be patients who are constantly switching insurances or thinking about changing their insurance. Nothing sounds like more of a nightmare than implanting a PDS successfully only to have the patient switch insurance and the new payer only allows off-label bevacizumab injections.

Furthermore, a patient may not be an ideal candidate if they've had a history of conjunctival procedures such as pterygium excision or glaucoma filtering procedures, given that the conjunctiva is such an important physiologic barrier to infection.

The patient should be able to undergo the informed consent process and understand the need for perioperative visits as well as the risks, benefits and alternatives to the current standard of care.

Surgical pearls for the PDS implant

For a vitreoretinal surgeon, this isn't a difficult procedure, but it is unique. It requires attention to details to ensure long-term surgical success (*Figure 2*, *Video*). Genentech has several great resources to help ensure success when integrating PDS into your clinical practice, and a surgical device liaison will be in the operating room with you for the first few cases. What's more, there are several enhancements in the implantation procedure that have led to improved outcomes since the Archway[1] and Ladder[2,3] trials.

Careful handling of the conjunctiva with non-toothed forceps and meticulous closure of the conjunctiva and Tenon's capsule after the surgery are paramount to avoid conjunctival erosion of the device. Think like a glaucoma specialist with the conjunctiva and not a retina surgeon!

Think like a glaucoma specialist with the conjunctiva and not a retina surgeon!

A traction suture, which we as retina specialists don't routinely use during our bread-and-butter vitreoretinal procedures, can also be very helpful, even in the setting of a well-trained assistant available to rotate the eye to allow improved exposure of the superotemporal quadrant. If the periocular block isn't complete, the patient can have a tendency to Bell's up, thus making the superotemporal quadrant more difficult to visualize and work in.

Tips for sclerotomy

As with any surgical procedure, each step builds upon the previous one, so it's important to be meticulous with each step to avoid a future problem. For example, when making the sclerotomy, use the fixed metal guide that comes with the implant so that the opening is approximately 3.5 mm.

It's paramount not to make the sclerotomy too large, because in the next step you'll cauterize the choroid with an endolaser probe, which can lead to some retraction of the scleral tissue, thus enlarging the scleral incision slightly.

An incision that's too large isn't optimal for placement, but it's correctable with a suture. We recommend recording your first few clinical cases and reviewing the surgical videos to improve upon any deficiencies in the first couple of cases.

Handling prolapsed vitreous

A vitrectomy isn't part of the standard procedure for PDS. Rarely, upon creation of the 3.5-mm sclerotomy, prolapsed vitreous may emerge along the edges. Given that a vitrectomy pack is opened as part of this procedure to allow placement of an infusion line in the event of hypotony, the cutter can be used prior to inserting the device to remove any residual vitreous from the sclerotomy. Upon insertion of PDS, the vitreous typically retracts into the eye. It's important to avoid a Wek-Cel vitrectomy.

Emphasize the need for post-op visits

As with any vitreoretinal procedure, standard postoperative visits should be planned at one day, one week and one month. It's important to set patient expectations before implantation that there will be at least three postoperative visits, assuming no complications.

Additionally, I would counsel the patient who's had a long history of intravitreal injections to expect there will be a slight decrease in vision for the first two to four weeks after the procedure while the eye heals.

Initially, the standard plan is to monitor patients at the same interval at which they were receiving injections previously. For example, if a patient was receiving injections every six weeks, I would plan to monitor every six weeks postimplantation until the planned refill at six months. After the initial refill, I would try to extend the monitoring interval to 12 weeks.

Under ideal circumstances, a PDS patient would be seen four times a year, with two of those visits for refill/exchange. Monitoring might be more frequent if the other eye has high-risk nonexudative AMD or if the patient is functionally monocular with the PDS implanted eye.

Rescue intravitreal injections can be given with the PDS implanted in the inferotemporal quadrant if exudation persists. Indeed, in Archway, 1.6 percent of patients (4/248) received supplemental ranibizumab before the first refill-exchange procedure.[1]

Potential post-op complications

Educate the patient about potential warning symptoms, including red eyes, ocular discomfort or foreign-body sensations, which may be precursors to complications such as conjunctival erosion or retraction. It may also be helpful to educate other eye-care providers who may be caring for the patient to evaluate the superotemporal conjunctiva for potential signs of erosion if these symptoms arise.

Given the risk of endophthalmitis, increasing floaters, eye pain and/or increasing redness should also be reported at any time after the implant. I often have patients ask me about the outcomes of endophthalmitis with PDS, and from the Archway trial the cases treated with vitreous tap and intravitreal antibiotics, with or without irrigation of the PDS with antibiotic, generally did well and didn't require device removal. However, outcomes after infectious endophthalmitis in PDS, as with postinjection endophthalmitis, may be variable and are driven by the causative infectious agent.

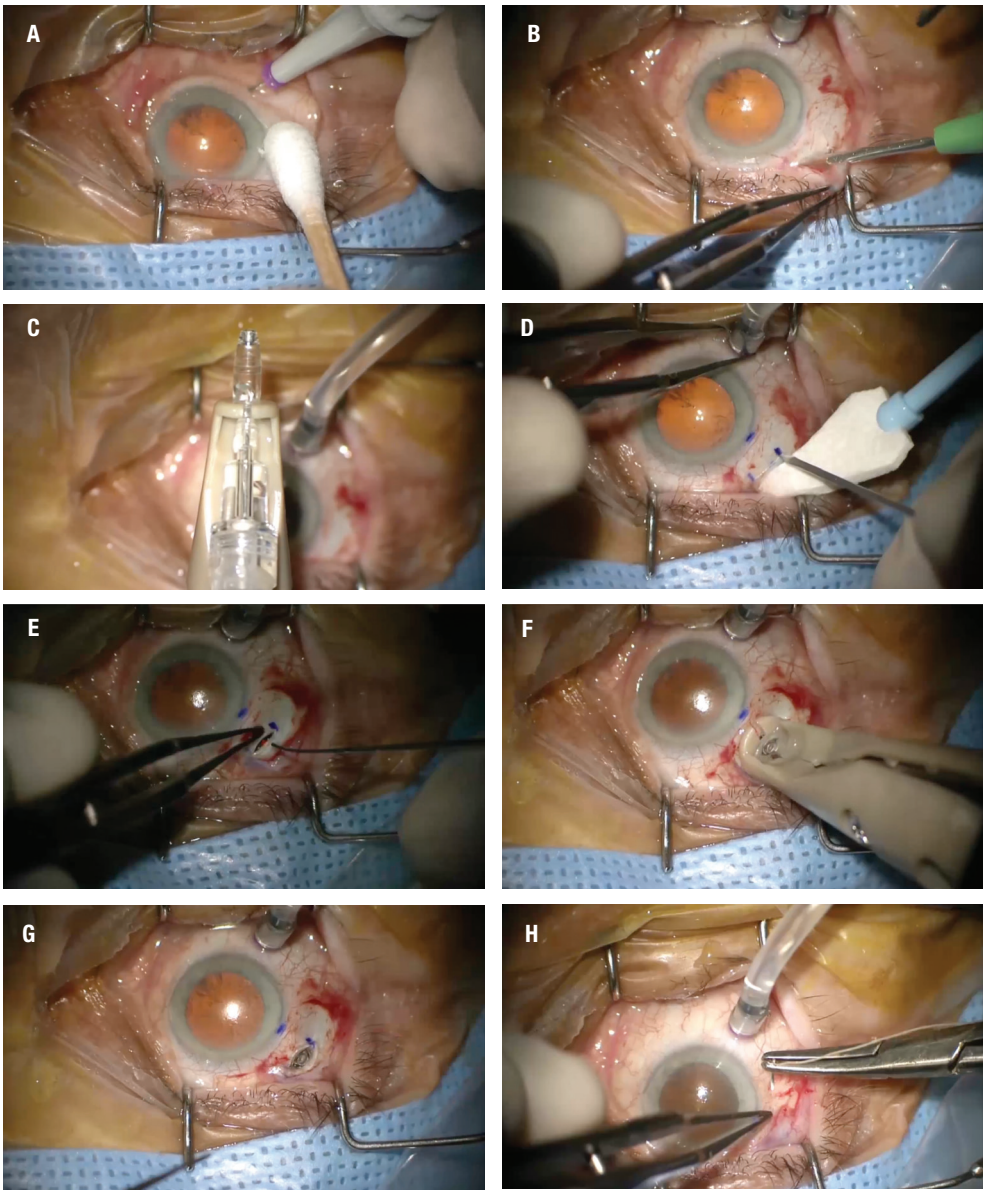


Figure 2. Key steps in the placement of the port delivery system implant, as demonstrated in the video at bit.ly/RetSpecMag_2022_03: A) Placement of the infusion cannula inferotemporally. B) Creation of a 6-x-6-mm Tenon's peritomy. C) Filling of the implant before insertion. D) Creation of the scleral dissection. E) Use of endolaser probe to photocoagulate the uvea. F) Insertion of device into the sclera. G) The device seated in the sclera. H) Closure of the conjunctiva. (*Courtesy Carl D. Regillo, MD*)

The refill procedure is probably the most foreign and most challenging part of the

(Continued on page 38)

Managing uveitis secondary to cancer immunotherapy

A range of factors to consider when patients on cancer treatment present with noninfectious uveitis.

Peter Y. Chang, MD

By Peter Y. Chang, MD

Take-home points

- Noninfectious uveitis secondary to cancer immunotherapy may occur in some patients with metastatic melanoma.
- Common complaints from patients with NIU secondary to immunotherapy include photophobia, blurred vision and floaters.
- Local steroid therapy with a steroid-eluting implant, such as the fluocinolone acetonide implant 0.18 mg, may be a good option for patients with this condition.
- The author shares a real-world case of a patient whose NIU secondary to immunotherapy was effectively managed with long-term, localized steroid therapy.

Adoption of immunotherapy to treat metastatic melanoma, non-small cell lung cancer and several other malignancies has contributed to the increased incidence of immunotherapy-driven noninfectious uveitis (NIU). By understanding the biological mechanisms underpinning this phenomenon and reviewing treatment options, retina specialists can be better prepared to manage these cases upon referral from an oncologist.

After exploring these topics, I'll present a case that illustrates the value of localized corticosteroid therapy—in this instance, use of the fluocinolone acetonide implant 0.18 mg (Yutiq, EyePoint Pharmaceuticals)—to treat NIU secondary to systemic immunotherapy for cancer.

Immunotherapy: Side effects and ocular manifestations

Immunotherapy is an effective means of assisting the immune system's ability to detect and destroy cancer cells, and it has been used in combination with other therapies to treat metastatic melanoma.[1,2] The underlying biologic mechanisms that boost immune response result in T-cell activation, increased production of cytokines, and enhanced T-cell-mediated immune responses.[3,4]

In Taiwan, Chia-Jui Chang, MD, and colleagues have recorded several dermatological, gastrointestinal, nephrological, neurological, pancreatic, endocrine, hepatic and ocular adverse events that were reported following immunotherapy administration, including dry eyes and NIU.[5] The root cause for uveitic manifestations may be the melanocytes present in the uveal tract.

In my experience, patients present with uveitic symptoms after two to three rounds of immunotherapy. Patients with NIU secondary to immunotherapy are

Bio

Dr. Chang is co-president and partner at the Massachusetts Eye Research and Surgery Institution, Waltham.

DISCLOSURE: Dr. Chang is a paid consultant and speaker for EyePoint Pharmaceuticals.

Case report: NIU in a woman with metastatic cutaneous melanoma

A 46-year-old woman with metastatic cutaneous melanoma presented with floaters and blurry vision six weeks after starting intravenous ipilimumab and nivolumab (the combination therapy was administered every three weeks).

On exam, visual acuity was 20/40 OU, and intraocular pressure was within normal limits. There were trace anterior chamber cells and no lenticular changes. Fundoscopic exam revealed 1+ vitreous cells and blurry optic disc margin OU with subtle chorioretinal folds in the peripapillary region that also involved the nasal macula.

Optical coherence tomography showed trace subretinal fluid in the peripapillary region OU (*Figure 1*), and fluorescein angiography imaging revealed optic nerve leakage with punctate hyperfluorescence consistent with leakage around the nerve and the macula (*Figure 2*).

The patient denied headaches, tinnitus, or other signs that would suggest Vogt-Koyanagi-Harada disease. Given that her symptoms presented close to the initiation of ipilimumab therapy, a diagnosis of immunotherapy-associated posterior uveitis was made. The patient initially received bilateral intravitreal dexamethasone implant 0.7 mg (Ozurdex, Allergan/AbbVie) injections, but her uveitis relapsed after three months as she continued to receive nivolumab.

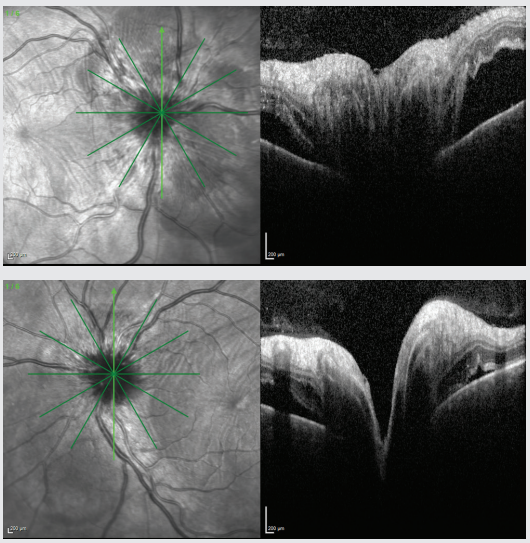


Figure 1. Optical coherence tomography of a 46-year-old woman who presented with floaters and blurry vision after undergoing immunotherapy for metastatic melanoma. Chorioretinal folds with underlying subretinal fluid involving the peripapillary region and nasal macula were observed.

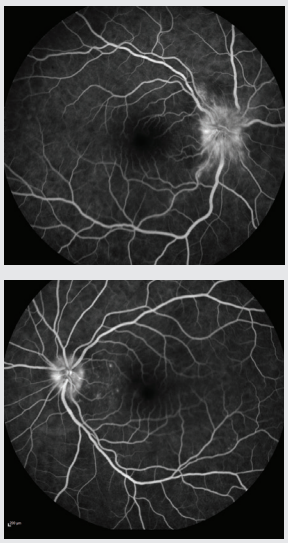


Figure 2. Fluorescein angiography revealed optic nerve leakage and multiple spots of punctate hyperfluorescence.

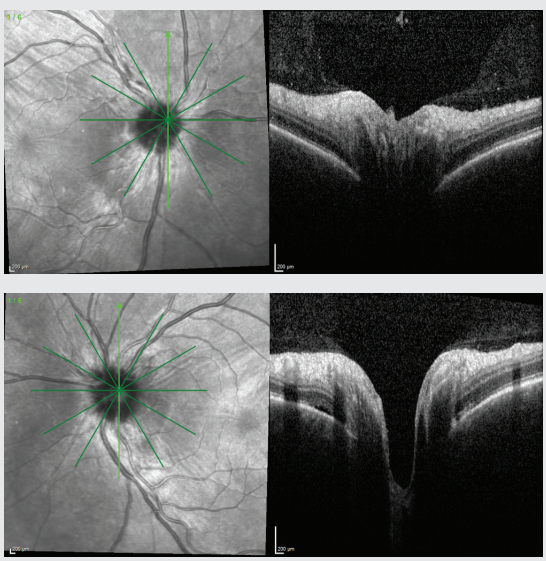


Figure 3. At two-month follow-up after receiving the fluocinolone acetonide implant 0.18 mg, optical coherence tomography depicted resolution of the peripapillary subretinal fluid observed at baseline. The resolution of fluid was consistent with the patient's improved visual function.

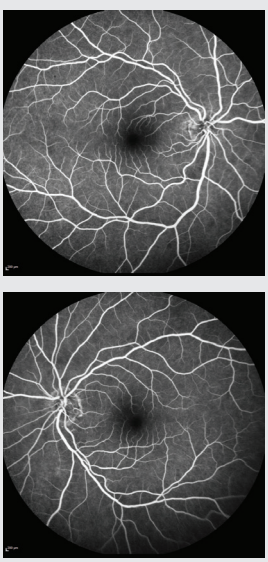


Figure 4. Resolution of angiographic leakage as seen on fluorescein angiography occurred two months after receiving the implant.

Because the immunotherapy was effective in halting her metastatic disease, a decision was made to proceed with fluocinolone acetonide implant 0.18 mg (Yutiq, EyePoint Pharmaceuticals) therapy in both eyes for long-term control of her uveitis. Two months after the initiation of the implant, OCT imaging showed resolution of the peripapillary subretinal fluid (*Figure 3*), and FA imaging showed that the angiographic leakages had resolved completely (*Figure 4*). Visual acuity returned to 20/20 OU.

One year after treatment, the patient hasn't developed IOP elevation, although a small posterior subcapsular cataract has formed, minimally affecting her vision. Her metastatic melanoma remains stable with nivolumab.

typically referred to me for examination by an oncologist.

Patients with anterior NIU typically report photophobia, redness and blurry vision. Those with posterior NIU typically have blurry vision, floaters and sometimes scotomas. Patients with panuveitis can have any or all of these signs and symptoms.

Therapeutic options

Several treatment options exist for patients with NIU who are otherwise healthy, including local and systemic corticosteroid therapy, as well as systemic immunosuppression. Each of these approaches has advantages and disadvantages.

Local steroid therapy in the form of drops, periocular and intravitreal injections may be appropriate for some patients with acute flare. In patients with chronic NIU, steroid-eluting implants that release fluocinolone acetonide or dexamethasone may be more appropriate. Still, long-term ocular exposure to steroids may be undesirable because of the increased risk of intraocular pressure elevation or, in phakic patients, cataract progression.

Long-term systemic steroid therapy may lead to any number of complications. These can include weight gain and decreased bone density, although long-term systemic steroids may mitigate the risk of cataract or glaucoma that can come with localized therapy. Systemic immunosuppression may be an effective approach in otherwise healthy patients. However, immunosuppression among patients who are undergoing cancer immunotherapy is counterproductive, so it's not advisable.

Localized steroid therapy

Clinicians encountering patients with NIU secondary to immunotherapy must determine how to treat a patient's ocular condition without significantly affecting their cancer treatments. Typically, when a patient fitting this profile presents to the clinic, I find that localized steroid therapy is a good fit because it keeps any treatment localized to the eye and, therefore, unlikely to interact with their cancer treatment. It also requires fewer office visits—an advantage for patients who are already preoccupied with appointments for cancer therapy.

I begin treatment with a course of steroid drops. This is often adequate, particularly in cases of anterior NIU. But in cases of posterior NIU or panuveitis, drops may not have enough ocular penetration. For these patients, intravitreal injections, periocular injections or sustained-release steroid implants may be effective.

In my practice, use of the sustained-release steroid fluocinolone acetonide implant 0.18 mg, which is indicated for chronic NIU affecting the posterior segment,[6] has been effective at treating patients undergoing immunotherapy who present with NIU in the posterior segment. The array of treatment options for elevated IOP alleviates concerns about the increased risk of glaucoma. I'm less concerned about premature cataract development in patients with NIU secondary to immunotherapy, because they're typically old enough that they're nearing the age for cataract surgery. The fluocinolone acetonide implant 0.18 mg is injected in an office setting and is designed to elute the active agent for 36 months.

Two other sustained-release steroid options exist for these patients: intravitreal dexamethasone implant 0.7 mg (Ozurdex, Allergan/AbbVie); and fluocinolone acetonide intravitreal implant 0.59 mg (Retisert, Bausch + Lomb).

I'm reluctant to use the intravitreal dexamethasone implant 0.7 mg in these patients because it has a shorter

(Continued on page 37)

Localized steroid therapy is a good fit because it's unlikely to interact with cancer treatments and it requires fewer office visits—an advantage for patients already preoccupied with appointments for their cancer threapy.

TKI vorolanib implant shows early signal

DAVIO Phase I results of EYP-1901 show reduced treatment burden in age-related macular degeneration.

By Richard Mark Kirkner, Editor

Vorolanib is a small-molecule, tyrosine kinase inhibitor that's been investigated as an oral treatment in patients with advanced solid tumors. It blocks downstream signaling of receptor tyrosine kinase activity, most notably, in both oncology and exudative retinal disease, vascular endothelial growth factor and platelet-derived growth factor receptors.[1]

And like the family of retinal anti-VEGF therapies, vorolanib has attracted interest as a potential treatment for neovascular age-related macular degeneration. EyePoint Pharmaceutical has been pursuing a program to develop EYP-1901, a bioerodible vorolanib-eluting implant using the Durasert platform, as a potential treatment for nAMD.

Recently reported interim eight-month results from the Phase I DAVIO trial have shown that 76 percent of eyes receiving the implant didn't need rescue with anti-VEGF injections for up to four months; 53 percent went up to six months without rescue; and 41 percent went as long as nine months.[2] The results showed a 79-percent reduction in treatment burden at six months and a 75-percent reduction at eight months, both of which were considered clinically significant.

With data from the DAVIO trial, EyePoint says it plans to initiate a Phase II trial later in the year. Here, David R. Lally, MD, of New England Retina Consultants in Springfield, Massachusetts, answers questions about EYP-1901 and the DAVIO trial. Dr. Lally is a primary investigator for the trial, and is a consultant to and speaker for EyePoint.

Q Can you describe the idea behind EYP-1901?

A The largest unmet need in wet AMD therapy is longevity of action of anti-VEGF therapies. The idea behind EYP-1901 is to give wet AMD patients and practitioners the flexibility to safely reduce the number of visits to the clinic through controlled and sustained—longer-lasting—intravitreal delivery of an anti-VEGF drug.

Q What's the mechanism of action of vorolanib, and how is the tyrosine kinase inhibitor (TKI) unique as a treatment for nAMD?

A Vorolanib is a validated TKI that blocks all VEGF receptors and the PDGF receptor with high affinity. In this fashion, all isoforms of VEGF, the main driver of the proliferation of blood vessels that are the hallmark of wet AMD, should be inactivated by vorolanib.

Q Can you describe the bioerodible properties of the insert?

A The previous iterations of Durasert (e.g., Yutiq, Iluvien, Retisert) were not bioerodible because they contained a polyimide covering that allowed for long-term sustained drug release. The polyimide is completely inert but doesn't degrade. For a wet AMD sustained-release medication, we preferred to develop a bioerodible insert with a six-month-to-one-year release profile. Therefore, the polyimide cover was removed for EYP-1901. So, the EYP-1901 implant consists of a core matrix of drug that should bioerode completely.

Q How would this potentially fit into the retina specialist's toolbox?

A If EYP-1901 proves safe, effective, and well tolerated, it will likely be used as a maintenance treatment for appropriate wet AMD patients who have received prior treatment with currently available, standard-of-care anti-VEGFs. With EYP-1901, we hope that some or even a majority of wet AMD patients will be able to go many months between visits and

(Continued on page 37)

Vorolanib is a validated tyrosine kinase inhibitor that blocks all VEGF receptors and the PDGF receptor with high affinity.

Using data for E/M coding

Checking in on where things stand with the updated evaluation and management guidelines a year after they went into effect.

By Ellen R. Adams, MBA

Bio
Ms. Adams is a consultant with Corcoran Consulting Group. She can be reached at 1-800-399-6565 or at www.corcoranccg.com.

It's been just over a year since the American Medical Association released significant changes to evaluation and management (E/M) coding.[1] In many ways, the documentation requirements under E/M 2021 are less onerous than the previous versions: Element counting, box checking and few relevant case examples made using E/M difficult.

The 2021 revisions don't require any specific history, review of systems or exam element documentation. The encounter is coded based on medical decision making (MDM). Though you continue to document the patient's relevant history and exam, under E/M the purpose of your exam documentation is for supporting your care and mitigating risk, not for selecting an exam code.

Straightforward approach to coding

Coding based on MDM is relatively straightforward. As with the previous versions of E/M and its more obscure grid, you must meet or exceed two of the three boxes in a code level to score an exam. For example, a patient with acute retinal detachment with a high chance of vision loss who requires urgent surgery slots nicely into the E/M rules as an E/M Level 5 (992x5), as you can see in Table 1.

For most of your exams, you'll rely on the third column, "Number and complexity of problems addressed," and the fifth column, "Risk of complications and/or morbidity or mortality of patient management."

However, at this point, you're no doubt wondering what that big, text-heavy fourth column is all about. What is "Amount and/or complexity of data to be reviewed and analyzed"? Can that column help code a complex exam? Ophthalmologists often dismiss the column, colloquially referred to as "Data," as irrelevant. In truth, it's of little use on a daily basis. But with a year's experience, we've learned this column has some usefulness. Let's explore this further so you have another coding tool in your toolbox.

Understanding the 'Data' column

The data column is easiest to explain by starting with E/M Level 3, 992x3 (*Table* 2). First, keep in mind that a Level 3 exam is for a stable, low-risk condition with a low risk from treatment. Setting aside the Eye Codes for this discussion (920x4 and 920x2), a Level 3 exam might be a three-month, background diabetic retinopathy patient with relatively stable disease, requiring continuation of intravitreal injection in one eye. But if your patient doesn't require any treatment at all, could you still code a Level 3 exam? In Table 2 note that, if you meet the requirements of only one of two categories of data, you might be able to code the exam as a Level 3 even absent of any treatment on the date of service.

For example, in Table 2 , Category 1, reviews of a referring physician's clinic note and of a fluorescein angiography done outside your practice would constitute two tests or documents to meet the data requirement.

Alternatively, if your patient is unable to communicate their history because of cognitive issues and a health-care proxy is available to provide that information, you meet the Category 2 requirement of "Assessment requiring an independent historian."

Some important points to remember at this stage of your data education:

- A review of external note(s) from each unique source means all of the exam notes from one outside provider. Four exams from Dr. Icee is considered one review point.
- Although the AMA doesn't clarify it, the review of each unique test doesn't specify who provided the test to you. A fluorescein angiogram and an optical coherence tomography from Dr. Icee

Table 1. American Medical Association evaluation and management office revisions

Codes	Elements of medical decision making (MDM)			
	Level of MDM (based on 2 out of 3 elements of MDM	**Number and complexity of problems addressed**	**Amount and/or complexity of data to be reviewed and analyzed***	**Risk of complications and/or morbidity or mortality of patient management**
99205 **99215**	**High**	**High** • One or more chronic illnesses with severe exacerbation, progression, or side effects of treatment. *or* • One acute or chronic illness or injury that poses a threat to life or bodily function.	**Extensive** (Must meet requirements of at least two out of three categories) **Category 1:** Tests, documents, or independent historian(s) *Any combination of three from the following:* • Review of prior external note(s) from each unique source.* • Review of the result(s) of each unique test.* • Ordering of each unique test.* • Assessment requiring an independent historian(s). *or* **Category 2:** Independent interpretation of tests • Independent interpretation of a test performed by another physician/other qualified health-care professional (not separately reported). *or* **Category 3:** Discussion of management or test interpretation • Discussion of management or test interpretation with external physician/other qualified health-care professional/appropriate source (not separately reported).	**High risk of morbidity from additional diagnostic testing or treatment** Examples only: • Drug therapy requiring intensive monitoring for toxicity. • Decision regarding elective major surgery with identified patient or procedure risk factors. • Decision regarding emergency major surgery. • Decision regarding hospitalization. • Decision not to resuscitate or to de-escalate care because of poor prognosis.

*Each unique test, order or document contributes to the combination of two or combination of three in Category 1 on subsequent tables.
Source: American Medical Association. Available at www.ama-assn.org/system/files/2019-06/cpt-revised-mdm-grid.pdf

are considered two tests.

- Ordering a unique test doesn't include tests for which you receive reimbursement, such as an OCT that you order, interpret and bill to insurance. No double-dipping by getting data credit and test reimbursement.
- An independent historian doesn't include American Sign Language or English translators.

More complex Level 4 data

With an understanding of Level 3 data, let's move to the more complex Level 4 (*Table 3, page 36*).

The first important point is that you must meet one of three categories. Note that the independent historian is in Category 1 in this table. The other Category 1 requirements are the same as the previous table. Also note you need three of the Category 1 tests, documents, or independent historian items, whereas in the Level 3 table you only need two.

Points to remember:

- Category 2, "Independent interpretation of tests." As with the "ordering of each unique test" in Category 1, the Category 2 tests can't be those for which you receive reimbursement. Thus interpreting an OCT done elsewhere would quali-

Table 2. E/M Level 3: Limited amount and/or complexity of data to be reviewed and analyzed

(Must meet the requirements of at least one of the two categories)

Category 1: Tests and documents

Any combination of two from the following:

- Review of prior external note(s) from each unique source.
- Review of the result(s) of each unique test.
- Ordering of each unique test.

or

Category 2: Assessment requiring an independent historian(s)

(For the categories of independent interpretation of tests and discussion of management or test interpretation, see moderate or high)

fy, but your documentation must be meticulous if you plan to use Category 2 test interpretation. Your chart note must include the name of the test, the date, reliability, and your independently drawn conclusion.

- Category 3, "Discussion of management or test interpretation," is just as it sounds. You must have a conversation with a provider outside your organization; text messages or emails don't count as a discussion. As with Category 2, you need to carefully document who you spoke with as well as the issues discussed and the outcome of the discussion.

Level 5: A higher bar

Let's move to Level 5 data. In Table 4, you'll notice the bar has gotten quite a bit higher. You must meet or exceed the requirement, so you must fulfill two of the three Categories. The Categories are the same as in Level 4 data; you just need to do more work. Careful documentation is a must if you plan to apply data to a Level 5 encounter.

Now that you have an understanding of what "data" means, you may think you'll never use this option, but consider this: You'll occasionally see patients who take time to determine appropriate treatment, but not enough to bill based on time; or who are complex or have potentially vision-threatening disease, but whom you won't be treating, perhaps because the patient has non-retinal pathology and you refer them elsewhere for treatment.

"Data" is the category that can allow you to be reimbursed appropriately for these cases. For example, you may have a young patient with optic neuropathy. Your suspicion is previously undiagnosed multiple sclerosis; you order an MRI (one Category 1 test, inadequate to qualify for Category 1) and call a neurologist to assure a consultation is arranged; the neurologist is aware of the MRI and will interpret it (Category 3 fulfilled). In this case, you would meet the billing requirements for E/M Level 4 for this unfortunate situation.

Admittedly, using "data" to code your exams will be an unusual event. When you have a difficult case but you won't ultimately be the treating physician, consider documenting data to be paid appropriately for the expertise you applied to triage the patient. As with any coding challenge, having additional tools at hand will help you do it correctly.

Table 3. E/M Level 4: Moderate amount and/or complexity of data to be reviewed and analyzed

(Must meet the requirements of at least one out of three categories)

Category 1: Tests, documents or independent historian(s)

Any combination of three from the following:

- Review of prior external note(s) from each unique source.
- Review of the result(s) of each unique test.
- Ordering of each unique test.
- Assessment requiring independent historian(s).

or

Category 2: Independent interpretation of tests

- Independent interpretation of a test performed by another physician/other qualified health care professional (not separately reported).

or

Category 3: Discussion of management or test interpretation

- Discussion of management or test interpretation with an external physician/other qualified health care professional/appropriate source (not separately reported).

Table 4. E/M Level 5: Extensive amount and/or complexity of data to be reviewed and analyzed

(Must meet requirements of at least two out of three categories)

Category 1: Tests, documents or independent historian(s)

Any combination of three from the following:

- Review of prior external note(s) from each unique source.
- Review of result(s) of each unique test.
- Ordering of each unique test.
- Assessment requiring independent historian(s).

or

Category 2: Independent interpretation of tests

- Independent interpretation of a test performed by another physician/other qualified health-care professional (not separately reported).

or

Category 3: Discussion of management or test interpretation

- Discussion of management or test interpretation with external physician/other qualified health-care professional/appropriate source (not separately reported).

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TKI vorolanib implant

(Continued from page 33)

injections while maintaining stable visual acuity and macular anatomy. There's also a potential for achieving stability in other VEGF-dependent retina conditions, such as diabetic retinopathy and retinal vein obstruction.

Q What's the most compelling finding of the interim Phase I DAVIO results?

A The eight-month data revealed that the reduction in treatment burden across all doses of EYP-1901 was substantial—approximately 80 percent—and no significant safety issues were observed.

Q Can you talk a little about the trial design?

A DAVIO is a Phase I multicenter, open-label, dose-escalation clinical trial that enrolled 17 patients, all of whom were diagnosed with wet AMD at least four months prior and received previous treatment for it. There were no exclusions for the presence of macular fluid at the time of enrollment, and the trial didn't include a control arm.

For eligibility, patients must have received at least three prior injections with an anti-VEGF product (bevacizumab, ranibizumab or aflibercept) in the six months prior to the screening visit, in the study eye.

The trial was designed as a 12-month study with an interim analysis planned at six months, and patients were observed monthly at a minimum. The primary endpoint was safety, and key secondary endpoints included best-corrected visual acuity and central subfield thickness as measured by optical coherence tomography.

One injection of EYP-1901 was given at day zero of the study. No retreatments (reinjections) with EYP-1901 occurred in this trial.

Criteria for rescue with standard-of-care anti-VEGF therapy included new fluid >75 µm from day zero, the loss of two or more lines in VA due to wet AMD, and/or new macular hemorrhage due to wet AMD.

Q How will this help inform the Phase II trial?

A Because of the safety and apparent efficacy seen in the Phase I trial, the Phase II wet AMD trial will commence later in the year. As with most early trials, Phase I will help to inform the dosing and inclusion/exclusion criteria of Phase II, while the excellent safety profile will give assurance to participating patients and investigators.

Q Anything else to add?

A With a minimum of eight months follow-up, seven of the 17 (41 percent) patients from the DAVIO Phase I trial remain rescue-free.

The company plans on starting a Phase II diabetic retinopathy study in 2022 and a third Phase II study, most likely in retinal vein occlusion, in 2023.

Further, with the success of the DAVIO Phase I trial, the bioerodible form of Durasert will likely be tested with other small molecules and other mechanisms of action. RS

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Managing uveitis in cancer

(Continued from page 32)

duration of action (i.e., rarely more than three to four months in NIU). The fluocinolone acetonide intravitreal implant 0.59 mg is more invasive and costly, and it has been associated with faster cataract progression and higher incidence of steroid-induced glaucoma. I use it only in the most refractory cases.

My experience with the fluocinolone acetonide implant 0.18 mg in patients who have NIU as a consequence of cancer immunotherapy has been positive, as the case on page 31 illustrates.

Bottom line

Patients with metastatic melanoma or other advanced malignancies who are undergoing immunotherapy may be referred to your clinic if they report ocular side effects to their oncologist. In cases of NIU affecting the posterior segment, I advise considering localized steroid therapy because it will stay contained to the eye and won't interfere with the patient's systemic cancer treatment. RS

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Pearls for the PDS

(Continued from page 29)

PDS therapy. It's a bit more precise than typical intravitreal injection and requires the refill exchange needle to be properly oriented to enter the PDS to allow refill-exchange.

It's important that no trapped air is in the refill exchange needle; an excess amount of drug is provided to account for this. A pair of low-magnification lighted loupes can help improve visualization of the device's silicone septum to allow proper placement of the refill needle and also proper alignment. Without proper alignment, excessive force may be applied to the device and increase the risk of possible device dislocation. Twisting motions of the needle or other maneuvers aren't necessary and can even bend the small 34-gauge needle. With magnification, proper placement and alignment, needle entry shouldn't encounter significant resistance.

The tactile response of piercing the device's fibrous capsule is also novel compared to the standard intravitreal injection. Don't be surprised if it feels a bit different than piercing the sclera. It's sometimes helpful to have a cotton-tip applicator in the other hand to stabilize the globe during the docking. Once the refill needle is docked, the most difficult part of the procedure is over, and depressing the plunger to allow new drug in and exchange the old drug out is very similar to any other intravitreal procedure.

Bottom line

With a number of more durable neovascular AMD treatments on the horizon, along with the relatively recent approval of the PDS itself, patients will show greater interest to learn if they're ideal candidates for PDS. Consider multiple factors to determine if a patient is a good candidate. That should include having a robust discussion of the risks and benefits of the operation. In patients who are ideal candidates, surgical preparation and collaboration with your local device liaison will be important to ensure success with the initial surgery and future refills. RS

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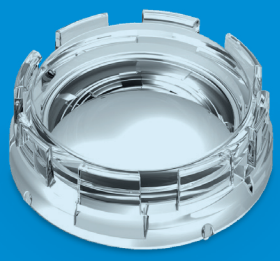

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