A PUBLICATION BY REVIEW of OPHTHALMOLOGY

RETINA SPECIALIST

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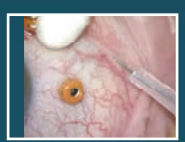
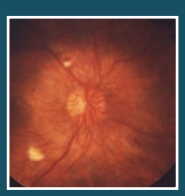
THE ROBOTS ARE COMING TO RETINA

The evidence and potential for robotic-assisted vitreoretinal surgery.
Page 24



Online Video



Also Inside

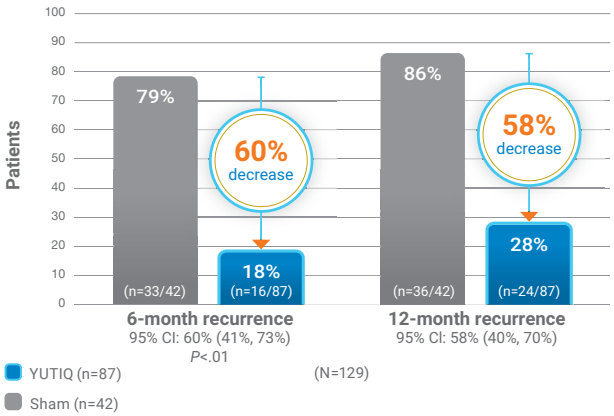
0.18 mg
YUTIQ®
(fluocinolone acetonide intravitreal implant) 0.18 mg

Discover continuous calm in uveitis[1]

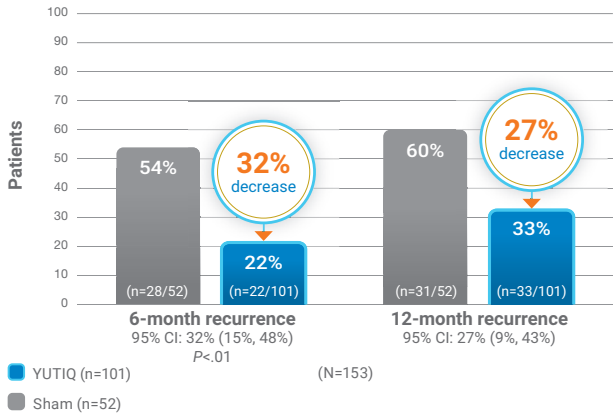
The durability of YUTIQ reduced the recurrence of posterior segment uveitis[1]

For patients with chronic non-infectious uveitis affecting the posterior segment of the eye, YUTIQ® (fluocinolone acetonide intravitreal implant) 0.18 mg is designed to deliver a sustained release of fluocinolone for up to 36 months.[1]

Study 1: Patients with uveitis recurrence at 6 and 12 months[1]



Study 2: Patients with uveitis recurrence at 6 and 12 months[1]



CI=confidence interval.

Analyses of the rate of uveitis reduction at 36 months are ongoing

Study overview: 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 use of confounding medications.[1,2]

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

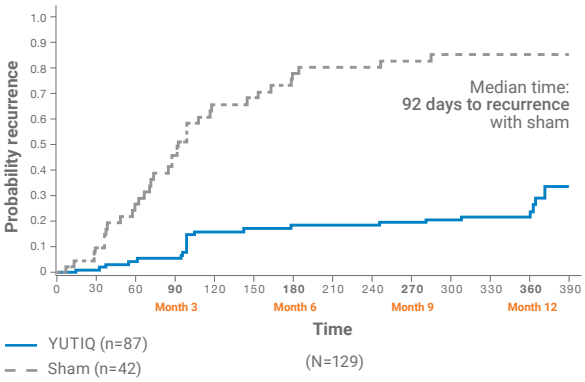
CONTRAINDICATIONS

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.

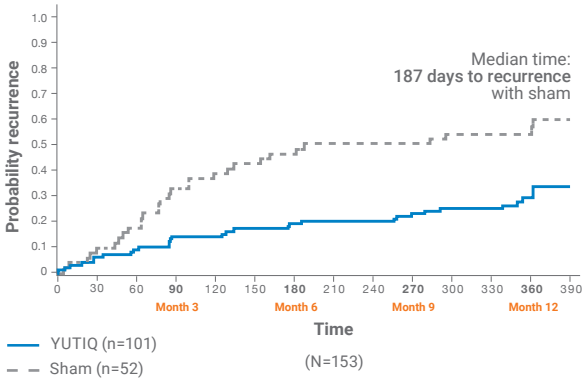
YUTIQ increased the time to next recurrence of posterior uveitis[1]

Study 1: Time to first recurrence of uveitis in the study eye within 12 months[1,2]



(N=129)

Study 2: Time to first recurrence of uveitis in the study within 12 months[1,2]



(N=153)

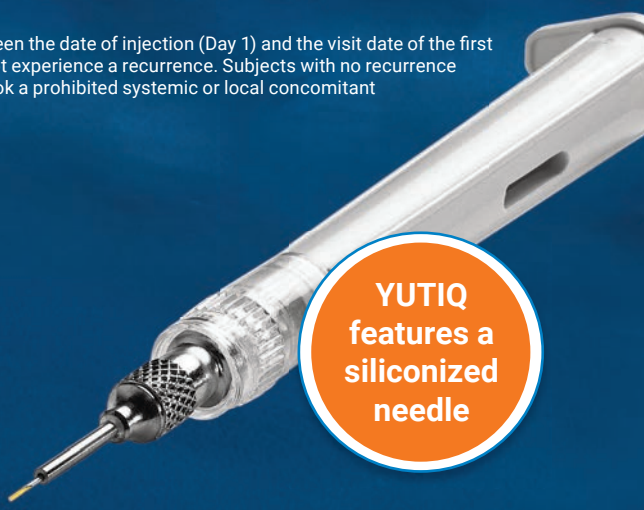
Median time to recurrence with YUTIQ was too low to evaluate.[2]

Analysis of median time to first recurrence[2]

Time to first recurrence of uveitis within 12 months was calculated as the number of days between the date of injection (Day 1) and the visit date of the first reported recurrence of uveitis in the study eye or the Month 12 visit date for subjects who did not experience a recurrence. Subjects with no recurrence prior to Month 12 who did not have recurrence assessed at Month 12 (for any reason) or who took a prohibited systemic or local concomitant medication prior to Month 12 were counted as having a recurrence of uveitis.

Offer your patients the calm they need

YUTIQ.com



IMPORTANT SAFETY INFORMATION *(cont'd)*

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 next page for Brief Summary of full Prescribing Information.

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

EyePoint PHARMACEUTICALS

480 Pleasant Street, Suite B300, Watertown, MA 02472

05/2021
US-YUT-2100082

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

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

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

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

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

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

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

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

(continued)

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

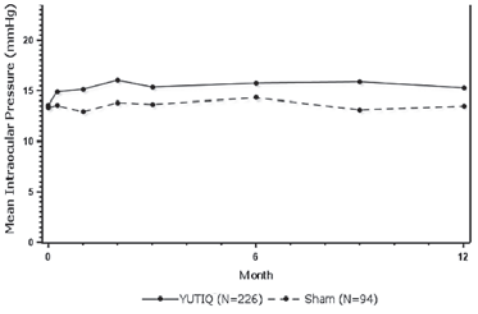
Ocular		
ADVERSE REACTIONS	**YUTIQ (N=226 Eyes) n (%)**	**Sham Injection (N=94 Eyes) n (%)**
Vitreous Hemorrhage	4 (2%)	0
Iridocyclitis	3 (1%)	7 (7%)
Eye Inflammation	3 (1%)	2 (2%)
Choroiditis	3 (1%)	1 (1%)
Eye Irritation	3 (1%)	1 (1%)
Visual Field Defect	3 (1%)	0
Lacrimation Increased	3 (1%)	0
Non-ocular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

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

Table 2: Summary of Elevated IOP Related Adverse Reactions

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

Figure 1: Mean IOP During the Studies



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

Manufactured by:
EyePoint Pharmaceuticals US, Inc., 480 Pleasant Street, Watertown, MA 02472 USA
Patented.

RETINA
SPECIALIST

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Jobson Medical Information

EDITORIAL

By Charles C. Wykoff, MD, PhD

Six and counting

Last month the Food and Drug Administration approved our sixth treatment for neovascular age-related macular degeneration, expanding our management toolbox with a truly differentiated option.

There is no question that more durable treatment options are needed. Repeatedly, data from patients with neovascular AMD managed with anti-VEGF therapy in routine clinical practice around the world have indicated that real-world outcomes fall far short of those achieved in prospective clinical trials with consistent monitoring and dosing.

Susvimo (Genentech/Roche), originally known as the Port Delivery System (PDS), filled with a 100-mg/mL solution of ranibizumab, is an attractive solution to our durability challenge. In particular, while the Phase III trial employed a refill interval of every six months, the median time to first refill was 15 months in the Phase II LADDER trial, suggesting that most patients may be able to be extended substantially longer.

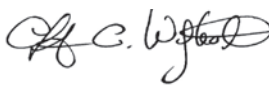
PDS development is a phenomenal case study of the challenges and opportunities of innovation. Originally conceived by the intriguing Eugene de Juan, MD, the concept was eventually acquired by Genentech. The program was nearly halted in early phase trials because of a high incidence of vitreous hemorrhage. Following modifications to the surgical technique, this adverse event was effectively abolished.

The surgical technique has continued to evolve during the ongoing Phase III trials. In particular, a tremendous amount of attention is now given to proper conjunctival and Tenon's capsule manipulation.

But, everything carries a risk/benefit ratio. Repeated intravitreal injections have proven remarkably safe over the last 15 years. The so-called black box warning in the Susvimo package insert regarding a 2 percent rate of endophthalmitis is worth noting. Other risks associated with the surgical procedure itself and with permanent residence of a foreign body attached to the eye wall have been described, but fortunately they appear to be minimized with meticulous attention to surgical detail.

We must consider all these issues along with longer-term follow-up and the impressive patient preference data reported to date as we discern where the PDS will fit into our management recommendations.

It's an exciting time in retina. With multiple additional pharmacotherapies, including KSI-301 (Kodiak Sciences), an anti-VEGF biopolymer conjugate and OPT-302 (Opthea), which targets VEGF C and D, in Phase III trials, as well as faricimab (Genentech/Roche) awaiting possible FDA approval, our toolbox appears ready to expand further. RS



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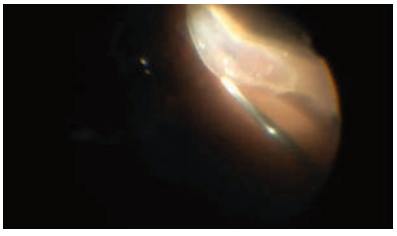
FEATURES

COVER STORY

DEPARTMENTS



LUXTURNA®
voretigene neparvovec-rzyl
for subretinal injection

PROMPT INTERVENTION
MAY MEAN A 2ND CHANCE AT LIFE'S STS

LUXTURNA® is the first gene therapy to help improve functional vision in patients with confirmed biallelic *RPE65* mutation–associated retinal dystrophy.[1]

If you wait and see, they wait and lose. Treatment is only possible while your patient still has viable retinal cells.

LEARN MORE AT
LUXTURNAHCP.com/RS

Not actual patients

IMPORTANT SAFETY INFORMATION

Warnings and Precautions

- **Endophthalmitis** may occur following any intraocular surgical procedure or injection. Use proper aseptic injection technique when administering LUXTURNA, and monitor for and advise patients to report any signs or symptoms of infection or inflammation to permit early treatment of any infection.
- **Permanent decline in visual acuity** may occur following subretinal injection of LUXTURNA. Monitor patients for visual disturbances.
- **Retinal abnormalities** may occur during or following the subretinal injection of LUXTURNA, including macular holes, foveal thinning, loss of foveal function, foveal dehiscence, and retinal hemorrhage. Monitor and manage these retinal abnormalities appropriately. Do not administer LUXTURNA in the immediate vicinity of the fovea. Retinal abnormalities may occur during or following vitrectomy, including retinal tears, epiretinal membrane, or retinal detachment. Monitor patients during and following the injection to permit early treatment of these retinal abnormalities. Advise patients to report any signs or symptoms of retinal tears and/or detachment without delay.
- **Increased intraocular pressure** may occur after subretinal injection of LUXTURNA. Monitor and manage intraocular pressure appropriately.
- **Expansion of intraocular air bubbles** Instruct patients to avoid air travel, travel to high elevations or scuba diving until the air bubble formed following administration of LUXTURNA has completely dissipated from the eye. It may take one week or more following injection for the air bubble to dissipate. A change in altitude while the air bubble is still present can result in irreversible vision loss. Verify the dissipation of the air bubble through ophthalmic examination.
- **Cataract** Subretinal injection of LUXTURNA, especially vitrectomy surgery, is associated with an increased incidence of cataract development and/or progression.

Adverse Reactions

- In clinical studies, ocular adverse reactions occurred in 66% of study participants (57% of injected eyes), and may have been related to LUXTURNA, the subretinal injection procedure, the concomitant use of corticosteroids, or a combination of these procedures and products.
- The most common adverse reactions (incidence ≥5% of study participants) were conjunctival hyperemia (22%), cataract (20%), increased intraocular pressure (15%), retinal tear (10%), dellen (thinning of the corneal stroma) (7%), macular hole (7%), subretinal deposits (7%), eye inflammation (5%), eye irritation (5%), eye pain (5%), and maculopathy (wrinkling on the surface of the macula) (5%).

Immunogenicity

Immune reactions and extra-ocular exposure to LUXTURNA in clinical studies were mild. No clinically significant cytotoxic T-cell response to either AAV2 or RPE65 has been observed.

In clinical studies, the interval between the subretinal injections into the two eyes ranged from 7 to 14 days and 1.7 to 4.6 years. Study participants received systemic corticosteroids before and after subretinal injection of LUXTURNA to each eye, which may have decreased the potential immune reaction to either AAV2 or RPE65.

Pediatric Use

Treatment with LUXTURNA is not recommended for patients younger than 12 months of age, because the retinal cells are still undergoing cell proliferation, and LUXTURNA would potentially be diluted or lost during the cell proliferation. The safety and efficacy of LUXTURNA have been established in pediatric patients. There were no significant differences in safety between the different age subgroups.

Please see a brief summary of the US Full Prescribing Information on the adjacent page.

Reference: 1. LUXTURNA [package insert]. Philadelphia, PA: Spark Therapeutics, Inc; 2017.

Spark THERAPEUTICS

LUXTURNA®
voretigene neparvovec-rzyl
for subretinal injection

Brief Summary of US Full Prescribing Information for LUXTURNA® (voretigene neparvovec-rzyl)

1 INDICATIONS AND USAGE
LUXTURNA (voretigene neparvovec-rzyl) is an adeno-associated virus vector-based gene therapy indicated for the treatment of patients with confirmed biallelic *RPE65* mutation-associated retinal dystrophy. Patients must have viable retinal cells as determined by the treating physicians.

4 CONTRAINDICATIONS
None.

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis
Endophthalmitis may occur following any intraocular surgical procedure or injection. Proper aseptic injection technique should be used when administering LUXTURNA. Following the injection, patients should be monitored to permit early treatment of any infection. Advise patients to report any signs or symptoms of infection or inflammation without delay.

5.2 Permanent decline in visual acuity
Permanent decline in visual acuity may occur following subretinal injection of LUXTURNA. Monitor patients for visual disturbances.

5.3 Retinal abnormalities
Retinal abnormalities may occur during or following the subretinal injection of LUXTURNA, including macular holes, foveal thinning, loss of foveal function, foveal dehiscence, and retinal hemorrhage. Monitor and manage these retinal abnormalities appropriately. LUXTURNA must not be administered in the immediate vicinity of the fovea. *[See Dosage and Administration (2.3) in full prescribing information]*

Retinal abnormalities may occur during or following vitrectomy, including retinal tears, epiretinal membrane, or retinal detachment. Monitor patients during and following the injection to permit early treatment of these retinal abnormalities. Advise patients to report any signs or symptoms of retinal tears and/or detachment without delay.

5.4 Increased intraocular pressure
Increased intraocular pressure may occur after subretinal injection of LUXTURNA. Monitor and manage intraocular pressure appropriately.

5.5 Expansion of intraocular air bubbles
Instruct patients to avoid air travel, travel to high elevations, or scuba diving until the air bubble formed following administration of LUXTURNA has completely dissipated from the eye. It may take one week or more following injection for the air bubble to dissipate. A change in altitude while the air bubble is still present can result in irreversible vision loss. Verify the dissipation of the air bubble through ophthalmic examination.

5.6 Cataract
Subretinal injection of LUXTURNA, especially vitrectomy surgery, is associated with an increased incidence of cataract development and/or progression.

6 ADVERSE REACTIONS
The most common adverse reactions (incidence ≥5%) were conjunctival hyperemia, cataract, increased intraocular pressure, retinal tear, dellen (thinning of the corneal stroma), macular hole, subretinal deposits, eye inflammation, eye irritation, eye pain, and maculopathy (wrinkling on the surface of the macula).

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

The safety data described in this section reflect exposure to LUXTURNA in two clinical trials consisting of 41 subjects (81 eyes) with confirmed biallelic *RPE65* mutation-associated retinal dystrophy. Forty of the 41 subjects received sequential subretinal injections of LUXTURNA to each eye. One subject received LUXTURNA in only one eye. Seventy-two of the 81 eyes were exposed to the recommended dose of LUXTURNA at 1.5 x 10^{11} vg; 9 eyes were exposed to lower doses of LUXTURNA. Study 1 (n=12) was an open-label, dose-exploration safety study. Study 2 (n=29) was an open-label, randomized, controlled study for both efficacy and safety *[see Clinical Studies (14) in full prescribing information]*. The average age of the 41 subjects was 17 years, ranging from 4 to 44 years. Of the 41 subjects, 25 (61%) were pediatric subjects under 18 years of age, and 23 (56%) were females.

Twenty-seven (27/41, 66%) subjects had ocular adverse reactions that involved 46 injected eyes (46/81, 57%). Adverse reactions among all subjects in Studies 1 and 2 are described in Table 1. Adverse reactions may have been related to LUXTURNA, the subretinal injection procedure, the concomitant use of corticosteroids, or a combination of these procedures and products.

Table 1. Ocular Adverse Reactions Following Treatment with LUXTURNA (N=41)

Adverse Reactions	Subjects n=41	Treated Eyes n=81
Any ocular adverse reaction	27 (66%)	46 (57%)
Conjunctival hyperemia	9 (22%)	9 (11%)
Cataract	8 (20%)	15 (19%)
Increased intraocular pressure	6 (15%)	8 (10%)
Retinal tear	4 (10%)	4 (5%)
Dellen (thinning of the corneal stroma)	3 (7%)	3 (4%)
Macular hole	3 (7%)	3 (4%)
Subretinal deposits*	3 (7%)	3 (4%)
Eye inflammation	2 (5%)	4 (5%)
Eye irritation	2 (5%)	2 (2%)
Eye pain	2 (5%)	2 (2%)
Maculopathy (wrinkling on the surface of the macula)	2 (5%)	3 (4%)
Foveal thinning and loss of foveal function	1 (2%)	2 (2%)
Endophthalmitis	1 (2%)	1 (1%)
Foveal dehiscence (separation of the retinal layers in the center of the macula)	1 (2%)	1 (1%)
Retinal hemorrhage	1 (2%)	1 (1%)

*Transient appearance of asymptomatic subretinal precipitates inferior to the retinal injection site 1-6 days after injection.

Immunogenicity
At all doses of LUXTURNA evaluated in Studies 1 and 2, immune reactions and extra-ocular exposure were mild. In Study 1 (n=12), the interval between the subretinal injections into the two eyes ranged from 1.7 to 4.6 years. In Study 2, the interval between the subretinal injections into the two eyes ranged from 7 to 14 days. No subject had a clinically significant cytotoxic T-cell response to either AAV2 or RPE65.

Subjects received systemic corticosteroids before and after subretinal injection of LUXTURNA to each eye. The corticosteroids may have decreased the potential immune reaction to either vector capsid (adeno-associated virus serotype 2 [AAV2] vector) or transgene product (retinal pigment epithelial 65 kDa protein [RPE65]).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Risk Summary: Adequate and well-controlled studies with LUXTURNA have not been conducted in pregnant women. Animal reproductive studies have not been conducted with LUXTURNA. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

8.2 Lactation
Risk Summary: There is no information regarding the presence of LUXTURNA in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for LUXTURNA and any potential adverse effects on the breastfed infant from LUXTURNA.

8.3 Females and Males of Reproductive Potential
No nonclinical or clinical studies were performed to evaluate the effect of LUXTURNA on fertility.

8.4 Pediatric Use
Treatment with LUXTURNA is not recommended for patients younger than 12 months of age because the retinal cells are still undergoing cell proliferation, and LUXTURNA would potentially be diluted or lost during cell proliferation.

The safety and efficacy of LUXTURNA have been established in pediatric patients. Use of LUXTURNA is supported by Study 1 and Study 2 *[see Clinical Studies (14) in full prescribing information]* that included 25 pediatric patients with biallelic *RPE65* mutation-associated retinal dystrophy in the following age groups: 21 children (age 4 years to less than 12 years) and 4 adolescents (age 12 years to less than 17 years). There were no significant differences in safety between the different age subgroups.

8.5 Geriatric Use
The safety and effectiveness of LUXTURNA have not been established in geriatric patients. Clinical studies of LUXTURNA for this indication did not include patients age 65 years and over.

17 PATIENT COUNSELING INFORMATION
Advise patients and/or their caregivers of the following risks:

Endophthalmitis and other eye infections: Serious infection can occur inside of the eye and may lead to blindness. In such cases, there is an urgent need for management without delay. Advise patients to call their healthcare provider if they experience new floaters, eye pain, or any change in vision.

Permanent decline in visual acuity: Permanent decline in visual acuity may occur following subretinal injection of LUXTURNA. Advise patients to contact their healthcare provider if they experience any change in vision.

Retinal abnormalities: Treatment with LUXTURNA may cause some defects in the retina such as a small tear or a hole in the area or vicinity of the injection. Treatment may cause thinning of the central retina or bleeding in the retina. Advise patients to follow up with their healthcare provider on a regular basis and report any symptoms, such as decreased vision, blurred vision, flashes of light, or floaters in their vision without delay.

Increased intraocular pressure: Treatment with LUXTURNA may cause transient or persistent increase in intraocular pressure. If untreated, such increases in intraocular pressure may cause blindness. Advise patients to follow up with their healthcare provider to detect and treat any increase in intraocular pressure.

Expansion of intraocular air bubbles: Advise patients to avoid air travel, travel to high elevations, or scuba diving until the air bubble formed following administration of LUXTURNA has completely dissipated from the eye. A change in altitude while the air bubble is still present may cause irreversible damage.

Cataract: Advise patients that following treatment with LUXTURNA, they may develop a new cataract, or any existing cataract may get worse.

Shedding of LUXTURNA: Transient and low-level shedding of LUXTURNA may occur in patient tears. Advise patients and/or their caregivers on proper handling of waste material generated from dressing, tears, and nasal secretion, which may include storage of waste material in sealed bags prior to disposal. These handling precautions should be followed for up to 7 days following LUXTURNA administration.

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Market forces may be gathering to exert price pressures on anti-VEGF drugs

With the recent approvals of the Susvimo ranibizumab port delivery system and the Samsung Bioepis-Biogen Lucentis biosimilar, scheduled to launch next summer, the market for anti-VEGF therapies is about to enter a new era of heightened competition that will cause downward pressures on drug prices.

Peter Downs, an author and analyst with Market Scope, a medical market data and analytics firm, gave that assessment during the OIS Retina@ASRS meeting last month.

"A couple of years ago there were only two competitors in terms of manufacturers in the anti-VEGF market in the United States," Mr. Downs said at the OIS meeting, meaning, of course, Genentech/Roche with Lucentis (ranibizumab) and Regeneron Pharmaceuticals with Eylea (aflibercept). Novartis' Beovu (brolucizumab), approved in 2019, makes three. Byooviz, Samsung Bioepis-Biogen Lucentis biosimilar, would make four.

With at least two more investigative Lucentis biosimilars and Outlook Therapeutics' ophthalmic formulation of Avastin (bevacizumab) "hot on their heels," and other anti-VEGF treatments in Phase III trials, "In five years we could have 10 or more manufacturers competing in this space," Downs said.

Quotable

"A couple of years ago there were only two competitors in terms of manufacturers in the anti-VEGF market in the United States. In five years we could have 10 or more."

— Peter Downs

Susvimo pricing

That doesn't even take into account Susvimo, which Genentech says it will price competitively with existing anti-VEGF platforms. For the first six months, the price of Susvimo is $9,250, which includes the implanted device and medicine, Shirley Dang, senior manager of corporate relations at Genentech, tells *Retina Specialist*. Refills will cost $8,000 every six months—the on-label interval. That adds up to a first-year price of $17,250, which Genentech says is 26 percent less than the yearly price of monthly Lucentis injections.

"As with all of its medicines, Genentech has taken a thoughtful and responsible approach to determining the price of Susvimo, and is committed to partnering with governments, regulatory and reimbursement authorities and non-governmental stakeholders to identify solutions that will help ensure its medicines are accessible for patients who need them," Ms. Dang says.

Mr. Downs has tracked the anti-VEGF prices Medicare pays since Lucentis was approved in 2008, and they have dropped steadily, according to Market Scope data. The Medicare price of Lucentis has gone from $2,025 a dose in 2008 to $1,535 this year. Eylea entered the market in 2012 at $1,961 a dose, just under the Lucentis price point at the time, falling to $1,833 this year. Even Beovu has seen a decline in price after only a year on the market, from $1,905 to $1,865 per dose.

Real-world costs

Of course, true annual costs vary depending on the treatment interval. Lucentis is approved for monthly dosing, Eylea for every four

IN BRIEF

Bausch + Lomb and Clearside Biomedical report that he Food and Drug Administration has approved XIPERE (triamcinolone acetonide injectable suspension) for suprachoroidal use for the treatment of macular edema associated with uveitis.

The FDA also granted 510 (k) approval for **iCare USA** to distribute the **EIDON** ultra-widefield lens module in the United States. The module enables the capture of 120-degree images of the retina in a single frame or up to 200 degrees with a mosaic function.

The FDA has also accepted **Novartis' su**pplemental Biologics License Application (sBLA) application to add diabetic macular edema as an indication for **Beovu** (brolucizumab).

GenSight Biologics has received FDA Fast Track Designation for **GS030,** which combines adeno-associated virus 2-based gene therapy with optogenetics to treat retinitis pigmentosa. PIONEER is a Phase I/II trial evaluating GS030 in patients with late-stage RP in the United Kingdom, France and United States.

weeks and up to eight weeks after three monthly loading doses, and Beovu for eight to 12 weeks after three loading doses. Add on top of that the treat-and-extend protocols retina specialists favor, and using 12 monthly injections to calculate annual cost probably only applies to a minority of patients.

While Susvimo, which had been called the Port Delivery System with ranibizumab (PDS) in clinical trials is FDA-approved for refilling every six months, the real-world interval may be longer. In the Phase II Ladder trial of PDS,[1] the median time to the first refill was 15.8 months for patients who received the 100-mg/ml formulation, the FDA-approved formulation for Susvimo.

In any event, the original price of Lucentis has proved to be a "ceiling rather than a floor," Mr. Downs says in an interview.

The impact biosimilars have had in other therapeutic areas, most notably oncology and rheumatology, may foretell the impact they'll have in ophthalmology, he says. "So the first biosimilar comes in around 80, 85 percent of price," he says. "But by the time you get the third one, it typically comes in at about 60 percent of the reference price." An unforeseeable factor is how quickly retina specialists accept biosimilars.

Another factor is the impact Avastin has in the market. Outlook Therapeutics' is developing an ophthalmic bevacizumab formulation, which would potentially cut out the specialty pharmacies that repackage the oncology drug for intravitreal injections. But its impact in the anti-VEGF market, adds Mr. Downs, "is very cloudy right now."

See related story: "Five things to know about biosimilars in retina," page 38.

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Vaccine hesitancy comes to the retina practice

Like employers everywhere, retina specialists are dealing with staff members who refuse to get vaccinated against the COVID-19 virus. Three retina specialists who commented on staff vaccinations during the COVID symposium at the American Society of Retina Specialists meeting in San Antonio last month share their experiences and thoughts on staff vaccines.

"I think that all medical staff should be vaccinated, and I feel a moral obligation myself to get vaccinated and I think the staff should feel that way as well," says John Thompson, MD, partner at Retina Specialists, a three-location practice in Maryland. "But I also understand that people feel like they have individual freedoms and this becomes an ethical conflict between the rights of the individual versus the rights of society."

He tells about a "good staff member who is very religious" who left the practice because she refused to get the vaccine. "The interesting thing about it is this young lady got COVID and her father got COVID back in earlier 2021," Dr. Thompson says. "Her father died from COVID, and yet she still refuses to get vaccinated. It just goes to show how strong somebody's religious beliefs can be."

Getty Images

A cause for controversy at retina clinics.

"Thankfully the substantial majority of our staff are vaccinated," says Sunir Garg, MD, codirector of retina research at the Retina Service of Wills Eye Hospital, Philadelphia, and a partner with Mid Atlantic Retina, a 17-location practice in Pennsylvania, New Jersey and Delaware. "Our clinical staff's vaccination rates are high, and vaccination rates are improving for our back office and billing staff."

He notes that federal, state and local mandates have "encouraged some of our staff that were otherwise on the fence to get vaccinated." He adds, "As we've seen in some hospital systems, a few of our staff told us that if they have to get vaccinated due to mandates, they are going to leave to get jobs that don't require vaccination. How do you navigate those waters?

"It's definitely a big issue. In this tight labor market, hiring staff has been tough enough without this additional challenge," Dr. Garg says. "Anyone leaving for other jobs over vaccination requirements is a big concern. Whether it is clinical or administrative personnel, if we don't have sufficient support then we cannot do our jobs. Ultimately, our patients suffer if we can't provide timely care."

"I think it makes sense to require vaccinations," says Abdhish

Bhavsar, MD, of The Retina Center, a three-office practice in Minnesota. "Navigating them is a human resource issue, and it should be done well, thoughtfully and appropriately, but it makes sense."

He cites a recent publication that reported that 0.5% of vaccinated healthcare workers were COVID symptomatic positive, and had persistent shedding of the virus for 30 days or more afterward. "We have to be aware of that even with vaccinations we still can get COVID," Dr. Bhavsar says. "Vaccination for the major diseases that we can transmit to others, including our patients and staff should be required for all healthcare workers, including COVID and even the flu."

Medicare cracking down on -25 modifier use

Medicare seems to be gearing up for more vigorous enforcement of use of the -25 modifiers for intravitreal injections, attendees at the American Society of Retina Specialists meeting were told.

In an interview, John Thompson, MD, explains the rationale for that conclusion: the Office of Inspector General of the Department for Health and Human Services, the agency that runs Medicare, issued a workplan in 2019 that stated as much. He relays the story of a retina practice that received an audit letter about two years ago, and submitted its records soon after that. After a lull during the COVID-19 pandemic, the practice received a follow-up notice last spring that the OIG was resuming its action.

John Thompson, MD, says the Office of Inspector General is ramping up audits of intravitreal injections.

The challenge for retina specialists is that they use the -25 modifier for intravitreal injections at a rate much higher than other ophthalmologists. Medicare hasn't given clear guidance on when it is or isn't appropriate to use the modifier to charge for an office visit on the same day as an intravitreal injection.

"I'm not sure they truly understand the difference between a retina specialist and an ophthalmologist, and that's part of the problem," Dr. Thompson says of the OIG auditors. "Because virtually every retina specialist is an outlier compared to a comprehensive ophthalmologist or a glaucoma specialist, because we use the -25 modifiers in patients that are examined on the same day as an intravitreal injection, something that happens much less frequently in non-retina practices."

As for a practice that's already under audit, Dr. Thompson says, "I think the best word of wisdom I can give is you need to hire an attorney," preferably one well-versed in Medicare audits and, if possible, specifically retina.

See related story, Coding Commentary, "Documenting IVI: Avoiding audit traps," page 46.

—Richard Mark Kirkner

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10 uses for external needle drainage

This technique can be valuable in a variety of vitreoretinal surgery scenarios.

By Parampal S. Grewal, MD, FRCSC, Tina Felfeli, MD, and Efrem D. Mandelcorn, MD, FRCSC

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Vitreoretinal surgical techniques should be tailored and targeted to the patient's unique pathology, as well as the surgeons' preference and experience. While pars plana vitrectomy techniques have improved and direct drainage of subretinal fluid is the more common approach, external needle drainage can be part of a vitreoretinal surgeon's armamentarium. Here, we present our approach to transcleral external needle drainage, and some of its applications in unique surgical scenarios.

Transcleral drainage: A brief history

Steve T. Charles, MD, first described transscleral drainage of subretinal fluid by using a 5/8-inch, 25-gauge needle during scleral buckling.[1] It has since been described with different gauges, ranging from 26- to 28-gauge,[2,3] as well as with different types of needles, including a guarded 26-gauge needle[4] and a 24-gauge intravenous catheter.[5] While this technique was originally described in 1985 with indirect visualization during scleral buckle surgery, recent literature has demonstrated its continued relevance in the era of vitrectomy with direct visualization.

More recently, Peter J. Belin, MD, and colleagues described a case series of 83 eyes with rhegmatogenous retinal detachment (RRD) that underwent external needle drainage during PPV, SB or combined PPV/SB.[3] Their findings demonstrated good safety outcomes.

Our preferred approach

Our preferred approach to external needle drainage is to use a 27-gauge, thin-walled TSK needle, guarded with a trimmed 70-buckle sleeve to limit intraocular entry and reduce the risk of retinal incarceration and iatrogenic break (*Figure and video*). This guarded needle is connected to the active extrusion tubing of the vitrectomy machine.

View the Video

Watch as Drs. Grewal, Felfeli and Mandelcorn demonstrate applications for external needle drainage in vitreoretinal surgery. Available at: https://bit.ly/RetSpec-Mag_2021_10

We perform external drainage in a transconjunctival, transscleral fashion, introducing the needle in the highest portion of the retinal detachment. Here are the key steps in our approach:

- First, viewing externally, engage the conjunctiva and sclera.
- Under direct visualization, with the needle tangential, depress the sclera to confirm the needle's location.
- Orient the needle in a more perpendicular fashion and slowly advance it until it's visualized in the subretinal space.
- Actively aspirate the SRF in a slow and controlled fashion using low active vacuum.

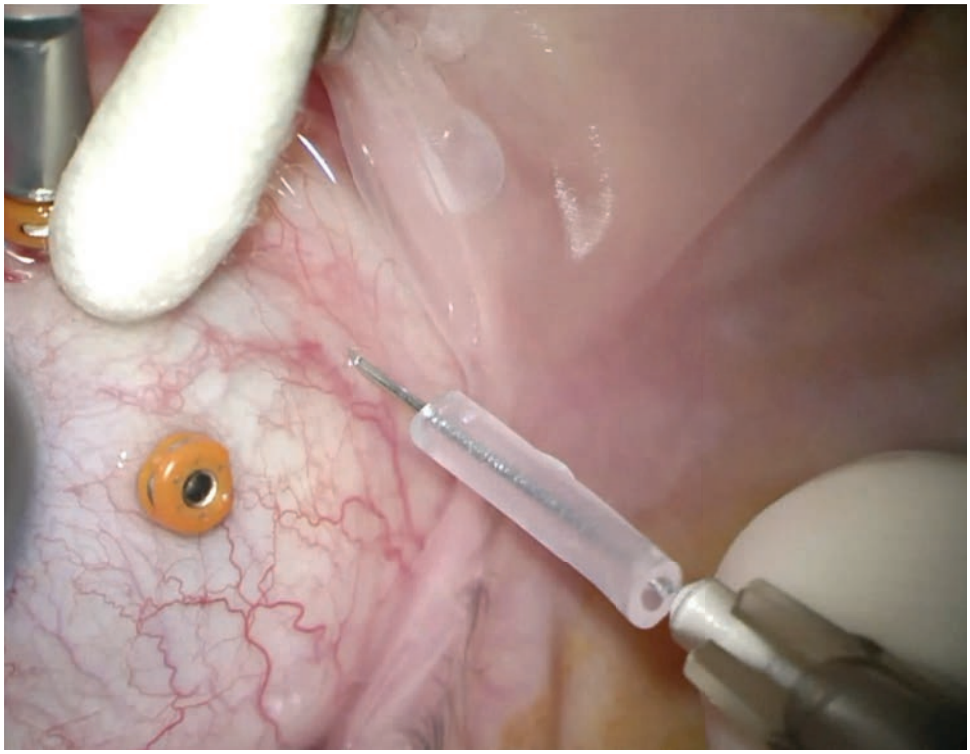
In cases of subretinal biopsy, the guarded needle can be attached to a syringe which can passively aspirate the SRF directly into the syringe.

Here, we summarize some of our favorite applications of external needle drainage.

1 Very bullous retinal detachment

The presentation of individual RRDs can vary significantly. Very bullous and mobile retinal detachments present a unique challenge. One challenge is the occurrence of iatrogenic retinal breaks during vitrectomy cutting, which can complicate the repair and increase the risk of anatomical failure and proliferative vitreoretinopathy.

Additionally, the vitreous overlying very



Our preferred approach to external needle drainage is to use a 27-gauge, thin-walled TSK needle, guarded with a trimmed 70-buckle sleeve.

mobile retina may be difficult to remove completely. In these cases, we like to use external needle drainage early on to flatten the retina. This creates a more controlled surgical setting by reducing the risk of iatrogenic retinal breaks, enabling a more complete removal of adherent vitreous and facilitating membrane removal and macular peeling as required.

2 RRDs with small, anterior retinal breaks

The varying nature and location of retinal breaks can require different approaches for optimal repair. Small, very anterior retinal breaks present a particular challenge. Complete drainage of SRF from the break itself can be challenging, especially in a phakic setting. Yet, drainage of SRF is important to apply optimal laser retinopexy to the break and achieving good fill with gas or oil.

Posterior drainage retinotomies are an option in this setting. However, they carry additional risks, including PVR. Perfluorocarbon is another option, but it introduces significant cost and risk of subretinal migration. External needle drainage is an effective, cost-saving option for reattaching the retina in cases of small anterior retinal breaks.

3 Drainage during chandelier-assisted scleral buckle/ combined SB-vitrectomy

External drainage during SB carries the risk of choroidal hemorrhage and retinal incarceration, which can carry significant morbidity. External needle drainage under direct visualization may reduce this risk compared with conventional external cutdown because it enables an improved view of the needle tip and a more controlled flow.

External needle drainage in this setting can be performed in combination with

External needle drainage under direct visualization may reduce the risk of choroidal hemorrhage and retinal incarceration during chandelier-assisted scleral buckle/ combined SB-vitrectomy.

chandelier illumination and visualization with the operating microscope.[6] Chandelier illumination is well-suited for external needle drainage when direct visualization is available and careful drainage of subretinal fluid can be performed in a controlled way, as the accompanying video shows.

4 Prevention of underfill of oil tamponade in RRDs

The accompanying video demonstrates two scenarios in which external needle drainage can prevent the underfilling of oil tamponade in RRDs. They are:

- ***Choroidal effusion.*** Silicone oil tamponade is commonly used for chronic RRDs and complex retinal detachments. The concern about oil underfill in RRDs with choroidal detachment can be an issue as it may lead to failure and redetachment.

Using the guarded needle, the choroidal detachment can be drained to restore the vitreous volume and ensure a full fill of silicone oil at the end of the case. We've found that using this maneuver is best after the fluid-air exchange. We usually increase the air pressure and then place a guarded needle on an open syringe with no plunger to allow for passive egress of the choroidal effusion.

- ***RD with macrocysts.*** Chronic RDs can be associated with macrocysts that usually resolve spontaneously postoperatively after tamponade. In cases of large cysts, this can result in silicone oil underfill. To maintain the integrity of the inner retina, these cysts can be drained and "popped" sequentially with an external needle that can be placed in the subretinal space.

5 Subretinal gas or air

This is a rare, challenging situation that may be encountered intraoperatively or after inadvertent subretinal injection of gas during pneumatic retinopexy.[7] It may be challenging to remove subretinal air, particularly if it's extensive, because it may become sequestered quite anteriorly at the retinal insertion to the pars plana.

By placing a guarded needle in the subretinal space, these bubbles of air or gas can easily be aspirated, either actively or passively, without the need to create large retinotomies for removal. External needle drainage is an elegant way to debulk subretinal air or gas (*Video*).

6 Lysing a subretinal band

Subretinal PVR and bands may limit retinal reattachment and are challenging to repair given their location. With large retinal breaks or in the setting of retinectomy, these can be accessed more directly and removed. In the absence of adjacent retinal breaks, however, various approaches have been described, including creating retinotomies near or overlying the band, cutting the band and/or removing it through such retinotomies.[8]

Retinotomies in the setting of preexisting PVR carry the risk of recurrence. An external needle approach in select cases is an option to facilitate direct lysis of subretinal bands without creating retinal breaks. Once the guarded needle is placed in the subretinal space, the sharp tip of the needle can be used to cut the subretinal band and separate it, effectively eliminating the traction. While it isn't possible to remove the band in this fashion, once cut, the traction is released, and removal may not be necessary.

7 Draining a suprachoroidal hemorrhage

Suprachoroidal hemorrhage is a dreaded surgical complication and makes access to the vitreous cavity problematic for vitrectomy surgery. Our strategy for addressing a suprachoroidal hemorrhage is to use an external drainage needle to remove the blood as we've previously described (*Video*).[9]

8 Tractional retinal detachments

Tractional diabetic RDs are often challenging to repair. Retinal breaks, if present, may be difficult to localize, particularly in the setting of extensive fibrovascu-

Retinotomies to remove subretinal PVR carry the risk of recurrence. An external needle approach in select cases is an option to facilitate direct lysis of subretinal bands without creating retinal breaks.

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Apellis

10 essential applications of external needle drainage in vitreoretinal surgery

1. Very bullous retinal detachment
2. Rhegmatogenous retinal detachment with small, anterior retinal breaks
3. Drainage during chandelier-assisted scleral buckle/combined scleral buckle-vitrectomy
4. Prevention of underfill of oil tamponade in RRDs with choroidals
5. Subretinal gas or air
6. Lysing a subretinal band
7. Draining a suprachoroidal hemorrhage
8. Tractional retinal detachments
9. RD without a definitive break
10. Exudative RD and subretinal biopsy

lar proliferation and vitreous hemorrhage. Further, complete and careful removal of preretinal proliferative membranes is essential to success, although it can be challenging with a mobile retina without counter-traction.

As in the very bullous RD, external needle drainage in this setting creates a more controlled situation. Once the SRF is debulked, the retina lies in a more physiological position. This improves visualization and the ability to identify small occult retinal breaks, and it can facilitate safer and more complete dissection of preretinal membranes (*Video*).

A small portion of retinal detachments may present without a definite retinal break. External needle drainage is a valuable option to drain SRF without creating a retinotomy.

9 RD without a definitive break

A small portion of retinal detachments may present without a definite retinal break.[10] One option is to create a posterior retinotomy to drain the subretinal fluid and reattach the retina.

In our experience, however, external needle drainage is a very valuable option in this setting because we can drain the subretinal fluid through the guarded needle, followed by air exchange with or without laser retinopexy of all suspicious areas of retinal break without inadvertently creating or enlarging any occult microbreaks during the air exchange (*Video*).

10 Exudative RD and subretinal biopsy

Exudative RDs are uncommon and can present challenging surgical scenarios. In select cases of exudative detachment, diagnostic or therapeutic drainage of SRF may be indicated or needed. Drainage retinotomy in this setting can be problematic given the absence of pre-existing retinal breaks and potentially elevated risk of PVR and redetachment. External needle drainage is an elegant solution in this setting to obtain SRF for diagnostic testing and to reattach the retina (*Video*).

Bottom line

Overall, we believe that external needle drainage is a valuable skill–with a short learning curve–in vitreoretinal surgery. It can be a useful approach in a variety of surgical scenarios including RRD cases (bullous detachments, and small and anterior breaks), when performing scleral buckle, preventing underfilling when using oil tamponade, addressing subretinal gas or air, lysing a subretinal band and draining a suprachoroidal hemorrhage, and for tractional RRDs, detachments with no definitive break and subretinal biopsy in exudative detachments. RS

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A petal-shaped blind spot

A case of acute macular neuroretinopathy developed in the context of myelofibrosis.

By Preston Luong, MD, and Amy Yuan, MD

Preston Luong, MD

Amy Yuan, MD

UW Medicine EYE INSTITUTE

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Dr. Olmos de Koo is an associate professor of ophthalmology and director of the retina fellowship program at the University of Washington.

DISCLOSURES: The authors have no relevant disclosures.

A 56-year-old male physician was referred urgently to the University of Washington retina clinic with a one-week history of a "small blind spot" in the right eye. The scotoma was just superior to fixation with a purple and yellow hue.

He recalled a similar scotoma in the left eye 20 years earlier. At that time, an evaluation by an ophthalmologist failed to reveal an etiology.

Otherwise, his ocular history was unremarkable. His medical history was notable for idiopathic myelofibrosis, initially diagnosed in 2001, for which he had undergone a recent splenectomy and matched unrelated donor peripheral blood stem-cell transplantation. His current medications included mycophenolate, cyclosporine and sirolimus.

Examination findings

Best-corrected visual acuity was 20/20 in both eyes. Pupils were equally reactive with no afferent pupillary defect. Intraocular pressures were normal, as were extraocular movements and peripheral visual field by confrontation. On Amsler grid testing, he had a wedge-shaped scotoma superonasal to the point of fixation in the right eye and a fainter wedge-shaped scotoma directly superior to fixation in the left eye. The anterior slit lamp exam was unremarkable.

Fundus examination revealed a subtle interruption of the foveal light reflex in the inferotemporal macula of the right eye, with an otherwise normal macular and peripheral exam (*Figure 1*).

Work-up

Spectral-domain optical coherence tomography of the right eye revealed a focal area of hyperreflectivity involving the outer plexiform and nuclear layers along with focal irregularity of the ellipsoid zone temporal and inferotemporal to the fovea (*Figure 2A*). SD-OCT of the left macula showed subtle focal outer retinal thinning and ellipsoid granularity nasal to the fovea (*Figure 2A*).

Near-infrared reflectance demonstrated a lesion with focal hyporeflectance inferotemporal to the fovea of the right eye and inferonasal to the fovea in the left, corresponding to the SD-OCT irregularities (*Figure 3, page 20*). Fluorescein angiogram showed normal perfusion in both eyes (*Figure 4, page 23*).

Diagnosis and management

Multimodal imaging demonstrated features consistent with a diagnosis of acute macular neuroretinopathy (AMN). At the one-month follow-up visit, the patient's symptoms were unchanged. The near infrared reflectance in the right eye showed a more consolidated hyporeflective lesion. SD-OCT showed a slight interval improvement in the ellipsoid zone disruption.

What's AMN?

Acute macular neuroretinopathy was first described 45 years ago by Pierre J.M. Bos, MD, and August F. Deutman, MD.[1] A subsequent large review of AMN found the typical demographic to be young women in their late 20s, with about half of cases having bilateral ocular involvement.[2]

The most common presenting symptom was a scotoma, often near the point of fixation, corresponding to wedge-shaped lesions on examination. They have been described to have either a petaloid, oval, or teardrop shape with the apex directed toward the fovea. Occasional associated findings include superficial retinal hemorrhages, macular edema and

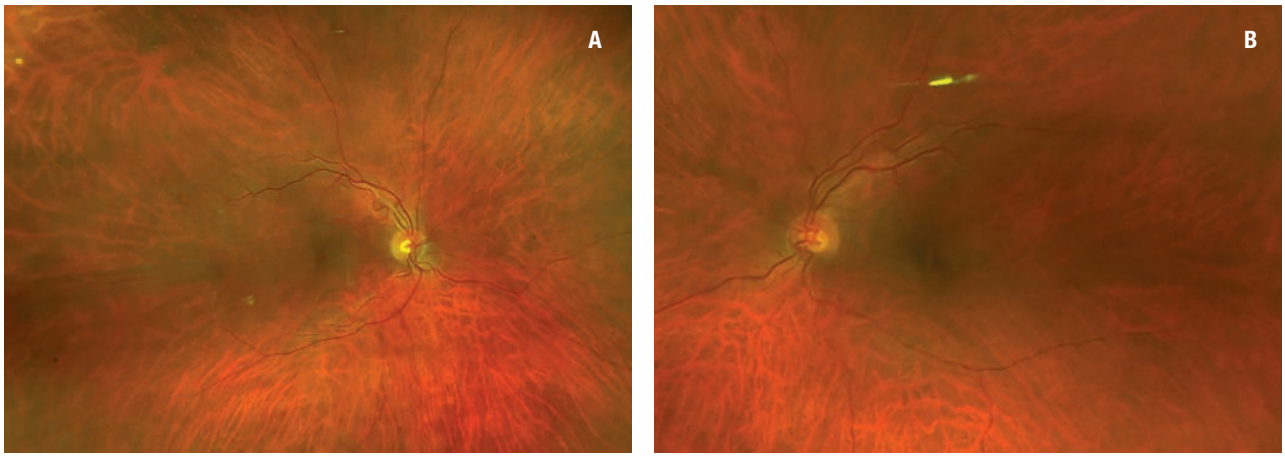

Figure 1. Fundus photography was relatively unremarkable in both eyes, showing a subtle interruption of the foveal light reflex in the inferotemporal macula of the right eye (A) with an otherwise normal macular and peripheral exam (B).

optic disc edema.

The differential diagnosis for AMN includes white-dot syndromes such as multiple evanescent white-dot syndrome (MEWDS) and acute posterior multifocal placoid pigment epitheliopathy (APMPPE), as well as punctate inner choroidopathy (PIC) and paracentral acute middle maculopathy (PAMM).

Multimodal imaging is useful for establishing the diagnosis in these cases. Infrared reflectivity classically shows perifoveal, eccentric hyporeflective lesions and has been reported to be the most sensitive and specific diagnostic study.[2] SD-OCT shows both ellipsoid and/or interdigitation zone disruption with focal overlying outer nerve and plexiform hyperreflectivity.

Fluorescein angiography has low sensitivity, but may show hypofluorescent lesions in either the early or late phases. Multifocal electroretinogram demonstrates diminished amplitudes at the areas corresponding to the patient's scotoma.

No proven medical or surgical treatment exists for AMN. Scotomas may improve spontaneously over time, but generally don't resolve completely.

Insights into pathophysiology

The pathophysiology of AMN is undetermined. However, since the advent of OCT angiography, a growing body of

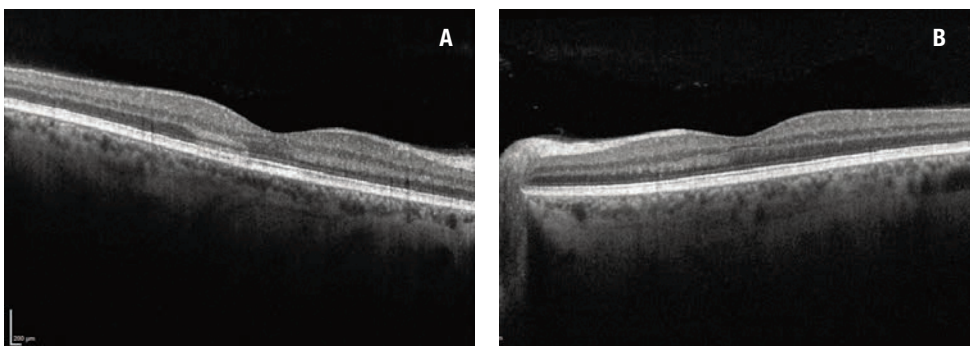

Figure 2. A) Spectral-domain optical coherence tomography of the right eye revealed a focal area of hyperreflectivity within the outer nuclear and plexiform layers along with disruption of the ellipsoid zone. B) SD-OCT in the left eye revealed subtle focal outer retinal thinning and ellipsoid zone granularity nasal to fovea.

evidence suggests that AMN may involve an abnormality of the microvasculature in the choriocapillaris or deep capillary plexus.[3]

The most common systemic association is a nonspecific preceding febrile illness. However, factors that may cause a disruption to blood flow either through vasoconstriction, decreased cardiac output or a prothrombotic state have been associated with AMN.

Very few associations between hematologic malignancies and AMN have been described. The first noted association between leukemia and AMN was reported in a 31-year-old woman with acute lymphoblastic B-cell leukemia, who presented with six weeks of vision loss.[4] A more recent case report described AMN in a patient with newly diagnosed acute promyelocytic leukemia.[5]

Suggested mechanisms for AMN in these patients included thrombocytopenia and anemia leading to focal ischemia of the outer retina, immature blast cells increasing the overall hyperviscosity of serum leading to venous stasis, and disseminated intravascular coagulation causing worsening of perfusion of the retinal microvasculature.[5]

Chemotherapy itself has also been linked to AMN. We found one report of AMN in a 28-year-old woman with refractory acute myeloid leukemia (AML) on gilteritinib therapy who was diagnosed with AMN.[6] She subsequently had an improvement in symptoms after discontinuing the chemotherapy agent. Gilteritinib is an inhibitor of FLT3, and retinal FLT3 is known to be upregulated in ischemic conditions.

(Continued on page 23)

Since the advent of OCT angiography, a growing body of evidence suggests that acute macular neuroretinopathy may involve an abnormality of the microvasculature in the choriocapillaris or deep capillary plexus.

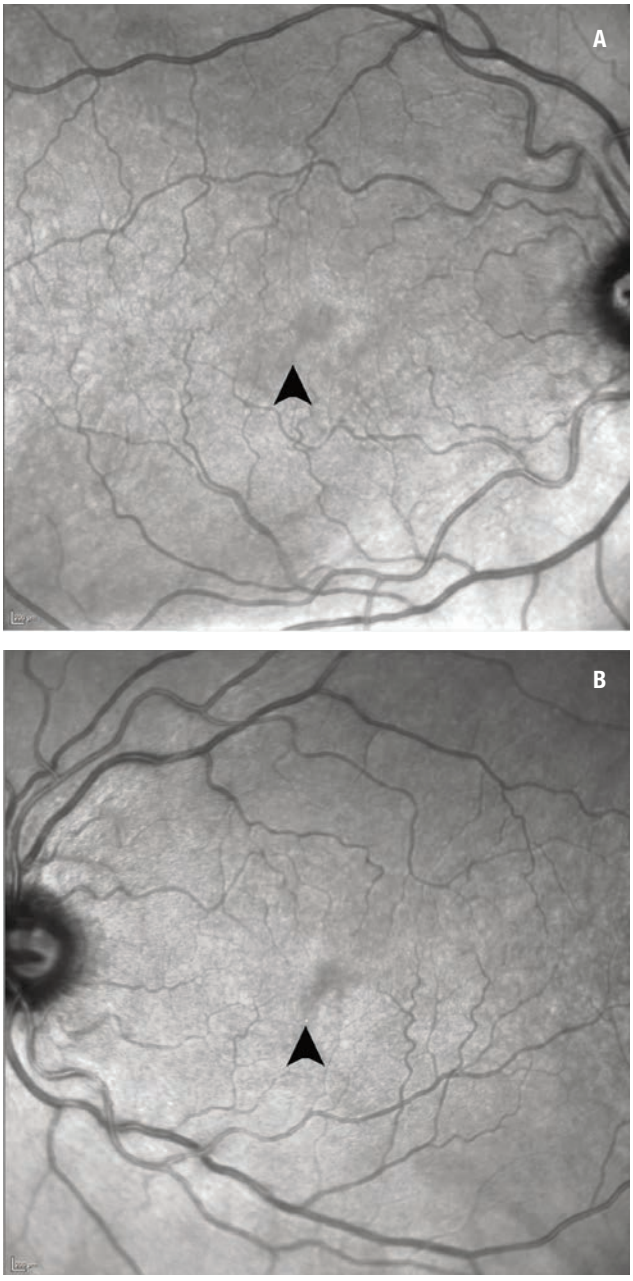

Figure 3. Near-infrared reflectance shows a focal area of hyporeflectance in the inferotemporal fovea of the right eye (A) and the inferonasal fovea of the left eye (B) (arrows).

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Managing a challenging RD

Repair of a retinoschisis-associated retinal detachment in a pregnant patient.

By Mercy Kibe, MD, Marez Megalla, MD, and Kristen Nwanyanwu, MD, MBA, MHS

Mercy Kibe, MD

Marez Megalla, MD

Kristen Nwanyanwu, MD, MBA, MHS

Bios

Dr. Kibe is the first-year vitreoretinal surgery fellow and **Dr. Megalla** is the senior vitreoretinal surgery fellow at Yale University School of Medicine, New Haven, Conn.

Dr. Nwanyanwu is an assistant professor of ophthalmology and visual science at Yale.

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

DISCLOSURES: Drs. Kibe, Megalla and **Nwanyanwu** have no relevant disclosures. **Dr. Hahn** is a consultant to DORC.

A 29-year-old, myopic, pregnant woman at 36 weeks gestation was referred for evaluation of a macula-on inferotemporal retinal detachment with a retinoschisis component as indicated by ultrasonography (*Figure*).

Timing and planning of surgery

Timing of surgical repair was complicated by the fact that the patient was in her third trimester of pregnancy. The American College of Obstetrics and Gynecology recommends delaying elective surgery until after delivery. However, pregnant women should not be denied medically necessary surgery at any trimester.[1] The optimal time for non-obstetric surgery in a pregnant patient is the second trimester, when the risk of preterm labor is lower compared to the third.[2]

Because this patient was so close to her due date and had an acute-on-chronic appearing retinal detachment, we elected to delay the repair until after delivery, with consultation from her obstetrics team.

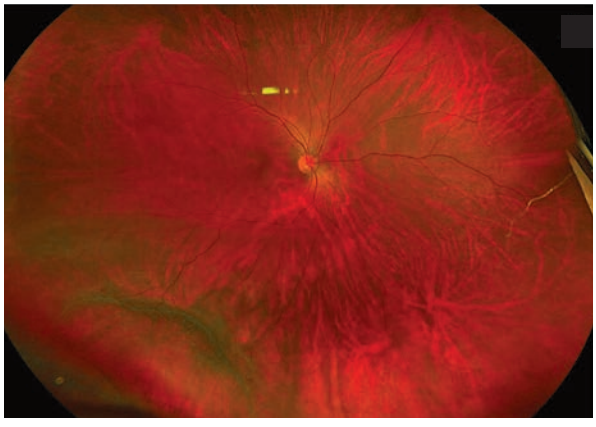
From the time of diagnosis to surgery, we followed her with weekly exams and fundus photography for documentation, which demonstrated only minimal progression of her detachment. Surgical repair was undertaken six weeks after initial presentation (two weeks postpartum).

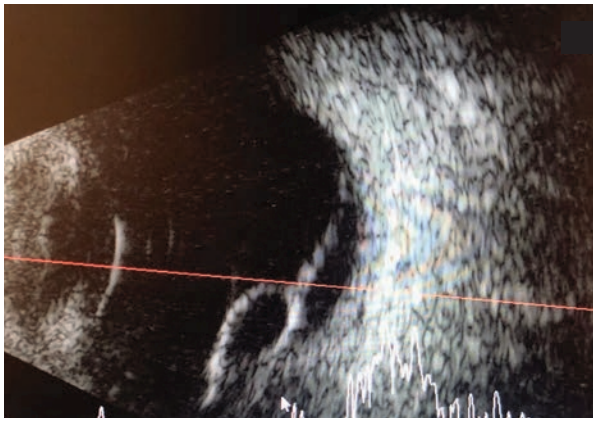
Making the repair

While observation may be appropriate in some cases of retinoschisis-associated retinal detachments, which can often remain stable and asymptomatic long-term, surgical repair is typically required in the setting of progressive symptoms.[3]

No consensus exists regarding the best surgical methods to repair retinoschisis-associated retinal detachments, although various methods of repair have been employed.[4]

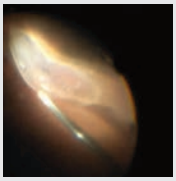
We elected a scleral buckle combined with a vitrectomy and gas tamponade (15% C_3F_8) because of the chronic-appearing cavity and inferior location. We also considered the potential challenges with positioning because she was a first-time mother of a newborn. During the case, we did not





Fundus photograph and B-scan at presentation showed a macula-sparing inferotemporal retinoschisis-associated retinal detachment in our 26-year-old pregnant patient.

View the Video



Watch as Drs. Kibe, Megalla and Nwanyanwu repair a retinoschisis-associated retinal detachment in a pregnant patient. Available at: https://bit.ly/VideoPearl_026

note any distinct break with scleral depression, but we did observe thinning over the schisis cavity.

We applied endodiathermy to mark the areas of thinning. We drained the subretinal fluid through a drainage retinotomy at 8 o'clock using soft-tip extrusion, then noted a flattening of the retinal schisis cavity. We then applied endolaser around the retinotomy and throughout the retinal schisis cavity. On subsequent postoperative visits, the retina remained attached.

Bottom line

Surgery in a pregnant patient needs to be coordinated with the obstetrics team and anesthesia providers, balancing the urgency of surgery, risks of delay and risks to the pregnancy.[5]

In a pregnant patient with a chronic-appearing retinoschisis-associated retinal detachment, one can consider close monitoring for progression of detachment and delay surgical repair until safe delivery. RS

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A petal-shaped blind spot

(Continued from page 20)

Mice lacking the *FLT3* gene in laboratory conditions have markedly reduced angiogenesis. Gilteritinib may play a role in impairing the retina's normal response to transient ischemic states and lead to the development of AMN.

Bottom line

To our knowledge, this is the first case of AMN associated with myelofibrosis. Microvascular ischemia at the level of the deep capillary plexus or choriocapillaris can have a wide variety of etiologies, and this report contributes to the case reports that show an association between AMN and a hematologic malignancy.

Interestingly, this patient's diagnosis of myelofibrosis was established shortly after his initial episode of what was most likely AMN in the contralateral eye. The paracentral scotoma might have been the presenting symptom of his underlying blood dyscrasia.

Because of this, we recommend that clinicians carry an index of suspicion for serious systemic conditions in patients who present with AMN. Consider ordering basic blood work, including a complete blood count with differential, when encountering a patient with potential symptoms of AMN. RS

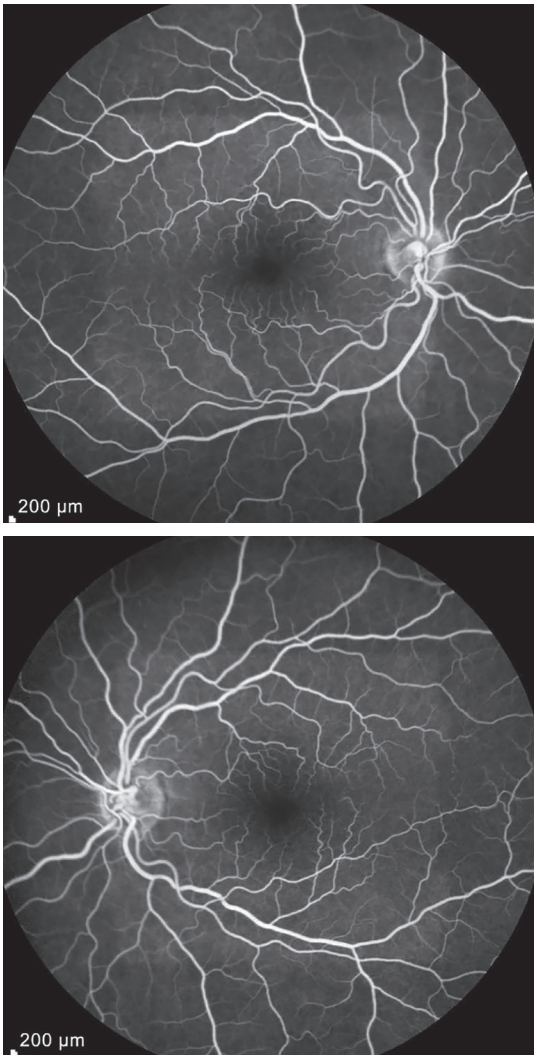

Figure 4. Fluorescein angiography was unremarkable in both eyes.

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The robots are coming to retina

An update of the science behind robotic-assisted vitreoretinal surgery and its potential future applications.

Carl S. Wilkins, MD

Richard B. Rosen, MD

By Carl S. Wilkins, MD, and Richard B. Rosen, MD

Take-home points

- Vitreoretinal surgery requires an extraordinary level of precision and accuracy. Robotic-assisted platforms are evolving to achieve levels of intraocular microsurgical control not currently attainable using standard manual techniques.
- Early trials with robotic-assisted vitreoretinal platforms have demonstrated promising results for macular surgery of epiretinal membranes and controlled subretinal delivery of pharmaceutical agents.
- Increasing availability of intraoperative optical coherence tomography will encourage the use of robotic-assisted surgery for subretinal drug delivery and intravascular manipulation.
- Robotic-assisted vitreoretinal platforms will allow microsurgical interventions beyond the level of human capabilities and, when combined with intraoperative imaging, should help transition vitreoretinal surgeons into a new era of subretinal therapeutics and beyond.

Bios

Dr. Wilkins is a clinical fellow in vitreoretinal surgery at New York Eye and Ear Infirmary of Mount Sinai, New York.

Dr. Rosen is retina service chief and vice chair of research at New York Eye and Ear Infirmary.

DISCLOSURES: Drs. Wilkins and **Rosen** have no relevant disclosures. Preceyes and Mount Sinai Health System are in a strategic collaboration. Mount Sinai has an equity investment in Preceyes, and Preceyes has installed a surgical system at New York Eye and Ear Infirmary.

The first-ever robotic-assisted surgery was reported by Yik San Kwoh, MD, and colleagues at Long Beach Memorial Medical Center in 1988, for which they used a robotic stereotactic biopsy platform used to aid in diagnosis of brain cancers.[1]

Since then, many fields of surgery have endeavored to use robotic technologies to aid in a variety of surgical procedures. Compared to other subspecialties, ophthalmologists have been relatively slow to adapt robotic-assisted platforms, with the first-ever in-human study published in 2018.[2]

Ophthalmic surgery, particularly vitreoretinal surgery, demands extreme precision at the level of 40 µm or less, while an experienced surgeon manifests a tremor of roughly 100 µm, due to circulation and breathing.[3,4] During static maneuvers this tremor can exceed 200 µm.[3,4] Because of this human limit, there's a need to address ways to improve manual dexterity and accuracy in vitreoretinal surgery. Robotics offer a potential avenue to do so.

Enhanced accuracy combined with haptic feedback for the surgeon may improve accuracy during delicate procedures such as fine macular work, retinal vessel cannulation and subretinal injections. The recent revolution of subretinal gene therapy, as exemplified by voretigene for *RPE-65* biallelic mutation (Luxturna, Spark Therapeutics), will likely make robotic-assisted platforms even more valuable because of their high level of precision and accuracy.

We anticipate that these platforms will open up new avenues for treatment not previously possible with manual surgery alone. Here, we review the current status of robotic-assisted vitreoretinal surgery and its future applications in clinical practice.

Figure 1. The Preceyes robotic-assisted platform uses a robotic arm operated directly by the surgeon (A), with a conical port adapter to allow insertion of surgical tools into the eye (B). (*Courtesy Preceyes*)

Categories of robotic-assisted platforms

The categories of robotic-assisted platforms in vitreoretinal surgery include hand-held assist devices and comanipulation and telemanipulation platforms. Hand-held devices, such as the Micron, are completely controlled. They're handled by the surgeon and are designed with the main objective of minimizing surgeon tremor in order to augment surgical capabilities.

Comanipulative devices, such as the SteadyHand Eye robot from Johns Hopkins University, function by integrating the surgeon's movements with limited robotic movements to optimize safety. The SteadyHand has five degrees of freedom and can mitigate unwanted surgeon movement by limiting rotational and X-Y-Z movement at a fixed incision point.[5,6] The comanipulative abilities provide enhanced safety and precision of depth compared to the simpler hand-held assist platform; however, it's larger and therefore may be more difficult to integrate into the operative workflow.

Telemanipulative platforms such as Preceyes (*Figure 1*) and the IRISS developed at UCLA offer the highest level of intraoperative precision due to the complete separation of the surgeon's hand from the robotic manipulator.

The Preceyes robotic platform's motion controller is operated by the surgeon, with the maneuvers translated to the robotic manipulator with a precision better than 20 µm. The IRISS platform has

(Continued on page 29)

The categories of robotic-assisted platforms in vitreoretinal surgery include hand-held assist devices, and comanipulation and telemanipulation platforms.

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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.

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ADVERSE REACTIONS

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

INDICATIONS

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

Please see brief summary of the full Prescribing Information on the following page.

References: 1. EYLEA® (aflibercept) Injection full U.S. Prescribing Information. Regeneron Pharmaceuticals, Inc. June 2021. **2.** Data on file. Regeneron Pharmaceuticals, Inc.

09/2021
EYL.21.09.0005

EYLEA® (aflibercept) Injection
For Intravitreal Injection

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

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

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

4 CONTRAINDICATIONS

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

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

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

5 WARNINGS AND PRECAUTIONS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

8 USE IN SPECIFIC POPULATIONS

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

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

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

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

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

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

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

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

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two robotic arms that allow the user's wrist seven degrees of freedom.[6] Though this type of platform is the largest, it has a head-mounted apparatus that attaches to most eye surgery beds and can be easily integrated into the operating room flow.

In the lab

Given their similarity to human eyes, porcine models have often been used in laboratory studies of new robotic-assisted platforms. In early studies, the IRISS platform demonstrated excellent efficacy with multiple vitreoretinal maneuvers, including core vitrectomy with posterior vitreous detachment induction, as well as cannulation of a retinal vein, without complications.

Other non-retinal procedures were also tested, including continuous curvilinear capsulorhexis and lens cortex removal.[7] In *ex-vivo* porcine eyes, the Preceyes platform demonstrated excellent fidelity in subretinal injection procedures when measured with real-time intraoperative optical coherence tomography. It achieved successful bleb creation in 100 percent of eyes using robotic assistance compared with 40 percent using manual delivery. Bleb leakage occurred in all manual cases, compared to only 20 percent of robotic-assisted procedures[7] (*Figure 2*).

Leakage is of extreme importance in subretinal therapy, which requires precise dosing of very expensive medications. Intraocular inflammation can also result from excessive escape of the agent into the vitreous.

This same robotic platform demonstrated reproducibility with cannulation of retinal veins when compared to manual attempts, with successful cannulation in 100 percent vs. 46 percent of porcine eyes in robotic-assisted and manual procedures, respectively.[8] Repeated cannulation of the same entry point was also demonstrated to be reliable. These studies show that vitrectomy with cannulation of retinal vessels or subretinal drug delivery can be reliably achieved with reduced efflux of subretinal medication and reproducible cannulation of the microvasculature.

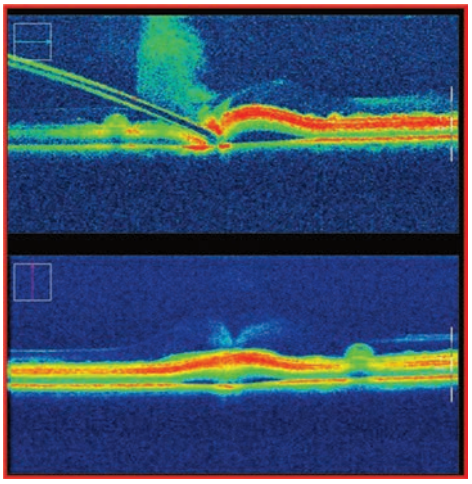

Figure 2. Subretinal bleb creation as measured by intraoperative optical coherence tomography during a manual procedure. Of note, on needle retraction, 100 percent of porcine eyes were shown to have efflux of subretinal injection, likely due to surgeon tremor.

In-human experience

The report of the first-ever successful human clinical trial with robotic-assisted vitreoretinal surgery was published by Thomas Edwards and colleagues at Oxford University John Radcliffe Hospital in 2018.[2] They used the Preceyes telemanipulation platform in patients undergoing 23-gauge macular surgery. They randomly assigned six patients to manual or robotic-assisted macular hole repair under general anesthesia. Patients were enrolled for epiretinal membrane or internal limiting membrane peel based upon preoperative clinical appearance and OCT morphology.

An additional six patients with submacular hemorrhage were recruited for pars plana vitrectomy with subretinal tissue plasminogen activator (tPA) injection, also randomized to manual or robotic-assisted intervention. Each surgery used intraoperative OCT (Rescan 700, Carl Zeiss

Porcine model studies show that robotic-assisted vitrectomy with cannulation of retinal vessels or subretinal drug delivery can be achieved reliably with reduced efflux and reproducible cannulation.

Meditec) for real-time assessment of residual membrane while peeling during macular hole repair, or to confirm delivery into the correct anatomic compartment during subretinal tPA injection.

For macular hole repair, times of surgery and flap creation were longer in the robotic group, but showed a trend toward reduced retinal microtrauma compared with manual surgery.[2] While the difference wasn't statistically significant, the number of subjects was small. The consensus of the surgeons involved was that with experience, the time to flap creation will drastically shorten, and that the trend toward reduced retinal trauma shows great promise in terms of improved clinical outcomes in the real world.

A second arm of the same study looked at subretinal macular hemorrhage patients who underwent subretinal tPA injection with air-fluid exchange under monitored anesthesia. All patients in both robotic and manual groups had successful subretinal bleb creation and postoperative displacement of hemorrhage. The investigators also successfully employed the "return to stored position" feature of the robotic system to return to a previously created microretinotomy for reinsertion of a microcatheter.[2]

Experienced vitreoretinal surgeons will be hesitant at first to employ this nascent technology for cases they're comfortable performing using traditional manual techniques.

Revolutionizing medication delivery

This feature of the technology promises to revolutionize medication delivery into microscopic spaces by eliminating undue trauma due to creation of false tracks, widening of the primary injection site, or injection into the wrong anatomic compartment with repetitive maneuvers. Reduction of tremor magnitude will also play a major role in the safety and efficacy of subretinal interventions, with less potential for unintended sub-RPE delivery or accidental retraction of the catheter leading to inadvertent efflux of medication. Additionally, repeated cannulation into the microvasculature will be accurate and reproducible, as laboratory research has demonstrated.[8]

Figure 3. The fourth generation da Vinci surgical robot. (*Intuitive Surgical*)

Another randomized controlled trial for submacular hemorrhage demonstrated similar times for delivery of subretinal tPA between manual (6.7 minutes) and robotic (7 minutes) intervention, with no significant difference between postoperative displacement of hemorrhage or visual acuities.[9] In this study, three separate training sessions were specified for surgeons and operating room staff, possibly contributing to the similar operating times between study groups. This suggests that efficiency in using the Preceyes system for performing delicate procedures improves with experience.

Potential barriers to implementation

A number of challenges remain before widespread adoption of robotic-assisted surgery can take place. Many experienced vitreoretinal surgeons will be hesitant at first to employ this nascent technology for cases they're currently comfortable performing with traditional manual techniques. Studies of robotic surgery in other fields such as gynecology have shown that only about 6 percent of patients surveyed preferred robotic-assisted surgery, mostly due to their perception of the speed of the procedure. Most patients had no preference (66 percent), while the rest preferred standard laparoscopic surgery (27 percent).[10]

Cost may also be prohibitive for many surgical centers, considering that other established platforms

such as da Vinci (Intuitive Surgical) cost up to $2 million and are far too large for ophthalmic use (*Figure 3*).

With decreasing reimbursements for many ophthalmic procedures, smaller surgical centers may not yield to pressure to integrate robotic platforms into the operating room. Additionally, training vitreoretinal surgeons to use these platforms will require an investment of time and resources that may not be available outside of tertiary referral centers.

Despite these challenges, it's clear that vitreoretinal surgery is headed toward even more delicate microscopic procedures with increased demand for better patient safety metrics and outcomes, paving the way to increased acceptance and utilization of robotic-assisted platforms.

Future applications

In light of recent developments in subretinal therapeutics, combining robotic-assisted platforms and intraoperative image-guidance appears to be the logical next step toward achieving advanced surgical maneuvers beyond the capability of manual techniques.[11]

Intraoperative OCT is already established in manual surgery. Its uses range from assessing residual membrane or hyaloid in macular pucker surgery to providing immediate feedback during bleb creation in subretinal therapeutics.[7] Telerobotic systems such as Preceyes provide "return-to-position" functioning, which, when combined with OCT, has the potential to enable surgeons to repeat image-guided subretinal injections while reducing the risk of inappropriate depth penetration or excessive medication efflux from the subretinal bleb.[8,9,11]

Telehealth is an additional area of interest for robotic platforms. Surgeons could perform complex procedures in distant locations without the need to travel. With an on-site, well-trained surgical team, this could bring expert surgeons to areas of need without the logistical difficulties and time demands of international outreach programs. It may ultimately be more cost-effective than the overall cost of mobilizing entire surgical teams to remote environments.

Bottom line

The precision and accuracy possible with the use of robotic-assisted vitreoretinal platforms will help vitreoretinal surgeons to potentially access areas previously inaccessible within the posterior segment. Combined with new intraoperative imaging capabilities, this technology is potentially transformative for vitreoretinal surgery.

Considering today's rapidly evolving subretinal drug therapy developments, and the push for patient safety and operative efficiency in modern health care, surgeons will increasingly look to integrated surgical and imaging technologies to advance the field of vitreoretinal surgery. Robotic-assisted platforms are a promising advancement, offering stability and accuracy to extend the limits of human abilities and enhance our therapeutic options.

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Training vitreoretinal surgeons to use these platforms will require an investment of time and resources that may not be available outside of tertiary referral centers.

Two tales of DR progression

Clinical trials show encouraging outcomes for treating diabetic retinopathy progression, but the real-world evidence tells a different story.


Sasha Narain, BA


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By Sasha Narain, BA, Kapil Mishra, MD, and Ehsan Rahimy, MD

Take-home points

- The impact that newer diabetes drug classes and emerging technology for monitoring glucose levels have on diabetic retinopathy progression remains to be elucidated, as early evidence suggests certain medications may worsen retinopathy.
- Clinical trials appear to show improvement in DR progression with anti-VEGF therapy, particularly when treating pre-proliferative disease.
- Despite significant medical and technological advances in routine diabetes care, real-world retinopathy progression rates remain high.

Bios

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Concurrent with the strides achieved in treating diabetic eye disease with anti-VEGF therapy, systemic disease control has improved dramatically with emerging oral glucose-control therapies and, more recently, glucose monitoring technology. In diabetic retinopathy, some, but not all, of these advances have shown significantly improved outcomes in clinical trials, but in real-world studies, progression rates from nonproliferative to proliferative disease still remain high, similar to seminal historical studies.

These current real-world studies highlight the impact of current local therapies on retinopathy progression, although it's important to recognize the limitations of big-data analyses before extrapolating conclusions regarding treatment and optimal timing of intervention.

Of the millions of people living with diabetes, one in three have some form of diabetic retinopathy, and more than one in 10 have vision-threatening DR.[1] Understanding the rate of progression of non-proliferative DR without diabetic macular edema to proliferative DR (*Figure 1*) and baseline characteristics that predict progression, may inform optimal treatment strategies. Here, we report on take-homes from recent literature of DR progression in this age of anti-VEGF agents and next-generation diabetes management, and how that compares to historical evidence.

Early evidence of DR progression

DR progression has been well-documented in clinical trials for decades. In 1971, the Diabetic Retinopathy Study evaluated the effect of photocoagulation on DR.[2] This multicenter, randomized clinical trial found that photocoagulation for eyes with proliferative disease with either argon or xenon arc reduced severe visual acuity loss (visual acuity 5/200 or worse) by approximately 50 percent compared with no treatment after five years of follow-up.

The Early Treatment Diabetic Retinop-

athy Study (ETDRS), another landmark study, assessed the effect of laser photocoagulation (scatter or focal) on DR and severe visual loss (*Figure 2, page 34*).[3] In observed fellow eyes, 26.7 percent of eyes with baseline macular edema and less severe retinopathy developed high-risk PDR after five years, as did 61.3 percent of eyes with macular edema and more severe retinopathy.

DR progression and newer diabetes drugs

More recent studies have also given us the opportunity to understand fellow-eye progression, particularly in more updated treatment schema. Significant advances in medicine and technology have expanded patients' and retina specialists' capacity to manage diabetes.

Newer diabetes drug classes that target distinct pathways, such as the sodium/glucose cotransporter member 2 (SGLT2) inhibitors, dipeptydil peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) agonists, offer alternatives for patients who struggle to control blood sugar levels with traditional treatments.

Continuous glucose monitors, such as Dexcom G6 (Dexcom) and FreeStyle Libre (Abbott), and diabetes coaching platforms for behavior modification, including Livongo and Virta Health, aim to smoothly integrate diabetes management into patients' lives.

The effects of these advancements on real-time DR incidence, prevalence and progression rates aren't yet understood. For example, semaglutide (Ozempic, Novo Nordisk), an increasingly popular GLP-1 agonist used to achieve optimal glycemic control, has been associated with worsening of DR in the pivotal SUSTAIN-6 clinical trial.[4] In the study, retinopathy complication rates occurred in 3 percent (n=50) of the treatment group vs. 1.8 percent (n=29) of the control arm. The study authors postulated that this increased risk of progression was due to the rapidity and magnitude of blood glucose reduction from semaglutide.[5]

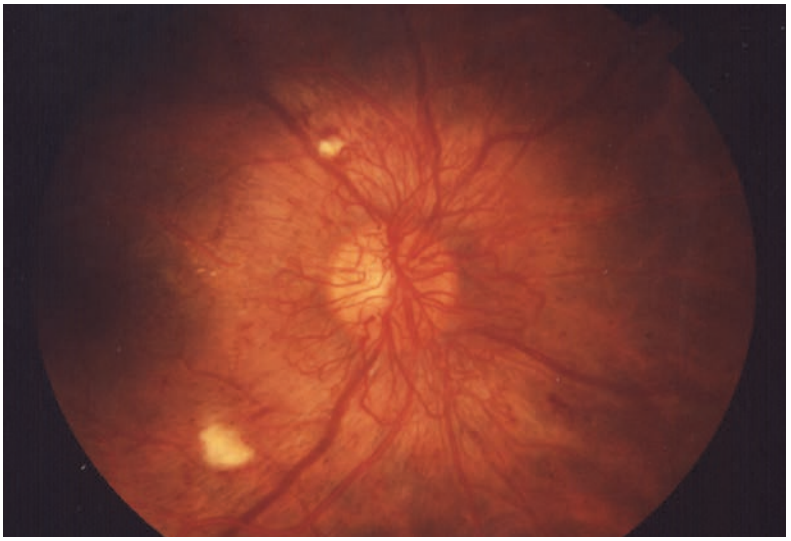

Figure 1. A classic presentation of proliferative diabetic retinopathy showing abnormal vessel growth. (*National Eye Institute*)

DR progression trends lower

A 2009 meta-analysis assessed the possibility of an effect of DR progression by more modern treatment strategies.[6] The meta-analysis included observational studies reporting the progression of DR to PDR and/or progression to severe vision loss at four-, five- and 10-year intervals in two different time periods: from 1975 to 1985; and 1986 to 2008. Analysis revealed that nearly 60 percent of studies reported progression to PDR and 35 percent reported progression to severe vision loss (SVL).

When stratified for time period, studies reporting outcomes after four years showed that 19.5 percent of patients in 1975–1985 developed PDR compared with only 2.6 percent in 1986–2008. Also in the earlier interval, 9.7 percent of patients developed SVL compared with 3.2 percent in 1986–2008. These trends were consistent with those seen for five- and 10-year outcomes.

When stratified by baseline DR status, PDR developed in 6.3 percent of participants without DR at baseline in 1975–1985 compared with 2.6 percent in 1986–2008. Likewise, 2 percent developed SVL in 1975–1985 vs. none in 1986–2008.

For participants with DR at baseline,

PDR developed in 39.7 percent in 1975–1985, and no studies reported progression to PDR during 1986–2008. Moreover, 17.5 percent of patients with DR at baseline progressed to SVL during 1975–1985, whereas 5.4 percent did so in 1986–2008.

The overall incidence of PDR and SVL observed in studies after 1985 were substantially lower than rates observed prior to 1985. These findings may be associated with the improvements in the overall care and management of diabetes, associated risk factors and earlier disease identification. One important limitation of this meta-analysis, however, is that baseline retinopathy was more severe in the earlier time period.

Anti-VEGF and DR progression

More recent clinical trials with fellow-eye data include the DRCR Retina Network Protocol W study, reported this year.[7] This study explored whether anti-VEGF intervention for severe non-proliferative disease can limit progression to PDR. Eyes with moderate to severe NPDR treated with aflibercept (Eylea, Regeneron Pharmaceuticals) experienced a more than two-fold reduction in the incidence of PDR, while showing no difference in visual acuity between aflibercept-treated and sham groups at two years. One third of sham eyes developed PDR after two years. Based on baseline severity, 68 percent of patients with severe NPDR developed DME or PDR after two years.

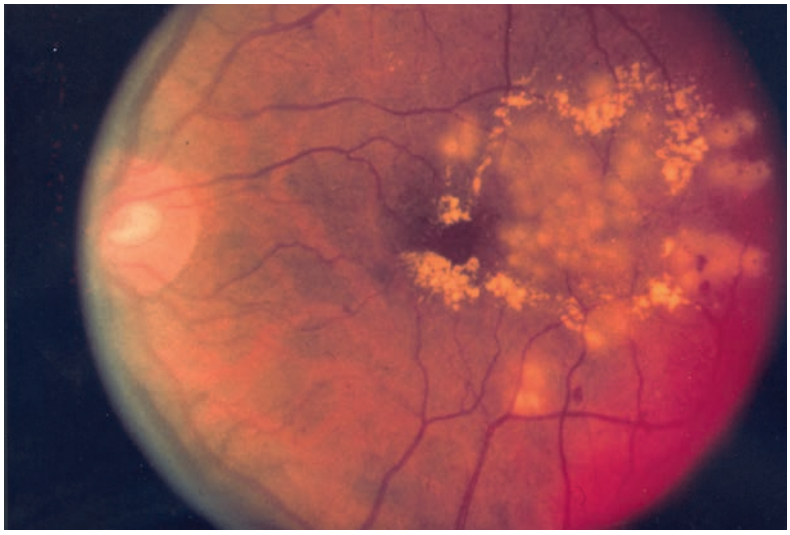

Figure 2. Diabetic retinopathy post-laser treatment, which has shown variable efficacy in arresting progression to proliferative disease. (*National Eye Institute*)

In the PANORAMA study, patients with diabetes and severe, treatment-naive NPDR were randomized into two different aflibercept regimens or sham.[8] Results showed that at week 52, the event rate for a two-step or greater worsening in Diabetic Retinopathy Severity Scale was 1.6 percent in the aflibercept 2q 16-week group and 0 percent in the aflibercept 2q 8-week/*pro re nata* group compared with 11.9 percent in the controls.

The event rate for worsening at week 100 was also significantly lower in aflibercept patients, and those treated every eight weeks had lower rates than patients on 16-week regimens. At week 100, worsening was observed in 4.5 percent of the 16-week aflibercept patients and 2.4 percent of their eight-week/PRN counterparts compared with 20.2 percent in controls.

Risk of two-step worsening of DRSS

The risk of a two-step or greater worsening of DRSS level was significantly reduced by 89 percent at week 52 and 81 percent at week 100 in the aflibercept 2q 16-week group and by 100 percent at week 52 and 93 percent at week 100 in the 2q 8-week/PRN group vs. controls. These results indicate that aflibercept treatment of severe NPDR may reduce the progression of PDR in certain patients.

With regards to disease already in the proliferative stage, Protocol S demonstrated that 70 percent of eyes treated with panretinal photocoagulation and 65 percent of eyes treated with intravitreal ranibizumab (Lucentis, Genentech/Roche), remained at a PDR level (DRSS $\leq$61), with no improvement to NPDR level following two years of treatment.[9]

These findings parallel those of the CLARITY study, in which 90 percent of

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20/79 VA

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

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eyes treated with PRP and 78 percent treated with intravitreal aflibercept remained at the PDR level and with no advancement to the NPDR level following one year of treatment.[10]

But in the real world …

As valuable as clinical trials are in understanding DR progression, population-based studies afford the opportunity to understand real-world data and possibly negate the higher patient compliance rates seen in clinical trials.

One study by Geeta Lalwani, MD, and colleagues graded DR severity on the ETDRS DRSS in almost 42,000 eyes of 22,000 patients with diabetes, from 1999 to 2016 using the Inoveon database of patients with diabetes who participated in a retina screening program at primary clinical centers.[11] The patients in the study were predominantly male (83 percent), while the ethnic distribution of the group was primarily Caucasian (50 percent) and Native American (41 percent).

The study found that 10 percent of all patients went on to develop a two-step DRSS worsening in five years. Patients with severe DR at baseline had higher incidence of two-step worsening. For patients with ETDRS DRSS scores of 43 to 53 and 47 to 53, almost 35 and 40 percent, respectively, had two-step DR worsening by year five.

Retrospective EMR database study

A separate study utilized the Vestrum Health database, which included electronic medical records from 251 retina specialists across the United States, to describe the natural history of disease progression from nonproliferative to proliferative DR in patients without DME at baseline.[1]

This retrospective analysis included 135,324 patients, with data collected between January 1, 2013, and June 30, 2019. At 24 months, the cumulative incidence of conversion to PDR across anti-VEGF-naïve eyes with mild, moderate, and severe NPDR was 4.2, 11.1 and 28.6 percent, respectively. By 48 months, the figures had risen to 7.9, 20.9 and 46.8 percent.

Separately, the incidence of DME development at 24 months in the mild, moderate, and severe NPDR groups was 14.7, 33.7 and 44.1 percent. By 48 months, the proportion developing DME had grown to 27.1, 51.2 and 60.6 percent. Hence, the high proportion of patients with severe NPDR that progresses to PDR potentially introduces the opportunity for earlier anti-VEGF therapy rather than waiting for conversion to PDR.

The high proportion of patients with severe NPDR that progresses to PDR potentially introduces the opportunity for earlier anti-VEGF therapy rather than waiting for conversion to PDR.

Anti-VEGF and conversion rates

A separate arm of this study evaluated how anti-VEGF therapy may impact the progression of DR to proliferative disease. This part of the study included 10,142 eyes that received anti-VEGF and/or laser photocoagulation treatment prior to PDR conversion during the eligible study period.

The results demonstrated an increasing separation over time of conversion rates to PDR from mild to moderate to severe disease between patients who received anti-VEGF treatment and those who didn't. The cumulative incidence of conversion to PDR ranged from 7.4 to 14.5 percent in patients with mild NPDR across treatment groups at 48 months, with the lowest incidence being in eyes that received prior anti-VEGF therapy (7.4 percent).

Similarly, for the moderate NPDR group, the conversion rate to PDR ranged from 11.6 to 20.9 percent at 48 months, with the lowest risk in the group receiving anti-VEGF therapy (11.6 percent), and the highest risk in the treatment-naïve group (20.9 percent).

Finally, in the severe NPDR group, progression to PDR ranged between 25.4 and 50.2 percent at 48 months. The highest risk of progression was in eyes with severe NPDR that had received prior laser but no anti-VEGF treatment (50.2 percent) and those that were entirely treatment-naïve (46.8 percent).

There was then a substantial separation

from the remaining groups, where conversion rates to PDR was the lowest in anti-VEGF treated eyes: anti-VEGF plus laser (25.4 percent); and anti-VEGF monotherapy (27.5 percent).

Bottom line

Taken together, when left untreated, nearly half of all eyes with severe NPDR progressed to PDR within four years in routine clinical practice. Baseline NPDR severity was a strong predictor of progression to PDR, consistent with previously published studies.

These recent findings are nevertheless significant, because they suggest that even with the significant medical and technological advancements that have been incorporated in routine diabetes care, real-world progression rates are similar to historical clinical trials from a different time period.

Several important questions still exist regarding DR progression in the modern era. How will anti-VEGF therapy for severe NPDR affect real-world progression rates and retina specialist practice patterns? If further data show differences in how oral medications influence DR progression, will ophthalmologists play a role in guiding systemic management? Understanding newer systemic therapies may become even more crucial for today's retina specialist.

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Five things to know about biosimilars in retina

A primer on the review and approval processes as the first anti-VEGF biosimilar prepares for launch in 2022.

Sonia T. Oskouei, PharmD

By Sonia T. Oskouei, PharmD

Take-home points

- The first biosimilar in ophthalmology, Byooviz, which references Lucentis (ranibizumab), is scheduled to launch in summer 2022.
- The data requirements for the regulatory approval of biosimilars differ from those for reference biologics, but biosimilars still have equivalent safety and efficacy standards for approval.
- Biosimilars in retina lack robust global reference data, but the United States has the opportunity to lead in this space and capture data and real-world evidence that can be referenced around the globe.
- Market research shows some hesitancy about and unfamiliarity with biosimilars among ophthalmologists, which follows trends in other specialties in which biosimilars are now well-established.

In September the Food and Drug Administration approved Byooviz (ranibizumab-nuna, Samsung Bioepis/Biogen), the first ophthalmology biosimilar referencing Lucentis (ranibizumab, Genentech/Roche) to treat retinal conditions including neovascular age-related macular degeneration. This landmark approval is anticipated to expand treatment options with lower-cost, high-quality therapies for the approximately 11 million Americans diagnosed with AMD.

While the Biden Administration has pushed for more biosimilar education and options to create competition and lower drug prices in the United States, some physicians remain cautious, with early market research indicating ophthalmologists may be among the most hesitant.

As Byooviz prepares to launch next summer, retina specialists and ophthalmologists will have more treatment options than ever before, including current on-label use of branded biologics, off-label use of bevacizumab (Avastin, Genentech/Roche), and biosimilars, as well as potential novel treatment options anticipated to enter the market. In preparation for these market advancements, here are five things to know as retina biosimilars come to market:

1 Biosimilars are safe and effective

A biosimilar is an FDA-approved biologic that is highly similar to, and as safe and effective as, an existing FDA-approved biologic, known as the reference product. Like generics, biosimilars are expected to produce the same clinical result as a reference product, but at a lower cost. However, unlike small-molecule generics that are manufactured from chemical compounds and identical to their reference product, biologics are large, complex molecules manufactured from living cells. Therefore, they can't be identically replicated, hence the

Bio

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DISCLOSURES: Dr. Oskouei is an employee of Cardinal Health.

term "biosimilar."

The data requirements for biosimilars differ from those for reference biologics, but this doesn't mean that biosimilars have lower approval standards. The FDA requires biosimilars to meet rigorous approval standards, which means patients and healthcare professionals can be assured of the safety, efficacy, and purity of biosimilars just as they would the reference products.

Since the first biosimilar approval in the United States in 2015, there are now 31 FDA-approved biosimilars referencing 11 originator products. They span multiple therapeutic areas including oncology, rheumatology, diabetes and now ophthalmology. Twenty of the 31 approved biosimilars are officially on the market, with the remaining products pending launches primarily due to patent litigation settlements between the brand and biosimilar companies.

2 Biosimilars are approved via a separate regulatory pathway

Through the Biologics Price Competition and Innovation Act enacted in 2010, an abbreviated approval pathway (351k BLA) was established for biosimilars to offer patients lower-cost, high-quality products. The biosimilars approval pathway essentially created a paradigm shift as to how providers evaluate the products, given that the data package required for biosimilar approval differs from what's traditionally required of originator biologics.

The goal of an originator biologic approval pathway (351a) is to establish standalone safety and efficacy, which results in the greatest regulatory weight being placed on the clinical studies. However, with the biosimilars approval pathway (351k), the greatest regulatory weight is put on the physiochemical characterization of the molecule since the goal of the pathway is to establish a high level of similarity with the originator biologic. This can result in a single, confirmatory clinical study conducted for the biosimilar in the most sensitive population to address any residual uncertainty after completing all other product analyses.

Once a high level of similarity is established with the originator biologic in terms of safety, efficacy and potency, extrapolation can occur. Extrapolation refers to the approval of indications held by the reference biologic without conducting additional clinical studies. Although the concept of extrapolation is not entirely new for biologics[1]–as it has been used for several years when originator biologics undergo manufacturing changes–the lack of familiarity with overall regulatory terms and the approval pathway associated with biosimilars can create hesitation among various stakeholders.

3 Ophthalmic biosimilars have the potential to alleviate financial burden associated with retinal conditions

Latest estimates reveal that overall savings from biosimilars could exceed $100 billion by 2024.[2] With an average discount range of 15 to 30 percent for the biosimilars thus far, these agents are expected to bring cost savings to some of the most common treatment options for retinal disorders, including AMD. PlatformQ Health has estimated that the U.S. economic burden from direct health-care costs due to AMD is $4.6 billion.[3] Through increased competition,

The data requirements for biosimilar approval differ from those for reference biologics, but this doesn't mean that biosimilars have lower approval standards.

biosimilars have the potential to alleviate some of the financial burden associated with current anti-VEGF therapies, enhancing accessibility and affordability of these critical treatments for patients.

4 Biosimilars may be met with caution in ophthalmology

Our own research from early 2021 indicates that ophthalmologists were hesitant to prescribe biosimilars.[4] Survey responses from 75 U.S. ophthalmologists revealed that 24 percent said clinical trials conducted on biosimilars are not appropriately powered to evaluate their efficacy and safety, and 35 percent have very limited knowledge of clinical trial design for biosimilars.

When asked about primary concerns with prescribing biosimilars once available, "uncomfortable from a clinical standpoint" and "payer coverage concerns" were equally rated as the top answers across all respondents. Both clinical and financial considerations were overall themes in the research, with the leading decision criteria for using an anti-VEGF biosimilar being "clinical studies and real-world evidence," followed by "cost/price discount."

Another factor that may uniquely impact ophthalmology biosimilars is the lack of international real-world data. In oncology and rheumatology, biosimilars were approved and available in Europe well before the United States, meaning that U.S. providers could access more than 15 years of combined real-world data when the products were approved by the FDA. However, because the FDA approval of Byooviz is one of the first ophthalmic biosimilar approvals globally (following European approval weeks earlier), providers and other stakeholders won't have the robust international data to reference. Rather, the United States has the opportunity to serve as leaders in this space and capture data and real-world evidence that can be referenced around the globe.

Additionally, the current prevalent off-label use of Avastin (bevacizumab, Genentech/Roche) is another consideration that will likely influence adoption decisions around the ranibizumab biosimilar. The intraocular use of compounded bevacizumab began while anti-VEGF drugs like ranibizumab were under development and has now been used for more than a decade.

Off-label bevacizumab's safety and efficacy were shown in early studies and is now backed by several years of data. It's one of the most commonly used anti-VEGF agents in AMD, and at a fraction of the cost of other treatment options. Therefore the pricing strategy (and the extent of discount), as well as payer contracts for the ranibizumab biosimilar will likely play a significant role in adoption.

Depending on the overall economic profile, the biosimilar could influence not only treatment decisions with the originator biologic, but also potentially current treatment decisions with compounded, off-label bevacizumab, other existing anti-VEGF agents, or even additional novel treatment options anticipated to come to market within the next year.

Overall, early insights gained with ophthalmologists on biosimilars are comparable to the market research findings with oncologists and rheumatologists prior to the first biosimilar approval in their respective areas. Past experiences can be leveraged to understand the types of considerations that go into adopting biosimilars, and proactive steps can be taken to address potential knowledge gaps before the launch of the first ophthalmic biosimilar.

5 Providers educating themselves about biosimilars is critical

Building awareness and understanding among providers and other key stakeholders will be key to biosimilar adoption in ophthalmology. As our research earlier this year revealed,[4] most providers lack familiarity and comfort with biosimilars,

(Continued on page 50)

Our own research indicates that ophthalmologists were hesitant to prescribe biosimilars. Twenty-four percent said clinical trials conducted on biosimilars are not appropriately powered to evaluate their efficacy and safety.

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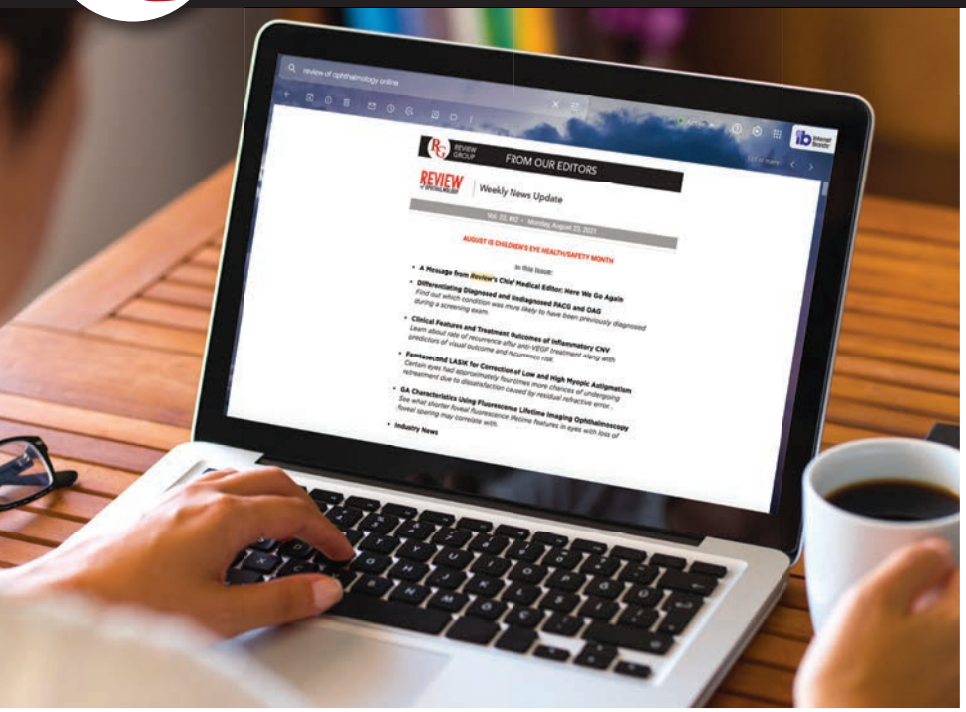

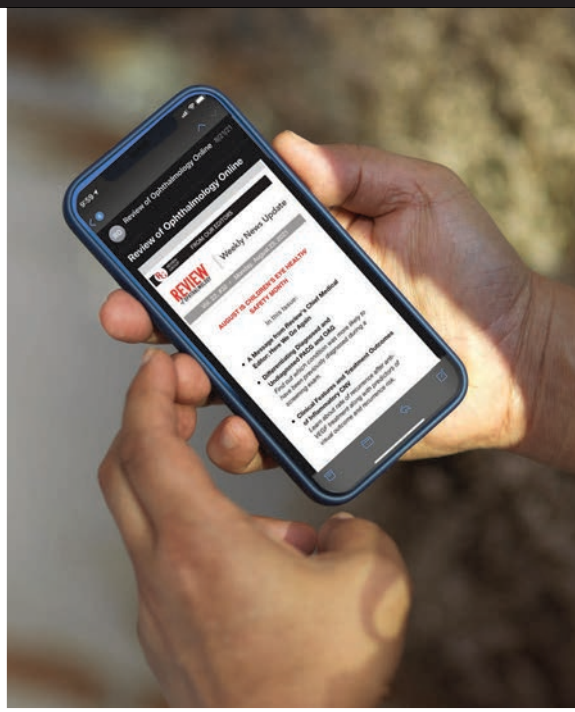

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REVIEW OF OPHTHALMOLOGY Weekly News Update

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AUGUST IS CHILDREN'S EYE HEALTH/SAFETY MONTH

In this Issue:

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A message from *Review*'s Chief Medical Editor, Mark H. Blecher, MD: Here We Go Again

I am, like most of you, totally over COVID. But as the cliché saying goes, "COVID isn't over us," which was mildly funny until it wasn't. We had a small happy window of normalcy this spring when marginally successful vaccinations caused the infection rate to plummet. The sun started to shine again ... and then it was gone. The smug satisfaction the vaccinated among us enjoyed was

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Mixed results in DME, PDR hemorrhage, ROP

Five abstracts on gene therapy and role of central subfield thickness in diabetic macular edema, vitreous hemorrhage and retinopathy of prematurity.

By Ashkan M. Abbey, MD

Ashkan M. Abbey, MD

Take-home points

- A post-hoc analysis of DRCR Research Network Protocols T and V showed that wide fluctuations in central subfield thickness in patients with diabetic macular edema may lead to worse vision.
- DME patients treated with ADVM-022 had significantly higher rates of intraocular inflammation than those treated with aflibercept.
- Early results from the ALTITUDE trial of RGX-314 in DME showed a 33 percent improvement in Diabetic Retinopathy Severity Scale.
- Aflibercept and vitrectomy/panretinal photocoagulation yielded similar two-year outcomes in patients with vitreous hemorrhage from proliferative diabetic retinopathy.
- A retrospective case series identified characteristics of infants in whom anti-VEGF treatment for retinopathy of prematurity failed.

The 39th annual scientific meeting of the American Society of Retina Specialists returned to a live format last month, albeit with a virtual component, after last year's all-virtual meeting. Despite the challenges of travel during the pandemic, retina specialists from around the world managed to converge on San Antonio.

Here, we present five notable abstracts from the meeting: a post-hoc analysis of DRCR Research Network Protocols T and V; results of the INFINITY Phase II trial of the one-time gene therapy ADVM-022 in diabetic macular edema; early results from the first cohort enrolled in the ALTITUDE trial of another one-time gene treatment, RGX-314, also in DME; a comparison of two treatment regimens for vitreous hemorrhage in proliferative diabetic retinopathy; and a retrospective case series of anti-VEGF treatment failures in infants with retinopathy of prematurity.

Fluctuations in central subfield thickness in DME

A post-hoc analysis used databases from the DRCR Research Network's Protocols T and V to explore the question if large fluctuations in central subfield thickness in patients with diabetic macular edema lead to worse vision over time.[1] The answer is, they may.

The study included 1,197 eyes, 559 from Protocol T and 638 from Protocol V. All eyes had at least three CST readings and visual acuity recordings at one year. The primary outcomes were VA at one and two years for each protocol, with the patients grouped into quartiles, presenter Matthew Starr, MD, said.

The study found significant VA differences based on the standard deviation of CST quartiles for both protocols while adjusting for mean baseline VA, baseline CST, lens status, hemoglobin A1c and treatment arm.

Bio

Dr. Abbey is director of clinical research at Texas Retina Associates, Dallas, and a clinical assistant professor of ophthalmology at the University of Texas Southwestern Medical Center.

DISCLOSURES: Dr. Abbey is a consultant to Alcon, Allergan/AbbVie, Alimera Sciences, EyePoint Pharmaceuticals, Genentech/Roche, Novartis and Regeneron Pharmaceuticals.

The first quartile had the least fluctuation and served as the reference group. The fourth quartile had the greatest fluctuation.

In Protocol T, the difference between the first and fourth quartiles after one year was -1.61 Early Treatment Diabetic Retinopathy Study (ETDRS) letters (95% CI, -3.51 to 0.30, p=0.986) and -3.59 (95% CI, -6.17 to -1.00, p=0.0066) after two years.

In Protocol V at one year, the difference between the first and fourth quartiles was -3.04 ETDRS letters (95% CI, -4.18 to -1.91, p<0.0001). At two years, the difference was -2.35 letters (95% CI, -3.58 to -1.13, p=0.0005).

In Protocol V, a higher proportion of eyes in the first quartile received anti-VEGF treatment than in the fourth quartile, raising the question of whether treatment frequency needs to be increased or if dual therapy with corticosteroids should be considered.

Dr. Starr said the primary study takeaways are that greater fluctuations in macular edema appear to be associated with worse vision outcomes in DME patients; that this method of analyzing CST may provide better insight into VA outcomes; and that CST fluctuations and the role of therapeutic agents and/or treatment intervals that limit CST fluctuations warrant further study.

Dr. Starr, of Mayo Clinic, Rochester, Minn., has no relevant disclosures.

Intravitreal gene therapy for DME: Results of Phase II Infinity trial

Adverum Biotechnologies sponsored the Phase II INFINITY trial to evaluate ADVM-022,[2] a single-injection intravitreal adeno-associated virus 7m8 gene therapy designed to create an intraocular aflibercept biofactory to reduce treatment burden in DME. While Adverum had already decided to discontinue the DME program for ADVM-022, the company still presented trial results.

The trial enrolled 36 patients with newly diagnosed DME–that is, within six months of screening–and who had received up to two previous anti-VEGF injections in the study eye. The patients received either a standard-of-care bolus of aflibercept or a single intravitreal injection of ADVM-022 in one of two doses: low dose (2 x 10^{11} vg/eye) or high dose (6 x 10^{11} vg/eye). They were evaluated monthly for 48 weeks.

Presenter Charles C. Wykoff, MD, PhD, said the study was unmasked in May after a patient who had severe comorbidities in the higher-dose ADVM-022 group developed hypotony. Two additional cases that required surgery were reported later. The inflammation in the higher-dose patients may have been related to the comorbid nature of the study population. Both ADVM-022 arms had higher rates of serious ocular adverse events than the aflibercept arm.

All three treatment arms showed improvements in visual acuity, but after week 24 the high-dose ADVM-002 group had a drop-off that continued through week 34. CST improvements were observed in all three arms with no meaningful differences. At weeks 12 and 24, more patients in the gene therapy arms also showed two- and three-step improvement in Diabetic Retinopathy Severity Scale compared to the aflibercept arm.

The rates of nonocular adverse events were similar between the arms, but 20 of 25 patients in the ADVM-022 arms developed anterior intraocular inflammation, three developed posterior IOI, and 15 had an iris-related event.

Notably, the OPTIC trial of ADVM-022 in patients with neovascular age-related macular degeneration demonstrated an acceptable safety profile while reducing the need for anti-VEGF injections by more than 80 percent while stabilizing central subfield thickness. Evaluating the differences in safety profiles between the two studies is a focus of ongoing research. Meanwhile, while Adverum has discontinued the program in DME, it's still investigating the lower dose in nAMD.

While Adverum had already decided to discontinue the DME program for ADVM-022, the company still presented INFINITY trial results.

Dr. Wykoff, is a partner in Retina Consultants of Texas and deputy chair of ophthalmology at Blanton Eye Institute, Houston. He is a member of Adverum Biotechnologies' scientific advisory board, and serves as an investigator for and receives grants from the company.

Early first-cohort results of suprachoroidal gene therapy for CI-DME

The Phase II ALTITUDE study is evaluating another single-administration gene therapy, RGX-314 (RegenxBio) in patients who have diabetic retinopathy without center-involved DME. RGX-314 is administered into the suprachoroidal space and uses the NAV AAV8 vector to deliver a soluble anti-VEGF fab transgene to provide continuous anti-VEGF expression.

Dennis M. Marcus, MD, reported on 20 eyes that have been enrolled in the first cohort of the study.[3] At three months, the rate of DRSS improvement in the RGX-314 group (n=15) was 33 percent vs. zero percent in the observation group (n=5). In the observational group, three patients had no change in DRSS, one patient had a one-step improvement and one had a two-step worsening. Among the RGX-314 patients, four had no change, three had a one-step improvement, four a two-step improvement and one a four-step gain. Three RGX-314 patients had a worsening of DRSS, two by one step, and one by two steps.

The treatment was well-tolerated, Dr. Marcus said. One vitreous hemorrhage occurred in a fellow eye. Common adverse events included conjunctival hyperemia and hemorrhage, which were predominantly mild and weren't considered to be drug-related. One case of mild episcleritis, reported two weeks after suprachoroidal administration of RGX-314, resolved with topical corticosteroids.

The overall early results of ALTITUDE fall within the range of three-month results of DME trials of aflibercept and ranibizumab, Dr. Marcus said. In a subgroup of RGX-314-treated patients with DR levels of 47 to 53, 43 percent had a two-step improvement in DRSS.

The overall early results of ALTITUDE fall within the range of three-month results of DME trials of aflibercept and ranibizumab in DME.

ALTITUDE is enrolling Cohorts 2 and 3 using a dose level of 5 x 10^{11} GC/eye with NAb- and NAb+ patients.

Dr. Marcus is a vitreoretinal surgeon at Southeast Retina Center in Augusta, Georgia. He is a consultant to and receives research grants from RegenxBio.

Aflibercept vs. vitrectomy/PRP for PDR hemorrhage

A vitreous hemorrhage from proliferative diabetic retinopathy can cause acute vision loss. Hani Salehi-Had, MD, reported results of DRCR Retina Network Protocol AB that compared two treatment plans: vitrectomy with panretinal photocoagulation, with aflibercept *pro re nata* (n=105); or 2-mg aflibercept with vitrectomy PRN (n=100).[4] Ninety-six percent of eyes in the aflibercept group and 85 percent in the vitrectomy group completed the two-year study.

The vitrectomy/PRP group had surgery within two weeks of randomization and, in the event of recurrent vitreous hemorrhage, received two monthly aflibercept injections and additional injections every four weeks as needed. The aflibercept group received injections at baseline and every four weeks up until week 12, with an evaluation at week 16 to defer injections if the therapy succeeded or for vitrectomy if the VH persisted. All participants had visits at weeks four and 12, then every 12 weeks out to two years.

Dr. Salehi-Had noted that mean visual acuity at 24 weeks was similar between the two groups, slightly favoring the vitrectomy group by 5 letters (p=0.06). Mean visual acuity at four weeks was 20/100 in aflibercept group and 20/63 in the vitrectomy/PRP group (p=0.003).

Mean visual acuity at 24 weeks and two years was 20/40 in each group. At 24 weeks, 70 percent of the aflibercept patients and

72 percent of the vitrectomy/PRP patients had ≥15-letter gains (p=0.99). At two years, those percentages were around 75 percent. On the loss side, 5 and 11 percent of patients lost ≥15 letters. Fewer patients in the aflibercept group had DME at 24 weeks, but at two years the difference was negligible.

At two years, almost all vitrectomy/PRP patients had VH clearance vs. about 80 percent of the aflibercept patients (p=0.001). More aflibercept patients had recurrent VH. About one-third of patients in each group received the alternative treatment.

Dr. Salehi-Had, a vitreoretinal surgeon at Retina Associates of Southern California in Orange County, has no relevant disclosures.

Infants with ROP who fail anti-VEGF therapy

A retrospective case series sought to identify and describe characteristics of infants with retinopathy of prematurity who fail anti-VEGF therapy.[5] Lucy T. Xu, MD, presented results of 211 eyes of 112 babies treated with anti-VEGF as initial therapy for type 1 ROP from 2011 to 2019 at Children's Healthcare of Atlanta. The study received the ASRS Fellows Forum Award.

The study population included six eyes of three patients who had been referred to the institution after they failed anti-VEGF treatment at outside centers. The study analyzed 23 eyes of 15 patients who failed treatment and 194 eyes of 100 patients in whom treatment succeeded.

The study used four separate criteria for treatment failure: need for repeat anti-VEGF treatment or laser before post-menstrual age (PMA) of 50 weeks; recurrent-plus; recurrent Stage 3; or Stage 4 or 5 ROP at any PMA.

Twenty-two of the failed eyes received bevacizumab; one was treated with ranibizumab outside the institution. The study found no association between treatment failure and bevacizumab dose, and the median time to failure was 10.1 weeks. Three eyes had first failure after 50 weeks PMA.

The study also elucidated five different manifestations of initial treatment failure: recurrent stage 3 (n=13, 56.5 percent); recurrent plus (n=11, 47.8 percent); retinal detachment (n=5, 21.7 percent); vascular arrest in zone I (n=2, 8.7 percent); and vitreous hemorrhage (n=1, 4.3 percent).

In all, nine of the failed eyes had RDs, including the five that had them with initial treatment failure. Of the remainder, three had RD with the second failure, all ow which were previously treated with laser; and one with the third failure after previous combined intravitreal bevacizumab/laser treatment followed by laser treatment alone.

The median follow-up was two years. Eighteen eyes, including all RD eyes, had follow-up of six months or more. The retina was fully attached in all but one eye, and fixation behavior was present in 10 eyes–but in only two of nine eyes that had RD.

Dr. Xu noted that the most common manifestations of treatment failure were recurrent plus and recurrent Stage 3. Almost all of the eyes that failed anti-VEGF treatment ultimately had favorable anatomic outcomes and half demonstrated fixation behavior, she said.

Dr. Xu, a vitreoretinal surgeon with The Retina Group of Washington in the Washington, D.C., region, has no relevant disclosures. Study authors received funding from the National Eye Institute.

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At two years, almost all vitrectomy/PRP patients had VH clearance vs. about 80 percent of aflibercept patients. More aflibercept patients had recurrent VH.

Documenting IVI: Avoiding audit traps

Documentation of intravitreal anti-VEGF injections is key as Medicare puts them under the microscope.

By Ellen R. Adams, MBA

In the course of your usual retinal clinic, you undoubtedly perform numerous intravitreal injections. Intravitreal injections are now common to the point that they're under scrutiny by Medicare and other payers.

It's somewhat logical for Medicare to be interested in the procedure and associated drugs. In 2018, the most recent for which data are available, Medicare paid providers $2.9 billion for injections of aflibercept (Eylea, Regeneron Pharmaceuticals) and ranibizumab (Lucentis, Genentech/Roche). In 2017, Medicare paid a total of $9 billion to ophthalmologists, with IVI drug expenses accounting for more than 38 percent of that total. The sheer cost to the Medicare trust fund impels the Office of the Inspector General to carefully monitor physician billing for these drugs.

Documentation to avoid traps

To meet billing requirements for Medicare and most commercial payers, your medical record should include adequate information to support the charge. Before you begin the procedure, you must confirm that a minimum of 28 days has passed since the previous injection in the same eye. The likelihood of denial is high if you perform intravitreal injections more frequently than every 28 days. For Medicare you'll most likely need to appeal more frequent treatments with a letter of medical necessity. With that trap avoided, your clinic note should include:

- ***A surgical plan or order.*** This should include the drug name, the dosage, and the indication, along with the physician's signature.
- ***Medical necessity.*** This should include the diagnosis, indications, and changes to the patient's condition; diagnostic test results; and patient consent for the procedure and acceptance of risks.
- ***Documentation of physician informed consent.*** This should consist of the signed consent form for first-time injection; any change in medication or eye injected; and consent signed annually thereafter.
- ***For new patients***, why one drug was selected over other options.
- ***For established patients***, a description of how the patient is responding to therapy at each visit.
- ***The operative note***. This must include the volume and dose of the injected drug, the lot number and expiration date, as well as how much (if any) was wasted or discarded. A notation of "no drug was wasted" or "only manufacturer overfill was discarded" may satisfy a payer's requirement.
- ***A notation of any complications.*** Clear documentation of the complication, including medication errors—or, conversely, if no complications occurred—is in order. If the wrong medication was used, be sure to educate the patient and consider not submitting a claim to insurance. Your malpractice carrier can advise you on next steps if this occurs.

Of course, as with all documentation guidance, your chart note must be clear and legible.

Getty Images

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Bio
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The 28-day trap

Medicare and other payers base their policies in part on the Food and Drug Administration-approved indications. Ranibizumab specifies 28 days between doses. Although the package insert for aflibercept is worded more broadly, it states that dosing once every four weeks is the maximum frequency. (Of course, 4 x 7 = 28!)

Rather than attempt to count weeks, Medicare used the original approved anti-VEGF for ophthalmology (ranibizumab) as the standard for these drugs. Some Medicare carriers often apply the same requirement for intravitreal injections of bevacizumab (Avastin, Genentech/Roche), although there are no FDA guidelines for ophthalmic use.

What to do if you're audited

If Medicare or another carrier asks for documentation of injections, be sure you or a highly trained staff member reviews any requested charts before sending them. Include in the packet:

- ***Notes with the patient's name and date of service.*** They should appear on every page.
- ***Relevant history and prior treatments to support medical necessity.*** If a prior visit contains the physician's order for the treatment under review, be sure to send that note.
- ***Any diagnostic test results supporting the need for continued treatment***. Include tests even performed at a prior visit.
- ***The operative note***. Include all of the information cited earlier.
- ***Any relevant correspondence***. For example, include referral letters that support the therapy.

Never alter any records after receiving a request. However, you may want to supplement the records you send to give the carrier assistance with their record review. This supplement may include:

- ***Explanations of common abbreviations you use.***
- ***A signature.*** This consist of either a log (for paper records) and/or your electronic health record protocol for physician signatures in electronic medical record.
- ***The insurance coverage policy.*** This is especially important if the reason for the treatment is uncommon.

Also, if the drug was used off-label, consider including peer-reviewed articles supporting your use.

Better yet, just avoid the audit

Be sure you know how your utilization compares to national averages. If you bill a significantly higher percentage of IVI compared with your peers, there's a strong likelihood that you'll be audited. This doesn't mean you're doing anything wrong; it just means you need to be especially diligent with your documentation—and be prepared. Having a reliable, trained and independent staff member or peer perform regular internal audits is invaluable to ensure that your documentation is adequate and appropriate.

Also, write or modify policies and checklists to formalize your intravitreal injection procedures as vulnerabilities are exposed. And don't forget to attend periodic training for yourself and staff members.

It can be easy to fall into a routine and let protocols erode over time. Avoiding that trap is important. With proper documentation, your continued use of these vision-saving drugs will be paid appropriately and you'll avoid audit traps.

If Medicare or another carrier asks for documentation of injections, be sure you or a highly trained staff member reviews any requested charts before sending them.

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Beware of social media nightmares

The pitfalls of physicians failing to maintain professional ethics online.

By David R. P. Almeida, MD, PhD, MBA

A common question that I'm asked involves examples of physicians breaking bad on social media. Although we routinely delve into the strategic and operational components of physician use of social media, it can be challenging to execute these without realizing you may be jeopardizing your professional ethics.

State medical boards instruct physicians always to be aware of the potential consequences for online behaviors that violate accepted standards.[1] Today, in the moonlight of the Halloween season, we will emphasize this point with a couple of real-life horror stories.

Don't violate patient privacy

An emergency room doctor in Rhode Island was fired and reprimanded by the state medical board because of a Facebook post on a trauma patient that physician had seen in the emergency room.[2] Although the physician didn't include the patient's name explicitly, enough details were present that others in the community could identify the specific individual.

This physician violated privacy laws and contravened the objective of ensuring privacy for health information. The clear takeaway is that physicians can face civil or criminal penalties for disclosing identifying patient information even without the patient's name.

A picture is worth 1,000 words

At Stony Brook University Medical Center in New York state, a medical student was disciplined for posing–that is, making the thumbs-up gesture–next to a cadaver.[3] This insulting, insensitive, and idiotic action exemplifies how one can take an error in judgment and make it significantly worse by posting it on social media.

Quotable

It's critical to always maintain patient privacy and avoid perilous content such as discriminatory speech or misinformation.

Consider and contemplate any clinical photo, diagnostic image or medical video before immortalizing it by posting it on social media. Failure to do so can and will result in you being haunted by previous poor choices.

How to avoid your own social media nightmares

Although it may seem redundant, please remember that your online behavior–as a retina specialist, physician, or any other licensed health-care professional–should mirror your offline professional reputation.

Maintain your professional ethics online and err on the side of caution when posting content, whether images or videos. It's critical to always maintain patient privacy and avoid perilous content such as discriminatory speech or misinformation. RS

Bio

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Sustained-release sunitinib comes to retina

A closer look at the extension study of GB-102 for treatment of neovascular age-related macular degeneration.

By Richard Mark Kirkner, Editor

Like a number of anti-VEGF drugs that have been developed to treat retinal disease, sunitinib is a cancer drug. First approved in 2006 to treat renal cell carcinoma and imatinib-resistant gastrointestinal stromal tumors, it's now also indicated for pancreatic neuroendocrine tumors. The drug is a small-molecule pan-vascular endothelial growth factor antagonist.

Graybug Vision is developing intravitreal sunitinib as a twice-yearly treatment for neovascular age-related macular degeneration and recently reported data from a six-month extension study of the ALTISSIMO Phase IIb trial.

The trial initially evaluated 1- and 2-mg doses of the sunitinib malate candidate, known as GB-102, in two phases. The 12-month treatment phase, or core trial, compared both doses given at baseline and six months with bimonthly 2-mg aflibercept. After an interim safety analysis early last year demonstrated a higher number of particle-migration incidents in the 2-mg vs. the 1-mg group, Graybug halted development of the 2-mg formulation. ALTISSIMO patients who received the 2-mg injection initially were switched to 1 mg for the second dose.

Graybug previously reported 12-month results that showed patients in the GB-102 1-mg arm had a median time of five months to first rescue treatment, and 48 percent went at least six months before needing any rescue treatment. An additional analysis showed a 58-percent reduction in injection frequency after starting GB-102 compared to before trial enrollment.

Secondary endpoints included change in best-corrected visual acuity and central subfield thickness. However, the trial wasn't appropriately powered to determine noninferiority to aflibercept. The extension study enrolled 11 patients in the core trial's GB-102 1-mg arm.

Arshad Khanani, MD, AM, managing partner and director of clinical research and fellowship at Sierra Eye Associates in Reno, Nevada, and a clinical associate professor at the University of Nevada, answers questions about GB-102 and the ALTISSIMO extension study. Dr. Khanani is a consultant to and receives research support from Graybug Vision.

Q What's novel about the mechanism of GB-102?

A GB-102 is a sustained-released formulation of sunitinib. The thought is that inhibition of receptor tyrosine kinase blocks all VEGF signals. The tyrosine kinase is specific to VEGF receptors 1, 2 and 3, which blocks all VEGF signals–A, B, C and D, as well as placental endothelial growth factors.
The drug disperses through a sustained-delivery platform of microparticles. The drug is placed into these particles that are designed to degrade in six months, essentially decreasing the treatment burden to two injections.

Additionally, if GB-102 proves to be a pan-VEGF inhibitor, data from other trials shows that blocking VEGF C and D can also optimize visual acuity. Durability is the most important play here.

Q What's the key takeaway from the ALTISSIMO extension study?

A This was a six-month extended observation phase in which patients were monitored without additional treatment. They were seen every month for evaluation and to determine how long the dose they received six months ago lasts.

Fifty-eight percent of the patients who completed the core trial signed up for the extension study; 55 percent of them actu-

ally achieved at least 12 months of duration. The fact that it's lasting more than six months in half the patients is very intriguing. It needs to be looked into more. What are the characteristics of patients that make GB-102 last almost a year in some of them?

Q What would that involve?

A We need to look into the baseline imaging characteristics, including intraretinal and subretinal fluid, and pigment epithelial detachments as well as pre-trial injection frequency in the patients who needed fewer injections.

Q What can be taken from the Phase II findings to help inform the design of the Phase III trial?

A We need to determine the right population that can benefit from GB-102. Also, the formulation enhancement that the company has already started is important because there were still some levels of particle migration in the 1-mg treatment group in ALTISSIMO. Obviously, going from 2 to 1 mg was very helpful in terms of lowering the number of treatment-associated adverse events, but that's ongoing work.

Q Where would a longer-duration therapy such as GB-102 potentially fit in the retina specialist's toolbox?

A We have great treatments that work, but obviously, patients need to receive treatment anywhere from every four to eight to 12 weeks, and then maybe with faricimab up to every 16 weeks. In the real-world we know that undertreatment leads to vision loss. Can GB-102 help our patients go six months between injections? ALTISSIMO confirmed that that can happen in a subset of patients, and CST results were similar to aflibercept, but there was some reduction in BCVA.

Looking deeper into it, we saw that reduction in BCVA was primarily driven by six patients: two of whom were difficult to treat, two who had unrelated adverse events, and two with particle dispersion. We're continuing to learn what's the best population for GB-102, and the rescue criteria are evolving to optimize visual acuity.

Q What's next in the development of GB-102?

A Work is already under way to optimize the technology and the platform to preserve the durability of microparticles of 1-mg GB-102 while minimizing the risk of dispersion. A potential further innovation is maybe putting sunitinib in an injectable implant or in microparticles in a different platform. The ultimate goal is to optimize the technology and develop additional formulations to preserve the durability of microparticles while minimizing the risk of dispersion. RS

Quotable

The ultimate goal is to optimize the technology and develop additional formulations to preserve the durability of microparticles while minimizing the risk of dispersion.

Five things to know about biosimilars in retina

(Continued from page 40)

but there's a strong desire for more education. In fact, 82 percent of survey respondents noted that educational information about safety, efficacy and performance would help them achieve a greater understanding of biosimilars.

It's never too early to start the education process. By leveraging various resources to drive proactive educational efforts, providers will be able to evaluate biosimilars effectively and help champion the biosimilar education process moving forward.

The approval of the first ranibizumab biosimilar represents significant, and much needed, advancement in expanding treatment options for patients with debilitating retinal disorders.

Cost, payer coverage, clinical data, and education all play a critical role in the future use of biosimilars in ophthalmology. With the entrance of biosimilars and the potential approval of new innovator products, ophthalmologists will soon have a broader range of treatment options for delivering high-quality, affordable care to optimize patient outcomes. RS

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