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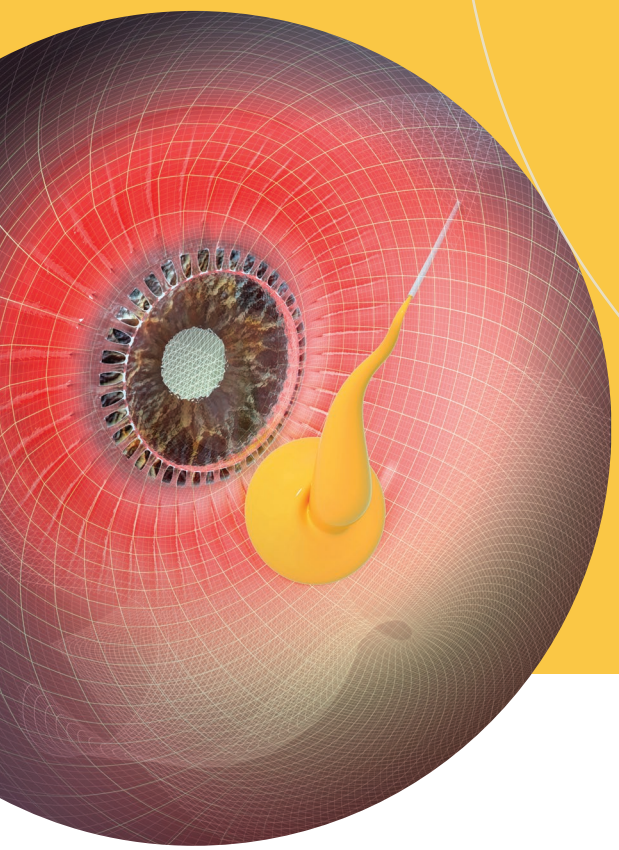

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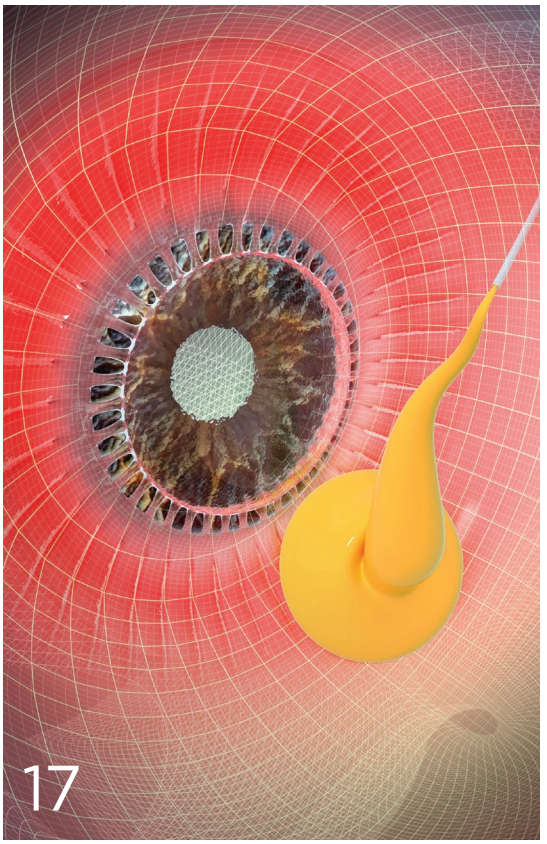

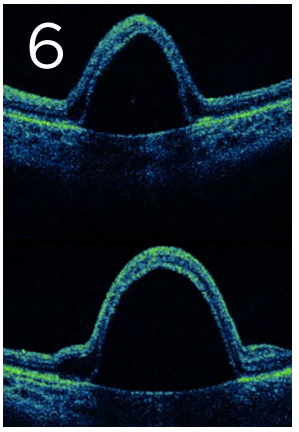

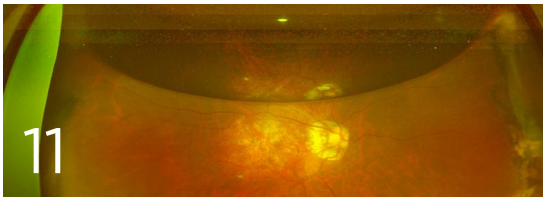

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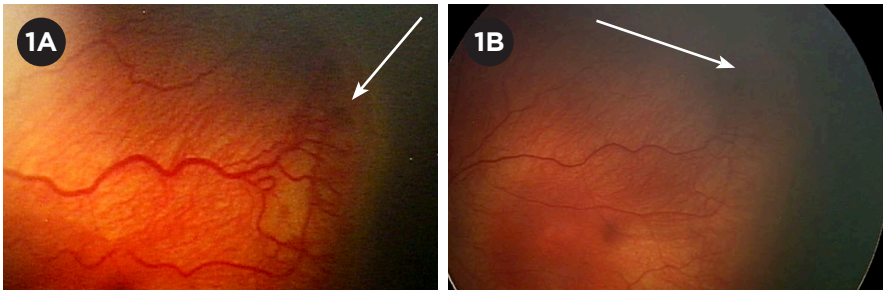
Fighting ROP With Anti-VEGF Therapy

In a major shift for pediatric ophthalmic care, drugs to inhibit aberrant intraocular angiogenesis have largely supplanted laser photocoagulation as first-line treatment for the most severe cases of retinopathy of prematurity (ROP).

"This is done fairly commonly now by many practitioners in the United States and throughout the world. It is becoming increasingly recognized and accepted, because it enables us to preserve the retina in children with very advanced zone 1 ROP or aggressive posterior disease," said Stephen J. Kim, MD, at Vanderbilt University in Nashville, Tennessee. "In the past, if you lasered these eyes at this stage, you would destroy much of their peripheral vision."



BEFORE AND AFTER. *In this case of stage 3 ROP, dilated tortuous vessels (plus disease) are evident before anti-VEGF treatment (1A). One week later, there is less tortuosity, reduced stage 3 ROP, and regrowth of physiologic vascularization (1B).*

Where We Are Now

Guidance on how and when to use anti-VEGF medications in ROP patients has emerged over the past several years from a few prospective clinical studies and some clinical trials comparing drug and laser treatment. (There also is an ongoing prospective, phase 1 dose de-escalation study sponsored by the Pediatric Eye Disease Investigator Group [PEDIG] and the NEI.[1]) And while most of the studies have investigated the use of bevacizumab (Avastin), attention to ranibizumab (Lucentis) has begun to rise.

Guidance statements. In 2017, the Academy's Ophthalmic Technology Assessment Committee (OTAC) reported finding Level II and III evidence in the literature that intravitreal therapy to inhibit VEGF is at least as effective as laser photocoagulation for achieving regression of acute ROP.[2]

And in an updated policy statement published in December, the American Academy of Pediatrics prominently included intravitreal anti-VEGF therapy among the recommendations for managing some types of ROP.[3] The statement was developed with representatives from the Academy, the American Association for Pediatric Ophthalmology and Strabismus, and the American Association of Certified Orthoptists.

Fear of systemic problems. The onset of off-label usage of VEGF inhibitors sparked concerns that circulation of the drugs elsewhere in the body might reduce systemic VEGF sufficiently to hamper organ development, and these concerns are still being debated today, said Amy K. Hutchinson, MD, at Emory University in Atlanta.

"There's a lot of controversy at the heart of this topic," Dr. Hutchinson said. "Some physicians are reluctant to use bevacizumab until more is known about its effects outside the eye on developing organs like the brain, kidney, and lungs. In addition, we are still studying bevacizumab to determine the smallest effective dosage to minimize such risks."

Residence time in the body. M. Elizabeth Hartnett, MD, at the University of Utah's John A. Moran Eye Center in Salt Lake City, said that the full-length antibody bevacizumab inactivates multiple VEGF isoforms and persists in the body for weeks. But, as a smaller antibody fragment, ranibizumab blocks fewer VEGF receptors and disappears from circulation faster, she noted.

"If you inject bevacizumab into the eye, it gets into the circulation and can be detected for several months after a

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BY LINDA ROACH, CONTRIBUTING WRITER, INTERVIEWING **M. ELIZABETH HARTNETT, MD, AMY K. HUTCHINSON, MD,** AND **STEPHEN J. KIM, MD.**

Melissa Chandler, CRA, OCT-C

single dose," she said. In contrast, preliminary data from a large, multicenter trial showed that serum VEGF levels in infants treated with ranibizumab returned to baseline within two weeks after a single intravitreal treatment,[4] she said. "Nonetheless, the studies suggest that more than one treatment with ranibizumab may be needed, and the repetition of use may extend the inhibition longer than the two weeks," she said.

"We need more information before advocating either drug for all types of treatment-warranted ROP. However, the evidence for zone 1 treatment-warranted ROP seems to favor consideration for anti-VEGF treatment," Dr. Hartnett said.

Variations in clinician preference. It is too early to know how the speed of anti-VEGF drug clearance from the body might affect safety or long-term outcomes of therapy, but on the premise that less systemic exposure is better, Dr. Kim prefers ranibizumab for treating ROP. "At Vanderbilt we have moved almost entirely to ranibizumab, and we generally avoid bevacizumab. The reasons are theoretical at this time but are based on ranibizumab's faster clearance and reduced chance for systemic inhibition of VEGF," he said.

In contrast, Drs. Hartnett and Hutchinson said they tend to use bevacizumab for zone 1 treatment-warranted ROP at a dose of 0.25 mg, or at lower doses as part of the PEDIG de-escalating dose study, for two reasons: 1) The literature on bevacizumab's effectiveness and apparent safety is deeper than it is for ranibizumab, and 2) bevacizumab is both cost-effective and widely available around the world.

A Look at Early Outcomes

Resolution and recurrence. Results from clinical trials have shown that a single intravitreal injection of either medication successfully resolved ROP in many eyes. But bevacizumab's greater potency compared with ranibizumab appears to result in fewer cases that required late retreatment for recurrent disease by six months postinjection.

For instance, in the RAINBOW trial (a randomized trial comparing low-dose ranibizumab with laser), preliminary analysis found that 31% of the ranibizumab infants had recurrent ROP requiring retreatment in the six months after the initial injection, Dr. Hartnett said.[4] That compares to a 23% retreatment rate at the same time point in children treated with bevacizumab during the ROP1 study.[5]

In addition, a study in 241 infants treated with bevacizumab found late reactivation of proliferative disease in 8.3% of the children, and retreatments had to be performed as long as 65 age-adjusted weeks after initial treatment.[6]

Anti-VEGF plus laser. "Given the risk of late recurrence of ROP with ranibizumab and loss to follow-up, we have a policy at Vanderbilt of performing laser treatment to avascular retina in all ranibizumab-treated eyes after normal retinal vascularization has ceased" and before the infants are discharged, Dr. Kim said.

More normal structure? Anti-VEGF therapy in eyes with zone 1 (the most posterior) ROP has a potential advantage over laser photocoagulation: the possibility that it can nondestructively enable healthy intraretinal blood vessels to mature and extend a bit across formerly avascular retina, Dr. Hartnett said. "Anti-VEGF offers an ability to extend normal retinal vascularization into zone 2 in some eyes. I think that's exciting," Dr. Hartnett said. Some case studies also suggest that anti-VEGF-treated eyes may be less myopic.[7]

Risk of avascular retina. Investigators in the CARE-ROP study have reported a high incidence of avascular retina in ranibizumab-treated eyes, Dr. Hartnett said. The rate was 84% in the higher-dose eyes, compared to 18% of eyes treated with bevacizumab in the ROP1 study.

"We can't directly compare these trials, of course, since they are not head-to-head studies and they had different enrollment criteria, [evaluated] different zones of disease, were from different regions of the world, and had different outcomes, but we can make observations about them." Nonetheless, she said, "We don't know what the observations mean in the long term." For instance, she said, "The avascular retina could stimulate VEGF and cause recurrent ROP. There also have been some reports of recurrent retinal detachment even up to 2.5 years after a single anti-VEGF treatment."

Difficulties evaluating developmental delays. To alleviate concerns about potential damage to the brain and other organs from systemic anti-VEGF exposure, researchers must find ways to tease out any VEGF-related anomalies from the natural history of prematurity, Dr. Hutchinson said.

"A handful of studies have been published with conflicting conclusions about whether bevacizumab is associated with poorer neurodevelopmental outcomes than laser. Since patients in these studies were not randomized, there is a strong potential for bias," she said.

Are Outcomes Improved?

The question of whether anti-VEGF therapy improves outcomes takes clinicians into unknown territory. Pediatric ophthalmologists are hoping that, as treated children enter their school years, normalized retinal structure will translate into better visual functioning than if they had been treated with laser monotherapy. But, like so much else in the anti-VEGF treatment field, this possibility remains to be demonstrated scientifically. "This is all anecdotal and theoretical," Dr. Kim said. "We don't know what will happen in five years or beyond with these children."

Dr. Hutchinson concurred. "I think most of us would agree that the published literature suggests that for zone 1 ROP, anatomical outcomes, recurrence rates, and rates of high myopia are better with bevacizumab than with laser. However, since we have not yet carefully studied retinal function in bevacizumab-treated eyes, we cannot say for certain that bevacizumab is the best treatment for zone 1 ROP," she said.

One of the first infants Dr. Hutchinson treated with bevacizumab is now 7 years old and appears to have overcome early developmental delays, she said. "He performed poorly on the Bayley infant skill and development test at age 2 and was labeled at having 'severe impairment,' but he is now excelling in school."

To progress beyond the anecdotal, it

would be helpful if future anti-VEGF trials for ROP included objective tests of retinal function, such as visual field and electrophysiological testing, Dr. Hutchinson said. "On the other hand, the longer we go without seeing obvious differences in the health and development in our formerly premature patients treated with bevacizumab, the more comfortable we start to feel," she said. But—as she acknowledged—"that might be a false sense of security."

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3 Fierson WM et al. *Pediatrics*. 2018;142(6). http://pediatrics.aappublications.org/content/142/6/e20183061. Accessed Jan. 9, 2019.
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6 Mintz-Hittner HA et al. *Ophthalmology*. 2016; 123(9):1845-1855.
7 Mintz-Hittner HA, Geloneck MM. *Eye Brain.* 2016;8:135-140.

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Dr. Kim is professor of ophthalmology and visual sciences, director of the ophthalmology fellowship program, and director of the Retina Division at Vanderbilt University in Nashville, Tenn. He also is chairman of the Academy's OTAC. *Relevant financial disclosures: None.*

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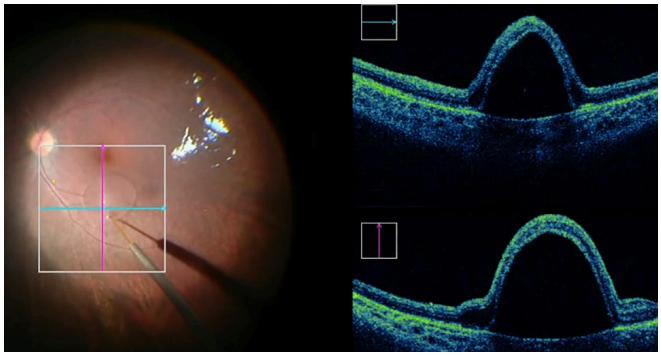
RPE65 Gene Therapy: A Report From the Clinic

Just weeks after Caspian Soto's birth, his parents started noticing something was awry: Their baby stared constantly at lights but avoided making eye contact. "We were new parents and weren't sure how concerned we should be," said his mother, Krista Soto. Then his eyes began to roll up and down, and his parents' worry increased.

After an emergency evaluation ruled out a tumor, an electroretinogram later spotted the telltale signs of Leber congenital amaurosis (LCA). Genetic testing confirmed that both parents carried a copy of a mutation in the *RPE65* gene and that Caspian was deficient in both copies. Caspian officially joined the 1,000 to 2,000 Americans with *RPE65* mutation–associated retinal dystrophy.[1] Without treatment, his prognosis was dim.

Fortunately, Caspian was a candidate for Luxturna (voretigene neparvovec-rzyl, Spark Therapeutics), approved in December 2017 for both LCA and early-onset retinitis pigmentosa (RP). In the fall of 2018, at the age of 4, he became one of the youngest patients to be treated with Luxturna, the first FDA-approved gene therapy for a genetic disease.

About two weeks after Luxturna treatment in the second eye, Caspian's parents began noticing some surprising changes in his ability to navigate his environment. His mother took him to a nearby children's museum to "test his vision." Together, they walked into an exhibit where LED stars dotted the ceiling. "He was so excited because he'd never been able to see anything like it," said Ms. Soto. "For an hour, we just lay on the floor together and looked up."



IN THE OR. *Subretinal delivery of voretigene with bleb visible with intraoperative video (left) and intraoperative OCT (right).*

How Luxturna Works

Approved for patients 12 months and older, Luxturna is an adeno-associated virus vector-based gene therapy that delivers a normal copy of the *RPE65* gene under the retina, said Ninel Z. Gregori, MD, at Bascom Palmer Eye Institute in Miami. The gene provides instructions for making an enzyme essential for normal vision, allowing retinal cells to function more normally.

"We don't treat the entire retina," said Steven T. Bailey, MD, one of the surgeons who treated Caspian at the Oregon Health & Science University (OHSU) Casey Eye Institute in Portland. "But we try to shore up central areas, where the treatment can be most useful."

Researchers hypothesize that earlier treatment is better because the retina is likely to have less severe damage, said Dr. Bailey. In phase 1 Luxturna trials, the final level of visual sensitivity was significantly better in 8- to 11-year-olds compared with 19- to 44-year-olds, said Dr. Gregori. "But in the phase 3 trial, even the most advanced patients had some improvement in vision."[2,3]

Before the Procedure

According to Spark Therapeutics, more than 35 patients have received treatment since FDA approval. Currently, the surgeries are done at only seven ocular gene therapy treatment centers, using a well-defined Spark protocol, said Dr. Gregori. The first step is to identify the best surgical candidates.

Confirm the diagnosis. "Other inherited retinal diseases [IRDs] can have a similar phenotype," said Dr. Bailey.

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BY ANNIE STUART, CONTRIBUTING WRITER, INTERVIEWING **STEVEN T. BAILEY, MD, NINEL Z. GREGORI, MD, CHRISTINE N. KAY, MD,** AND **KRISTA SOTO.**

Steven T. Bailey, MD

"So we need to ensure that we're targeting the right disease with this gene therapy. Genetic testing confirms that the patient is deficient in both copies of the *RPE65* gene."

Rule out poor candidates. It's also essential to select only patients who have viable retinal cells. "We use optical coherence tomography [OCT] to assess for viable cells during the patient selection process," said Dr. Gregori.

Arrange approval. "The manufacturer has a team of liaisons who help physicians communicate with patients, billing departments, and insurers to achieve approval," said Dr. Gregori, "but it's not an instantaneous approval process." The $850,000 price tag might have something to do with this.

Ms. Soto's first question was: How do we raise a million dollars? "In my wildest dreams, I never anticipated it would be covered by insurance," she said. And up until a few days before surgery, she didn't know what their out-of-pocket fee would be. In the end, their insurer covered most of the cost, and Spark covered the rest.

Begin steroids. Because injection of the virus puts the eye at risk for inflammation, patients are started on oral prednisone three days before surgery—21 days in total, said Dr. Gregori. Local corticosteroids are also used at the time of and after surgery.

The Procedure

The patient's eyes are treated on separate days, with a recommended minimum interval of six days. On the day of surgery, the pharmacy prepares two sterile syringes of the drug, said Dr. Gregori.

Choosing anesthesia. Depending on the patient, the procedure is done under general anesthesia or local anesthesia with IV sedation, said Dr. Gregori.

Visualize the vitreous. Although the vitrectomy has been tolerated quite well in these patients, surgeons have made certain alterations to ensure best outcomes, said Dr. Bailey. "For example, I've found that using a dilute Kenalog solution is useful for visualizing the vitreous and ensuring that we've successfully induced a posterior vitreous detachment."

Gently remove the vitreous. "With a 23- or 25-gauge vitrectomy, we remove the vitreous in a standard fashion," said Dr. Gregori. "Once we separate the gel from the retina, we're very cautious that we don't cause peripheral breaks or detachments when we remove the vitreous. Elevating the vitreous off the macula at the proposed injection site allows the needle to penetrate the retina without being caught on the vitreous." Removal of the sticky peripheral vitreous can be challenging in these eyes, she added, explaining that it is sometimes preferable to leave it, rather than doing a full vitrectomy and risking an iatrogenic retinal break.

Dr. Bailey emphasized that inspecting for any retinal breaks should not wait until the end of the procedure as with standard vitrectomies. "We perform scleral indentation to look for peripheral retinal breaks prior to the subretinal delivery of Luxturna. Because gene product in the vitreous cavity poses the risk of an inflammatory response, the idea is to limit ocular manipulations that may result in gene product escaping the subretinal space and entering the vitreous cavity."

Injection site and blebs. "Avoiding vessels, we go along the major arcade, but we must inject at least 2 mm from the fovea," said Dr. Gregori. "You can do this in one of two ways: Either inject Luxturna directly without elevating the retina, or first elevate the retina with a small subretinal balanced salt solution [BSS] bleb and then inject Luxturna into that space."

The second of these options is beneficial in two ways, said Dr. Bailey. "You're less likely to inject Luxturna into the vitreous cavity during initial bleb formation, and you can confirm the bleb is extending toward the fovea prior to injection. If the bleb moves away from the fovea, the surgeon can stop the injection and select one or more alternative sites to ensure the entire macula is treated," he said.

Observe with OCT. Dr. Gregori and Janet L. Davis, MD, pioneered the use of intraoperative OCT during a choroideremia gene therapy trial a few years ago. Now, surgeons use intraoperative OCT during Luxturna surgeries. (View a video from Dr. Gregori and Dr. Davis, "OCT-Assisted Delivery of Luxturna," at aao.org/clinical-video/oct-assisted-delivery-of-luxturna.)

With OCT in the OR, said Dr. Gregori, "we're able to confirm that we're injecting into the subretinal, rather than suprachoroidal, space. More important, the macula stretches with injection of this large volume of medicine, putting it at risk of a macular hole and loss of the virus into the vitreous cavity. We can observe any overstretching, wait a few minutes while the fluid is absorbed, and then inject more. Or we can form a second bleb to cover the seeing area, watching to confirm that a hole has not formed."

Intraoperative OCT also allows the surgeon to see how much pressure he or she is applying to the retina with the subretinal cannula during initial bleb formation, said Dr. Bailey.

Injection: manual or machine. In the Luxturna clinical trials, the surgeon had a surgical assistant manually inject 300 mL of the medicine, said Dr. Bailey. "We switched to a foot pedal delivery device because we found it can deliver the product in a slower, more controlled manner." With either method, the surgical assistant must give feedback to the main surgeon about the volume of medicine that has been injected, said Dr. Gregori. She added that both methods have their advantages, and surgeons may decide which they prefer.

Do an air-fluid exchange. An air-fluid exchange is recommended to remove any gene product that may be in the vitreous cavity to reduce the risk of an inflammatory response, said Dr. Bailey. "I have an assistant aim the infusion line more peripherally, not in the direction of the bleb," he said. "Otherwise, pressure from the infusion line may push Luxturna out of the retinotomy."

After the procedure, patients should avoid airplane travel until the air is reduced to 10% or less, which may take up to two weeks in eyes with retinal degeneration, said Dr. Gregori.

After the Procedure

Surgeons see these patients the first day, week, and month after surgery, at which point they are usually sent

back to the referring retina specialist, said Christine N. Kay, MD. She's a vitreoretinal specialist in Gainesville, Florida, who has sent three patients to Dr. Gregori and colleagues at Bascom Palmer. She sees these patients as needed postoperatively, typically right after they are released from their treatment center and one month, three months, and six months after treatment. "Spark also requests that patients return to the surgical treatment center at six months for repeat outcomes testing," she said.

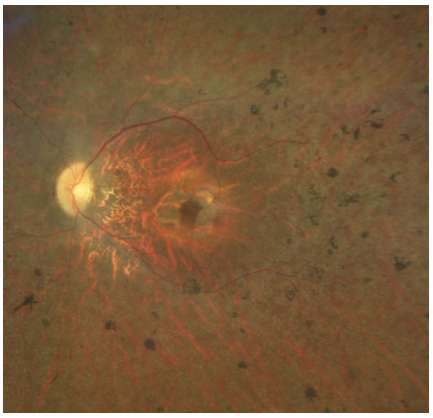
Tests and monitoring. The first postoperative visit includes checking vision and intraocular pressure and looking for inflammation, said Dr. Bailey. "With subsequent visits, we use OCT to make sure all subretinal fluid has been absorbed and to assess the retinal anatomy." Subsequent visits may include repeat visual fields and electroretinograms to assess the treatment effect, he said.

Potential complications. Patients continue with postop oral prednisone and corticosteroids drops on a relatively rapid taper over several weeks, said Dr. Bailey, and cases of inflammation have been minor so far. "As with any surgery, we worry about retinal detachment," he said. "We may assess the peripheral retina with ultrasound if an indirect ophthalmoscopy exam is too challenging to do in a young child." If retinal holes are visible, added Dr. Gregori, it's important to laser those right away.

Patients' Quality of Life

"I can't even describe how Caspian's life has changed," said Ms. Soto, explaining that he started preschool a couple of weeks after his treatment. "I no longer felt scared that he wouldn't be able to see the classroom space and be ostracized because of it. I didn't worry that he would feel 'othered' because of his headlamp [which he used to rely on before treatment]."

A time of transition. She hastened to add that Caspian still faces obstacles. For example, being reintroduced to social situations with improved vision has brought its own set of challenges, such as learning to read facial cues. At first, Caspian was scared about the adjustment, and he balked at letting go of his



TREATED EYE. *Fundus photograph of a patient with biallelic* RPE65 *mutations who received voretigene therapy in both eyes.*

headlamp and walking cane.

"Although patients are often much happier, there are many adjustments that come along with seeing better, such as being able to stay out later at night to play with peers and other social or behavioral considerations," said Dr. Kay. "It's important to help the patient and family navigate that process."

Visual sensitivity. Two patients Dr. Kay has seen postoperatively have experienced dramatic improvements in visual sensitivity. "Within two weeks of surgery, the 10-year-old had significant improvement in his ability to navigate in dimly lit rooms, play outside at night, and ride a bike home in the dark," said Dr. Kay. "Easter eggs were brighter, and he saw a rainbow for the first time." Although the patient's visual function subjectively improved overall —indeed, he had objective improvement in visual acuity in one eye—there was a slight decline postoperatively in visual acuity in the nondominant eye (possibly due to foveal detachment). However, the patient is unaware of this.

Visual fields. The second patient that Dr. Kay referred to Bascom Palmer —a 17-year-old with a milder phenotype of *RPE65*-associated LCA—experienced a dramatic improvement in his visual fields with a return of one isopter of light. Dr. Gregori considers the boy's results the best of the patients she's treated so far. "Even his central acuity function improved, which is interesting since foveal detachment was avoided in this patient, and the cone cells rely on Müller cells, not just retinal pigment epithelial cells," she said. "The enhanced retinal milieu may improve the function of the cones as well."

Long-term prognosis? "We have about three years of data proving sustained responses using the trials' outcome measures," said Dr. Kay. Despite improvement in visual function after this gene therapy, however, photoreceptor degeneration continues at about the same rate as the natural history, said Dr. Gregori. "The question is: What happens later on? How long do the cells continue making this protein? Will we need to reinject at some point?"

Ms. Soto said that unknowns like these are definitely the most difficult part of the process. Still, she says she's incredibly grateful that her child's surgeons fully prepared her to have realistic expectations. "The journey doesn't end here, but there is so much exciting stuff happening in this field," she said. "It's pretty amazing."

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2 Bennett J et al. *Lancet.* 2016;388(10045):661-672.

3 Russell et al. *Lancet.* 2017;390(10097):849-860.

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Dr. Gregori is associate professor of clinical ophthalmology at Bascom Palmer Eye Institute at the University of Miami Health System and chief of the ophthalmology section at Miami Veterans Affairs Medical Center in Miami. *Relevant financial disclosures: None.*

Dr. Kay is a vitreoretinal specialist at Vitreoretinal Associates in Gainesville, Fla. *Relevant financial disclosures: Spark Therapeutics: C; Foundation Fighting Blindness: S.*

Ms. Soto is the mother of Caspian Soto, a patient at OHSU Casey Eye Institute in Portland. *Relevant financial disclosures: None.*

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EXTRA **MORE ONLINE.** For information about how to identify patients who may benefit from gene therapy, view this article at aao.org/eyenet/archive.

Ninel Z. Gregori, MD

Rhegmatogenous Retinal Detachment: Features, Part 1

Retinal detachment is a condition in which the neurosensory retina is separated from the retinal pigment epithelium. If untreated, permanent loss of vision may occur. Types of retinal detachment include rhegmatogenous, exudative, tractional, combined tractional-rhegmatogenous, and macular hole–associated detachment. Rhegmatogenous retinal detachment (RRD) is the most common of these. Part 1 of this 2-part article covers RRD risk factors, features, and examination. Next month, part 2 covers management.

Defining RRD

The word rhegmatogenous is derived from the Greek word *rhegma*, which means broken. The pathogenesis of RRD involves vitreoretinal tractional forces that result in a full-thickness retinal break. Liquefied vitreous gel then enters the subretinal space through the break, causing separation of the neurosensory retina from the underlying retinal pigment epithelium.[1]

Total RRD denotes separation of the entire retina; subtotal RRD refers to detachment of most of it. Subclinical retinal detachments are those with subretinal fluid extending more than 1 disc diameter from the break but less than 2 disc diameters posterior to the equator. If subretinal fluid extends less than 1 disc diameter, the condition is defined as a retinal break without detachment.[2]

Risk Factors

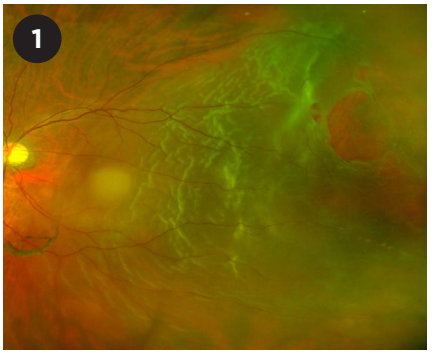
Risk factors for RRD include high myopia, trauma to the eye or head, RRD in the fellow eye, underlying hereditary vitreoretinopathy, previous intraocular surgeries, and previous viral retinitis. Other risk factors are intraocular procedures (especially vitreous manipulation), laser capsulotomy, pseudophakia/aphakia,[3] and retinal lesions such as lattice degeneration, snail track degeneration, snowflake degeneration, vitreoretinal tufts, meridional folds, retinoschisis, and white lesions (with or without pressure).[2]

Clinical Features

Patients with RRD may present with floaters, photopsia, and/or a "curtain" defect that obscures part of the visual field. Visual acuity (VA) ranges from excellent to poor, depending on whether the macula is still attached. In patients with macula-off RRD, vision usually is decreased. If the area of detachment is large, an afferent pupillary defect may be present.

Intraocular pressure (IOP) can be low or high. Low IOP results from increased outflow of intraocular fluid through the subretinal space and peripapillary connective tissue, particularly if the optic disc border is involved. High IOP may occur with chronic RRD, in which photoreceptor outer segments transgress into the anterior chamber and trabecular meshwork, impeding aqueous outflow. This is also known as Schwartz-Matsuo syndrome. Other features of chronic RRD may include a pigmented demarcation line at the detachment border, intraretinal macrocysts, atrophic thinned retina, subretinal white precipitates, and signs of proliferative vitreoretinopathy (PVR), such as fixed retinal folds.

Assessment of RRD requires a thorough 360-degree fundus examination. When visualization of the fundus is poor, as in patients with dense cataract or vitreous hemorrhage, an ultrasound B-scan may be useful.



RRD. *Macula-off primary rhegmatogenous retinal detachment with multiple breaks located within 1.5 clock hours of the highest border of the detachment (consistent with Lincoff rules).*

Examination

Binocular indirect ophthalmoscopy (BIO) of the fundus. BIO with a lens

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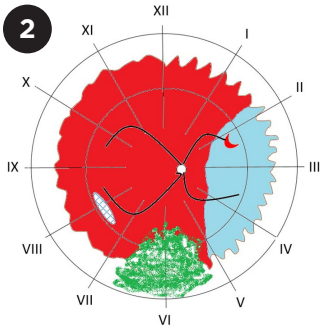
of 20 or 28 D allows visualization of the peripheral retina. For some eyes, scleral depression during indirect ophthalmoscopy or contact fundus lens examination using the slit lamp (e.g., Goldmann 3-mirror lens) may help view smaller peripheral retinal breaks.

Examination. This should include the following steps:

1. Identify the extent of detachment. The detached area will appear opaque and corrugated, with undulating retinal folds during eye movement. The borders of the detached tissue usually are convex, and the subretinal fluid is clear and nonshifting. (See "Differentiating the Main Types of Retinal Detachment," with this article at aao.org/eyenet, for pearls to differentiate tractional and exudative retinal detachment from RRD.) Other features that may accompany RRD include a positive Shafer's sign (pigment in the anterior vitreous), vitreous hemorrhage, and lower IOP than in the fellow eye.

2. Find all retinal breaks, which will help guide the surgical approach. It is important to note the size, number, and location of each break. Lincoff rules are useful for identifying the precise location of the retinal break in cases of primary RRD.[3] If there are multiple breaks, the highest retinal hole is considered the primary hole. (See "Lincoff Rules.")

The location of retinal detachment plays a major role in management and prognosis.



AMSLER-DUBOIS RETINAL CHART. *The innermost circle represents the equator, the middle circle represents the ora serrata (scalloped edges), and the outermost circle represents the junction of the pars plana and pars plicata. Lesions commonly associated with RRD are marked: a horseshoe tear (2 o'clock position) with a torn vessel, a resultant retinal detachment (extending through 3 clock hours), lattice degeneration (8 o'clock), and vitreous hemorrhage inferiorly (green area).*

3. Determine whether the RRD is macula-on or macula-off (Fig. 1). Although visual prognosis is much better for macula-on RRD that spares the fovea, urgent intervention is still needed.

4. Check for associated features. Retinal lesions that predispose to retinal breaks, such as lattice degeneration, should be identified. Also look for features that might affect management and prognosis, such as coexisting vitreous hemorrhage and PVR.

5. Document the findings on an Amsler-Dubois chart or in the electronic medical record, using color codes and symbols to represent retinal lesions (Fig. 2).

Ultrasonography. If the fundus view is obscured, dynamic B-scan ultrasonography is helpful to confirm RRD and determine the status of macular involvement, presence of posterior vitreous detachment, location of retinal break (occasionally), and chronicity of RRD (mobile or fixed).

Typical ultrasound findings for RRD include high reflectivity, a high spike on the A-scan, a membrane within the vitreous cavity, and mobility during eye movements. Posterior vitreous detachment is characterized by a posterior hyaloid face, low reflectivity, a low spike on the A-scan, and a high degree of mobility during eye movements (Fig. 3, online with this article, demonstrates the ultrasound appearance of a funnel retinal detachment).

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EXTRA **MORE ONLINE.** See this article at aao.org/eyenet/archive for an ultrasound image of a total retinal detachment and a table differentiating 3 types of retinal detachment.

Lincoff Rules: Finding the Break in Primary RRD

Rule 1. In superior-temporal or superior-nasal detachments: The primary break is within 1.5 clock hours of the highest border (in 98% of cases).

Rule 2. In total detachments or superior detachments that cross the 12 o'clock meridian (vertically above the disc): The primary break is at 12 o'clock or the break is a triangle with the apex at the ora serrata and the base at the equator, extending from 11 to 1 o'clock (in 93% of cases).

Rule 3. In inferior detachments: The higher side of the detachment indicates the side of the disc where the primary break lies, and the break is found below the horizontal meridian (in 95% of cases).

However, in inferior detachments where right/left borders are equally high, the break is in the inferior retina at 6 o'clock.

Rule 4. In inferior bullous detachments: The primary break is located above the horizontal meridian.

SOURCE: Lincoff H, Gieser R. *Arch Ophthalmol.* 1971;85(5):565-569.

Digital drawing by Nathalie Chiam

Rhegmatogenous Retinal Detachment: Management, Part 2

Last month, Ophthalmic Pearls discussed risk factors, features, and examination of rhegmatogenous retinal detachments (RRD). This month, the authors continue with a discussion of RRD management.

After Dx: How to Proceed

RRDs with superior breaks that threaten the macula require urgent vitreoretinal intervention. While awaiting definitive management, patients should maintain a posture that prevents the subretinal fluid from detaching the macula.

Definitive management of RRD includes barrier laser retinopexy in select situations, pneumatic retinopexy, primary scleral buckle, primary pars plana vitrectomy (PPV) with intraocular tamponade or combined scleral buckle and vitrectomy.

Barrier laser retinopexy. This procedure is indicated for localized detachments such as subclinical retinal detachment. This is usually performed with the patient under topical anesthesia. Patients must be forewarned that, despite this treatment, the RRD may progress and require additional intervention, including surgery.

Pneumatic retinopexy. Pneumatic retinopexy is indicated for specific RRD cases, including those with break(s) confined to the superior 8 clock hours, with all breaks being confined within 2 clock hours. Contraindications include large (giant) retinal tears, proliferative vitreoretinopathy (PVR), advanced glaucoma, poor compliance with head posturing, individuals who need to travel by air, and, in some cases, pseudophakia.

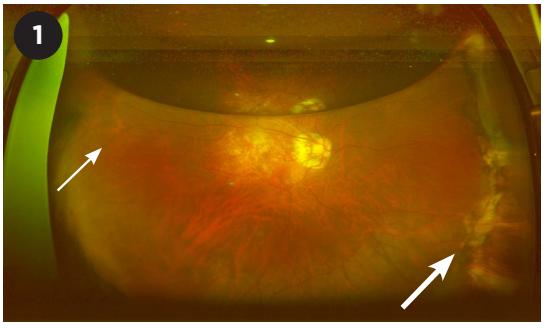
The procedure, which is performed with the patient under regional anesthesia, entails transconjunctival intravitreal injection of an expansile gas bubble, plus retinopexy to the retinal breaks. In general, retinopexy is done using cryotherapy or laser photocoagulation. Transconjunctival cryopexy usually is performed before gas injection, during a single outpatient visit. For laser retinopexy, gas injection is performed initially, followed by laser photocoagulation several days later. The expansile intraocular gases include 100% sulfur hexafluoride (SF_6, 0.6 mL), perfluoroethane (C_2F_6, 0.4 mL), and perfluoropropane (C_3F_8, 0.3 mL).

Reattachment can be achieved with a single pneumatic retinopexy procedure in 80% of cases and with ≥1 procedure in 98%.[1]

Although pneumatic retinopexy is minimally invasive, the risk of new or missed retinal breaks is greater with this procedure than with more invasive surgery such as vitrectomy or scleral buckle.[2] Other possible complications include gas migration into the subretinal space, central retinal artery occlusion from elevated IOP, vitreous incarceration at the wound, accelerated cataract formation, and endophthalmitis.

Scleral buckle and pars plana vitrectomy. All breaks must be located, then treated with cryotherapy or laser retinopexy. Vitreoretinal traction must be relieved by either scleral buckling or vitrectomy. In most cases, the subretinal fluid is drained internally (via the retinal hole during vitrectomy) or externally (by scleral cut-down in primary scleral buckle surgery), if needed.

Scleral buckle surgery. This extraocular procedure should be considered



AFTER COMBINATION SURGERY. *Ultra-widefield fundus photograph of an eye that underwent scleral buckle and PPV with gas. The photograph was obtained several weeks postoperatively. A partially resorbed gas bubble is visible (small arrow), and the indent from the buckle can be seen supporting the peripheral retina (large arrow).*

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for young, phakic patients with tear(s) anterior to the equator. It is not suitable for patients with a giant retinal tear or PVR.

Transscleral cryotherapy is performed around the retinal break, and the external scleral indentation from the buckle helps to support the break. The buckle-induced indentation aids in adhesion between the neurosensory retina and the retinal pigment epithelium, while relieving vitreous traction on the retina.[3] Several types of scleral buckling material are available, including encirclage and segmental and radial buckles. The procedure is usually performed in the operating room while the patient is under regional anesthesia or, rarely, general anesthesia.

Surgical steps are as follows:

- 360-degree conjunctival peritomy
- Slinging recti muscles
- Localizing the break with binocular indirect ophthalmoscopy (BIO)
- Cryotherapy with or without external drainage of subretinal fluid
- Inserting the segmental and/or encircling scleral buckle
- Suturing and tightening of the buckle
- Checking of central retinal artery perfusion to determine need for anterior chamber paracentesis
- Antibiotic wash around the buckle
- Closing the conjunctiva
- Subconjunctival antibiotic and steroid injections

Intraoperative complications include scleral perforation and recti muscle trauma/slip. In cases requiring subretinal fluid drainage, the surgeon must be aware of risk for suprachoroidal hemorrhage, hypotony, and retinal incarceration at the drainage site. Postoperative complications include PVR formation, re-detachment, buckle migration/extrusion, buckle-related infections, refractive changes, ocular motility disorders, anterior segment ischemia, and glaucoma (from vortex vein or ciliary body compression).

Among suitable cases, reattachment can be achieved with a single primary scleral buckle procedure in 80% to 90%.[4]

Pars plana vitrectomy. PPV may be indicated for posterior retinal break, multiple breaks in different meridians, giant retinal tear, concurrent PVR, and dense vitreous hemorrhage obscuring the retinal break(s). PPV is performed in the operating room while the patient is under regional anesthesia or, rarely, general anesthesia.

Steps include:

- Creating three sclerostomy ports (for the infusion cannula, illumination probe, and vitrectomy handpiece)
- Core vitrectomy, shaving the vitreous base, and relieving any traction over the retinal break
- Using perfluorocarbon liquid to flatten the retina and displace the subretinal fluid via the original retinal break (optional step, depending on surgeon preference)
- Retinopexy around retinal breaks; laser is often used
- Fluid-air exchange
- Injecting vitreous substitute such as isoexpansive gas or silicone oil

Nonexpansile intraocular gas tamponade, such as SF_6 20%, C_2F_6 15%, or C_3F_8 15%, will usually last two weeks, three weeks, and eight weeks (respectively) due to different rates of resorption. Patients should be advised about the postoperative posturing necessary to allow the buoyant vitreous substitute to tamponade the break. This posturing is maintained until most of the gas bubble has been resorbed.

If silicone oil tamponade is used, it is typically removed three to six months after surgery; in some eyes, it is retained indefinitely.

The success rate of PPV for RRD ranges from 64% to 96%, depending on the complexity of the case.[5]

Intraoperative complications include trauma to intraocular structures (e.g., iatrogenic retinal breaks or iatrogenic cataracts) and vitreous/retina incarceration at sclerotomy wounds. Postoperative complications may include endophthalmitis, sympathetic ophthalmia, glaucoma, and cataract.

Combined scleral buckle and pars plana vitrectomy. This combination is sometimes needed for simple RRD (Fig. 1). Although most comparative studies of scleral buckle, PPV, and the combination procedure showed no significant differences in success rates for single-session surgery, a few have demonstrated that PPV alone is superior to scleral buckle alone for primary RRD.[5] In a retrospective study at Singapore National Eye Centre, patients who received the combination procedure had better anatomic success rates than those who underwent PPV alone (90% vs. 80%, $p < .001$).[6]

In complicated RRD cases, combining scleral buckle and PPV can improve visualization of breaks during PPV and provide better support of the peripheral retina.

Timing of Intervention

The urgency to repair RRD depends on the status of the macula and other patient-specific characteristics. Even if the macula is on (fovea spared), urgent intervention may be necessary. When the fovea is already detached (macula-off), reattaching the retina may be less urgent. Some experts suggest that the number of days of foveal detachment may indicate the urgency of surgery. Thus, if the fovea has been detached for two days, surgery should be performed within two days.[7]

In a study of patients with macula-off retinal detachment, those who underwent surgery within three days of developing central vision loss had better visual outcomes postoperatively.[8] However, the visual outcomes for cases in which surgical repair was delayed for 10 days did not differ significantly from outcomes for cases not surgically repaired until a month following the loss of central vision.[8]

Conclusion

The management of RRD requires a detailed assessment to ensure identification of all breaks. This facilitates the planning and execution of surgical intervention. Surgical treatment entails locating and sealing all breaks as well as relieving vitreous traction. Prompt intervention may produce better visual outcomes. Care should be taken to select the most appropriate procedure or procedures, with consideration given to the timing of intervention.

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Acknowledgment: We thank the Ocular Imaging Department, Singapore National Eye Centre, for providing the retinal photographs in Parts 1 and 2 of this series.

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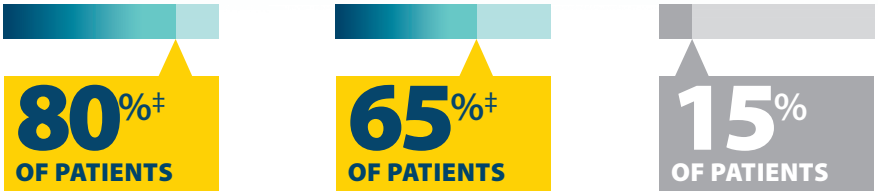
Now Approved *for an expanded indication in* ***Diabetic Retinopathy (DR)***[1]

EYLEA® (aflibercept) Injection For Intravitreal Injection

POWER AGAINST

In PANORAMA, EYLEA significantly improved DR severity scores at week 52[1]

Proportion of patients achieving a ≥2-step improvement in ETDRS-DRSS* score from baseline (primary endpoint)[1,†]



EYLEA 2 mg every 8 weeks[§] (n=134)

EYLEA 2 mg every 16 weeks[‖] (n=135)

sham (n=133)

‡*P*<0.01 vs sham.

The recommended dose for EYLEA in DR is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (approximately every 25 days, monthly), additional efficacy was not demonstrated in most patients when EYLEA was dosed every 4 weeks compared to every 8 weeks. Some patients may need every-4-week (monthly) dosing after the first 20 weeks (5 months).[1]

Efficacy and safety data of EYLEA in DR are also derived from VISTA and VIVID.[1] The percentage of patients with a ≥2-step improvement on the ETDRS-DRSS from baseline at 100 weeks was 38%, 38%, and 16% in VISTA and 32%, 28%, and 7% in VIVID with EYLEA 2 mg every 8 weeks after 5 initial monthly doses, EYLEA 2 mg every 4 weeks, and control, respectively (secondary endpoint).[1]

PANORAMA study design: Multicenter, double-masked, controlled study in which patients with moderately severe to severe NPDR (ETDRS-DRSS: 47 or 53) without central-involved DME (CI-DME) (N=402; age range: 25-85 years, with a mean of 56 years) were randomized to receive 1) 3 initial monthly EYLEA 2 mg injections, followed by 1 injection after 8 weeks and then 1 injection every 16 weeks; 2) 5 initial monthly EYLEA 2 mg injections, followed by 1 injection every 8 weeks; or 3) sham treatment. Protocol-specified visits occurred every 28±7 days for the first 5 visits, then every 8 weeks (56±7 days). The primary efficacy endpoint was the proportion of patients who improved by ≥2 steps on the ETDRS-DRSS from baseline to week 24 in the combined EYLEA groups vs sham and at week 52 in the EYLEA 2 mg every-16-week and EYLEA 2 mg every-8-week groups individually vs sham. A secondary endpoint was the proportion of patients developing the composite endpoint of proliferative DR (PDR) or anterior segment neovascularization.

VISTA and VIVID study designs: Two randomized, multicenter, double-masked, controlled studies in which patients with DME (N=862; age range: 23-87 years, with a mean of 63 years) were randomized and received 1) EYLEA 2 mg administered every 8 weeks following 5 initial monthly doses; 2) EYLEA 2 mg administered every 4 weeks; or 3) macular laser photocoagulation (control), at baseline and then as needed. Protocol-specified visits occurred every 28 (±7) days. In both studies, efficacy endpoints included the mean change from baseline in best-corrected visual acuity (BCVA), as measured by ETDRS letters, at 52 weeks (primary endpoint) and 100 weeks (secondary endpoint).

INDICATIONS AND IMPORTANT SAFETY INFORMATION

INDICATIONS

EYLEA 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).

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.

*Early Treatment Diabetic Retinopathy Study–Diabetic Retinopathy Severity Scale: An established grading scale for measuring the severity of DR.
†Full analysis set.
§3 initial monthly injections, followed by 1 injection after 8 weeks and then 1 injection every 16 weeks.
‖5 initial monthly injections, followed by 1 injection every 8 weeks.

REGENERON

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Start with EYLEA to help stop progression to PDR[1]
Visit STARTEYLEA.COM to learn more

DISEASE PROGRESSION[1]

EYLEA can help prevent DR vision-threatening complications that can lead to blindness[1]

Significantly fewer patients developed PDR or ASNV with EYLEA at week 52[1]

Composite endpoint of patients who developed PDR or ASNV at week 52 (event rates) (secondary endpoint)[1,†]

EYLEA 2 mg every 8 weeks[§] (n=134)

EYLEA 2 mg every 16 weeks[‖] (n=135)

sham (n=133)

‡*P*<0.01 vs sham.

All patients were treatment-naïve to focal or grid laser photocoagulation, panretinal photocoagulation, and any anti–vascular endothelial growth factor (anti-VEGF) treatment.[2] Composite endpoint of developing PDR or anterior segment neovascularization (ASNV) was diagnosed by either the reading center or investigator through week 52. Event rate was estimated using the Kaplan-Meier method.[1]

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

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.

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

References: 1. EYLEA® (aflibercept) Injection full Prescribing Information. Regeneron Pharmaceuticals, Inc. May 2019. **2.** Data on file. Regeneron Pharmaceuticals, Inc.

05/2019
US-LEA-14375

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:

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 CRVO in 2 clinical studies (COPERNICUS and GALILEO) and 91 patients following BRVO in one clinical study (VIBRANT).

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

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

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

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

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

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

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

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

8 USE IN SPECIFIC POPULATIONS.

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

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

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

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

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

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

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

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

REGENERON

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

Issue Date: 05/2019
Initial U.S. Approval: 2011

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

US-LEA-13708(2)a(2)

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Drug Delivery for the Posterior Segment

Born of necessity and scientific advance, new drug delivery devices for treatment of retinal disease and uveitis are now emerging.

By Lori Baker-Schena, MBA, EdD, Contributing Writer

ADVANCES IN POSTERIOR SEGMENT DRUG DELIVERY systems are occurring at breakneck speed—and are a "welcome and timely addition to our armamentarium," said Dilraj S. Grewal, MD, a vitreoretinal and uveitis specialist.

"The number of patients we are treating has increased exponentially, and often we are seeing them frequently for regular intravitreal injections," said Dr. Grewal, at Duke University in Durham, North Carolina. "We need to find ways to reduce the treatment burden on the patients, of course, as well as on the providers because it takes an entire army to get these injections to the patients every month."

Dr. Grewal sees great promise in the latest developments in drug delivery approaches that are designed to help retina and uveitis patients improve and maintain vision over longer time frames than are provided by currently available treatments. Interestingly, the spate of next-generation devices using sustained-release technology and minimally invasive techniques has its roots in a decades-old history of innovation (see "Legacy of Innovation").

As the field advances, *EyeNet* asked its editorial board members to indicate which devices—either brand-new to the market or still in trials—they consider the most intriguing or important in terms of potential to change patient care. Then Emmett T. Cunningham, MD, PhD, MPH, founder of the Ophthalmic Innovation Summit, helped refine the list.

For each device, an ophthalmologist close to the product (see financial disclosures, last page) provided information and opinions. Invariably those who consult or serve as an investigator for emerging products are also the most qualified to knowledgeably discuss them.

Originally published in May 2019

Yutiq

Manufacturer: EyePoint Pharmaceuticals
Status: FDA approved on Oct. 12, 2018; commercially launched on Feb. 4, 2019
Interviewing Quan Dong Nguyen, MD, MSc

How does this technology work?
Approved for the treatment of chronic noninfectious posterior segment uveitis, Yutiq is a nonbioerodible intravitreal microinsert containing 0.18 mg fluocinolone acetonide. It uses the company's proprietary Durasert technology to release the drug consistently over 36 months.

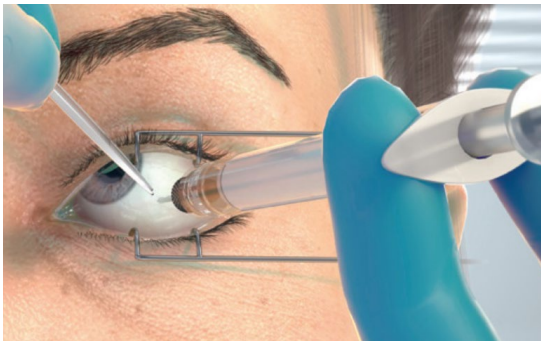
Yutiq is supplied in a sterile single-dose preloaded applicator that can be administered through a 25-gauge needle in the physician's office.

What are the benefits of this device?
Yutiq offers convenience because it can be injected with a small-gauge needle as an office procedure. Also, Yutiq is injected into the vitreous, not anchored in a particular location, so it may reduce the incidence of cataract compared with static placement.

According to the company, you can use J-code J7313 to bill for 18 units.

What are the research findings?
In a phase 3, double-masked, randomized trial, 87 eyes of patients with chronic noninfectious posterior segment uveitis were treated with Yutiq and 42 eyes received sham injections.[1] At 24 months of the three-year trial, the recurrence rate in Yutiq eyes was 59.8% versus 97.6% with the control eyes. Macular edema was resolved in 84.1% of Yutiq-treated eyes and 57.1% of control eyes that had edema recorded at baseline. Drops to lower intraocular pressure (IOP) were used in 41.4% of Yutiq treated eyes and 33.3% of control eyes. Cataracts were extracted from 64.3% of Yutiq patients with phakic eyes and 14.3% of control patients with phakic eyes.

What are the drawbacks to this device?
Before inserting this device into the vitreous of potential patients, physicians must thoroughly evaluate the uveitis to rule out any infectious causes. Yutiq is indicated for noninfectious uveitis, and if a case is of infectious etiology, the steroid insert could activate the pathogen. Additionally, physicians need to discuss with the patients the potential risk of cataract worsening and IOP elevation.



How has the device affected patient quality of life?
In selected patients—whether the disease manifests solely in the eye or in association with systemic diseases—it is not advised to employ systemic treatment, with its potentially debilitating side effects, when local therapy may be possible to control the inflammation and preserve the vision. Yutiq has shown that it can help patients achieve and maintain inflammation control, thus potentially decreasing disease recurrences and preventing cumulative ocular damage that can lead to suboptimal visual function.

Xipere

Manufacturer: Clearside Biomedical
Status: Phase 3 trials complete; NDA submitted to FDA on Dec. 19, 2018
Interviewing Rahul N. Khurana, MD

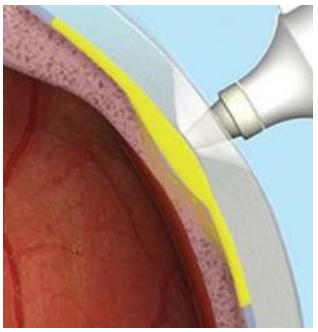
How does this technology work?
Xipere (formerly suprachoroidal CLS-TA) is a proprietary suspension of triamcinolone acetonide for treatment of macular edema associated with uveitis. It is formulated for injection in the suprachoroidal space using a microneedle measuring 1,000 µm in length. Once injected, the corticosteroid rapidly disperses to the choroid and retina, where it is designed to remain for an extended amount of time. The injection can be performed in the clinic.

What are the benefits of this device?
Not surprisingly, ophthalmologists traditionally have tended to associate "suprachoroidal space" with "hemorrhage," assuming that delivering therapeutics to that area would result in complications with bleeding, and that the high choroidal blood flow would wash away the drug. Yet I was excited about the possibility that we could deliver drugs to the choroid and retina while minimizing exposure to the anterior segment—this could be a great

benefit to patients in minimizing complications from steroids. And the research has demonstrated that the incidence of elevated IOP is low compared with other local injections of steroids.

What are the research findings?

The phase 3 PEACHTREE trial randomized 96 patients to receive two 4.0 doses of suprachoroidal CLS-TA 12 weeks apart, and 64 patients as controls to receive a sham procedure at the same 12-week interval.[2] Results showed that 47% of the CLS-TA treated patients gained at least 15 letters in best-corrected visual acuity from baseline at week 24, compared with 16% of control patients. Additionally, the treated patients experienced a mean reduction from baseline of 157 µm at week 24 compared with a 19-µm mean reduction in the control patients. PEACHTREE showed resolution of uveitic inflammation, with 68% of study patients having resolution of vitreous haze versus 23% in the control arm.



No serious adverse events were reported. Elevated IOP included high pressure, ocular hypertension, and glaucoma. All told, 9.4% had elevated IOP of greater than 10 mm Hg; 10% were prescribed IOP-lowering drops.

What are the drawbacks to this device?

With any new technology, there will be a learning curve for mastering the technique; it will take time for retina specialists to get comfortable accessing the suprachoroidal space. But we are accustomed to doing injections in the vitreous already, and it's a relatively small step to learn to inject into the suprachoroidal space.

In addition, 12% of study patients complained of eye pain during the procedure compared with 4.7% of controls, and the pain resolved after the procedure.

A Legacy of Innovation

Today's innovations are part of a pioneering legacy in research for vitreoretinal diseases. Dr. Grewal points to Vitrasert (Chiron, later Bausch + Lomb), the first sustained-release posterior segment drug delivery system that laid some of the foundation for today's breakthroughs. Approved by the FDA in March 1996, Vitrasert consists of a 4.5 mg pellet of ganciclovir coated with a biocompatible polymer and is designed to deliver the drug over five to eight months. It was indicated for the local treatment of cytomegalovirus retinitis in patients with acquired immunodeficiency syndrome (AIDS).

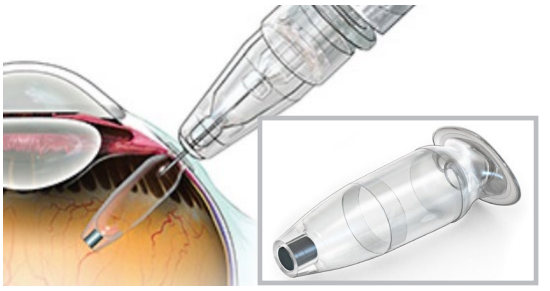
Other breakthroughs that followed included:

- **Retisert (Bausch + Lomb).** The FDA approved this intravitreal implant on April 8, 2005, for the treatment of chronic noninfectious uveitis affecting the posterior segment. Its microdrug reservoir contains 0.59 mg fluocinolone acetonide and delivers sustained levels of the drug for approximately 30 months. "This is a great product in terms of controlling inflammation but requires surgery for placement, and its side effects are increased incidence of cataract and IOP elevation, which may also require concurrent or additional surgery for control," Dr. Grewal said.
- **Ozurdex (Allergan).** This biodegradable sustained-release intravitreal corticosteroid implant containing 0.7 mg dexamethasone, designed to last approximately six months, was FDA approved for the treatment of macular edema following retinal vein occlusion on June 17, 2009, said Dr. Grewal. It was approved for treatment of noninfectious uveitis affecting the posterior segment of the eye in 2010 and diabetic macular edema in 2014.*
- **Iluvien (Alimera).** The FDA approved this nonbioerodible, sustained-release intravitreal implant on Sept. 26, 2014, for the treatment of diabetic macular edema. It delivers 36 months of continuous low-dose corticosteroid dosing with a single injection.

"We continue to see good safety data on the long-term tolerance of these sustained-release drug delivery systems as well as their effectiveness," said Dr. Grewal.

*On Dec. 28, 2018, Allergan voluntarily recalled 22 lots of Ozurdex, noting that a silicone particle of approximately 300 µm in diameter may detach from the needle sleeve during administration.

How has the device affected patient quality of life?
Xipere represents an approach that is viable and extremely efficacious. Data from the phase 3 trial show that 1 in 2 patients had significant vision gain with resolution of macular edema, and 2 of 3 patients had resolution of their intraocular inflammation.



Port Delivery System

Manufacturer: Roche/Genentech
Status: Phase 3 trial began in September 2018
Interviewing Carl C. Awh, MD

How does this technology work?
The Port Delivery System with ranibizumab (PDS) consists of a permanent intraocular implant filled with a specialized formulation of ranibizumab. The device, which is slightly longer than a grain of rice, is surgically implanted at the pars plana and covered by conjunctiva and Tenon capsule. It can be refilled in the office using a customized needle. The PDS provides continuous delivery of ranibizumab into the vitreous.

What are the benefits of this device?
The PDS may reduce the treatment burden on patients, caregivers, and physicians. Real-world analyses consistently demonstrate that [because of treatment burden] many patients with neovascular AMD (nAMD) receive fewer than the optimal number of intravitreal injections over time, with outcomes inferior to those demonstrated in pivotal trials.[3]

Continuous delivery of ranibizumab into the vitreous with the PDS offers an expected interval between in-office refills that is significantly longer than the current monthly or bimonthly intravitreal anti-VEGF injections, and it has the potential for equivalent outcomes.

What are the research findings?
The phase 2 LADDER (Long Acting DElivery of Ranibizumab) trial compared the PDS to monthly ranibizumab injections in patients with nAMD and a history of favorable response to prior anti-VEGF treatment.[4] The trial enrolled 243 patients and evaluated three different doses of ranibizumab in the PDS. Outcomes were favorable in all groups, but of particular note were the outcomes in the highest dose group using 100 mg/mL. Most patients in this group (80%) went at least six months without requiring a refill, with a median time to first refill of 15 months. In addition, vision outcomes were comparable to those achieved with monthly ranibizumab injections.

What are the drawbacks to this device?
A surgical procedure in the OR is necessary to implant the PDS and this must be considered when comparing the PDS to standard intravitreal injections. In the LADDER trial, the optimized surgical and refill procedures were generally well tolerated. In the PDS arms, the rate of postoperative vitreous hemorrhage with the optimized surgery procedure was 4.3%. The rate of endophthalmitis in the primary analysis population was 1.6%. We will learn more in the phase 3 trial. As with all surgical procedures, there will be continual refinement as surgeons gain experience.

How has the device affected patient quality of life?
In the LADDER trial, patients with the PDS were evaluated monthly, so there was no reduction in office visits. However, if the phase 3 trial shows similar outcomes and leads to commercial availability, there could be significant improvements in outcomes for patients who might otherwise struggle to get the optimal number of intravitreal injections.

GB-102 for Wet AMD

Manufacturer: Graybug Vision
Status: Phase 1/2a study initial data analysis reported January 2019; phase 2b study enrollment expected to begin in 2019
Interviewing Pravin U. Dugel, MD

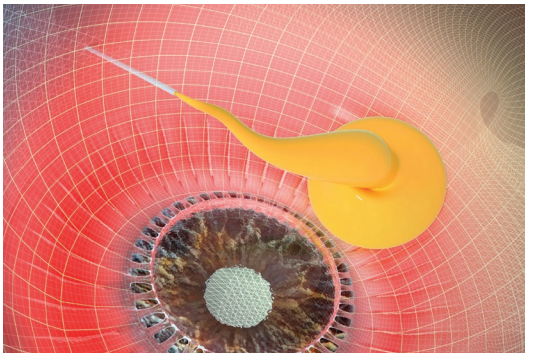
How does this technology work?
GB-102, for the treatment of wet AMD, encapsulates sunitinib malate within bioabsorbable microparticles. After intravitreal injection (IVT), these particles aggregate to form a depot in the inferior vitreous. This depot elutes the drug such that IVT may be necessary only twice a year. Sunitinib blocks cell receptors associated with angiogenesis, proliferation, vascular permeability, and fibrosis.

What are the benefits of this device?
GB-102 will allow us to provide a more sustainable treatment strategy. In contrast to monthly injections, GB-102 delivers the drug on a constant rather than pulsatile basis. Also, because it is a tyrosine kinase inhibitor delivery device, it has possibilities for wider applications, such as treatment of diabetic macular edema and retinal vein occlusion.

What are the research findings?
In the phase 1/2 ADAGIO study, GB-102 demonstrated safety and efficacy, with the duration of effect reaching six to eight months from a single IVT injection.[5] The study involved 32 patients with wet AMD who were evenly divided into four dosing groups: 0.25 mg, 0.5 mg, 1 mg, and 2 mg. GB-102 was well-tolerated with no dose-limiting toxicities, drug-related serious adverse events, or inflammation, and 88% and 68% of patients were maintained on a single dose of GB-102 at three and six months, respectively.

What are the drawbacks to this device?
In the clinical trial, at the highest dose, some microparticle dispersion caused a slight decrease in visual acuity. A new manufacturing process was developed that eliminated the microparticle dispersion, and this newer version of the drug will be used for phase 2b clinical studies.

How has the device affected patient quality of life?
Current treatment alternatives for wet AMD illustrate the great divide between clinical studies and real life. Whereas clinical studies are done in a pristine fashion, the reality is that patients have a difficult time handling the monthly IVT injection requirements. Taking off work, finding a ride, depending on a caregiver—this is a huge treatment burden on the patient and is not reflected in clinical trials. I see this new technology closing the gap and reducing the number of injections necessary to positively impact the patient's quality of life.



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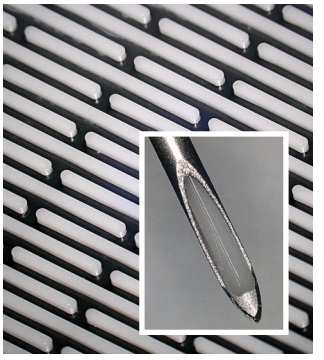
Dexamethasone Intravitreal Implant (AR-1105) With PRINT Technology

Manufacturer: Aerie Pharmaceuticals
Status: AR-1105 phase 2 trial began in spring 2019; AR-13503 (Rho kinase/protein kinase C inhibitor) phase 2 trial to be initiated Q2 2019
Interviewing Theresa G.H. Heah, MD, MBA

How does this technology work?
AR-1105 is a bioerodible implant for treatment of patients with macular edema due to retinal vein occlusion or diabetic macular edema. Delivered through an intravitreal injection using a 25-gauge needle, the implant is intended to release dexamethasone over a six-month period. It uses PRINT (particle replication in nonwetting templates) technology in which a mold is created that contains precisely shaped and sized drug particles from the nanometer to millimeter range. This technology allows for drug delivery directly to the back of the eye and control of the elution rate.



What are the benefits of this device?
The potential benefits include six-month duration of sustained efficacy, improved administration due to a smaller needle size, and possibly a better safety profile due to lower peak drug levels.

The versatility of the PRINT technology also allows us to explore novel drug pathways in retinal disease. For example, in the first quarter of 2019 the company filed an investigational new drug (IND) application with the FDA for its second retinal product—a bioerodible implant containing the Rho kinase/protein kinase C inhibitor AR-13503 to treat wet AMD and diabetic macular edema via a 27-gauge needle with an intended release over a four- to six-month period.

What are the research findings?
A study was conducted focusing on the reproducibility and uniformity of PRINT manufacturing using dexamethasone intravitreal implants.[6]

Results showed that PRINT could be used to manufacture fully biodegradable dexamethasone intraocular implants with uniform size, shape, and dosages—with high reproducibility.

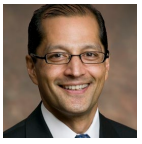
What are the drawbacks to this device?
One challenge: ensuring the drug molecules can be kept in an efficacious concentration in the implant.

How has the device affected patient quality of life?
We believe that AR-1105 and AR-13503 will potentially provide a longer duration of efficacy with reduced number of injections, positively impacting patients' quality of life.

1 Nguyen QD. 24-month evaluation of fluocinolone acetonide intravitreal insert treatment for noninfectious posterior uveitis. Presented at Retina Subspecialty Day 2018, Oct. 26, 2018; Chicago.
2 Khurana RN. Suprachoroidal delivery of CLS-TA for uveitic macular edema: Results of the phase 3 PEACHTREE trial. Presented at Uveitis Subspecialty Day 2018, Oct. 27, 2018; Chicago.
3 Ciulla TA et al. *Ophthalmol Retin.* 2018;2(12):1179-1187.
4 Awh C. LADDER trial of the port delivery system for ranibizumab: Preliminary study results. Presented at the Annual Meeting of the American Society of Retina Specialists, July 25, 2018; Vancouver, British Columbia, Canada.
5 Boyer DS. New developments in drug therapy for retinal disorders. Presented at the Hawaiian Eye & Retina Annual Meeting, Jan. 21, 2019; Kona, Hawaii.
6 Sandahl M et al. *Invest Ophthalmol Vis Sci.* 2018;59(9):5671.

Meet the Experts

Carl C. Awh, MD Vitreoretinal surgeon and president of Tennessee Retina in Nashville, Tenn. *Financial disclosures: Allergan: C; Apellis Pharmaceuticals: S; ArcticDx: C,O,P; Bausch + Lomb: S,C; Genentech: S,C; Hoffman-LaRoche: S; Katalyst Surgical: C,O,P; Merck: S; Ophthotech: S; PanOptica: S; Volk: C.*



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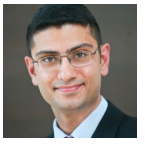

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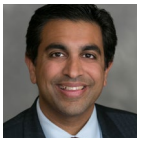

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Programs

Saturday, Oct. 12

Update on a Treatment Option for Wet Age-Related Macular Degeneration, Diabetic Macular Edema, and Diabetic Retinopathy
Speakers: Jordana G. Fein, MD, MS, and Ehsan Rahimy, MD
Presented by Regeneron Pharmaceuticals and designed for U.S. retina specialists.

Sunday, Oct. 13

CONNECTiiNG THE DOTS: Evidence Based Perspectives on Dry Eye Disease
Speakers: Terry Kim, MD, W. Barry Lee, MD, FACS, Marguerite B. McDonald, MD, FACS, and Elizabeth Yeu, MD
Presented by Novartis Pharmaceuticals and designed for U.S. eye care specialists.

Monday, Oct. 14

Life is Beautiful When the Pupil Behaves
Speakers: Eric D. Donnenfeld, MD, John A. Hovanesian, MD, Steven M. Silverstein, MD, Denise M. Visco, MD, and Keith A. Walter, MD
Presented by Omeros Corporation and designed for U.S. cataract surgeons.

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