



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,” page 41).

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, page 44) 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. For more about the ins and outs of reporting on early-stage drugs, devices, and techniques, see Opinion, page 11.

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 nonbio-erodible 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.

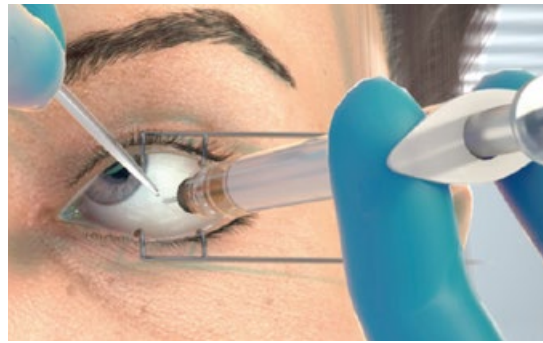
According to the company, you can use J-code J7313 to bill for 18 units.

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.

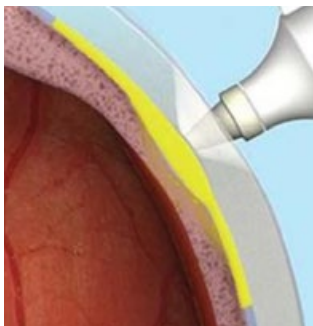
What are the benefits of this device?

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.*

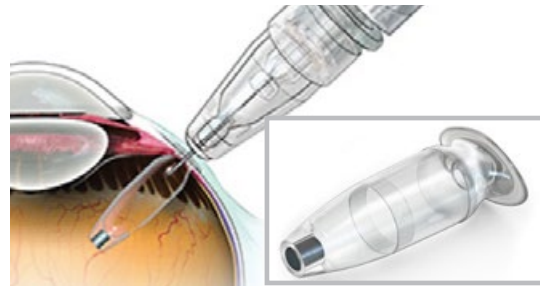
- **Iluvien (Alimera).** The FDA approved this nonbioerodible, sustained-release intravitreal implant on Sept. 26, 2014, for the treatment of diabetic macular edema. It delivers 36 months of continuous low-dose corticosteroid dosing with a single injection.

"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 addi-

tion, 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 micro-particles. 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?

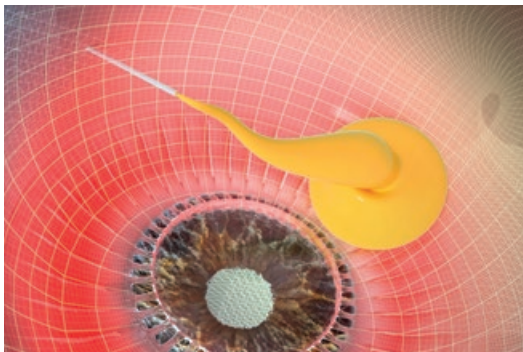
In the phase 1/2 ADAGIO study, GB-102 demonstrated safety and efficacy, with the duration of effect reaching six to eight months from a single IVT injection.⁵ The study involved 32 patients with wet AMD who were evenly divided into four dosing groups: 0.25 mg, 0.5 mg, 1 mg, and 2 mg. GB-102 was well-tolerated 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.

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.

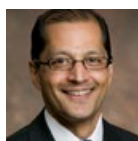
- 1 Nguyen QD. 24-month evaluation of fluocinolone acetonide intravitreal insert treatment for noninfectious posterior uveitis. Presented at Retina Subspecialty Day 2018, Oct. 26, 2018; Chicago.
- 2 Khurana RN. Suprachoroidal delivery of CLS-TA for uveitic macular edema: Results of the phase 3 PEACHTREE trial. Presented at Uveitis Subspecialty Day 2018, Oct. 27, 2018; Chicago.
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- 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



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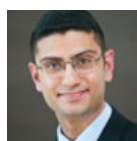
in Nashville, Tenn. *Financial disclosures:* Allergan: C; Apellis Pharmaceuticals: S; ArcticDx: C,O,P; Bausch + Lomb: S,C; Genentech: S,C; Hoffman-LaRoche: S; Katalyst Surgical: C,O,P; Merck: S; Ophthotech: S; PanOptica: S; Volk: C.



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See disclosure key, page 8.