The eye, despite its diminutive size of roughly 8 grams, is a tremendous target for drug delivery systems. The anatomic accessibility of the eye and the capacity to directly visualize and image ocular tissues to measure the response to therapy are distinct advantages of ophthalmic drug delivery compared with other organs in the body.

Yet there exist many challenges to delivering a therapeutic agent to the appropriate intraocular location, not the least of which is the blood-ocular barrier. The intravitreal injection has been the mainstay of treatment for the retina specialist for more than a decade in treating a number of blinding conditions such as macular degeneration, retinovascular disease, and diabetic retinopathy. The high treatment burden of repeated injections has led to the introduction of several innovative approaches, including drug eluting polymers, surgically implanted reservoirs, and suprachoroidal drug delivery.

In this installment of Practical Retina, David Levine, MD, and Steven Yeh, MD, of the Emory Eye Center in Atlanta, and Thomas A. Albini, MD, of the Bascom Palmer Eye Institute in Miami highlight several exciting drug delivery systems recently U.S. Food and Drug Administration approved, as well as emerging technologies in late-phase clinical trials.

**Emerging Drug Delivery Systems for Posterior Segment Disease**

by David Levine, MD; Thomas A. Albini, MD; and Steven Yeh, MD

The use of intravitreal injection therapy for age-related macular degeneration, retinal vascular disease, and uveitis has revolutionized our ability to effectively treat a myriad of posterior segment diseases and is the preferred method for drug delivery to the posterior segment. Within the United States alone, the number of intravitreal injections has increased dramatically from 4,500 injections in 2001 to more than 2 million injections by 2012, and this number continues to rise.

Given the rapidly increasing number of intravitreal therapeutics and treatment burden for patients, there has been considerable interest in the development of therapies that improve durability. Novel approaches in drug delivery systems include the development of longer-acting intravitreal medications, refillable drug reservoirs, and a suprachoroidal drug delivery platform. An understanding of these technologies will be needed both for their implementation in clinical practice and for the assessment of each platform’s benefit-risk profile. This review summarizes emerging drug delivery platforms that aim to provide advantages to currently administered intravitreal therapies.

**FLUOCINOLONE ACETONIDE 0.19 MG (ILUVIEN)**

Fluocinolone acetonide 0.19 mg is an injectable fluocinolone acetonide insert (Iluvien; Alimera Sciences, Alpharetta,
recurrence was significantly lower in patients treated with the 0.18 mg fluocinolone acetonide implant. Campochiaro et al. demonstrated its efficacy for the treatment of DME with a low-dose and high-dose implant in the FAME Study. A total of 956 patients with DME, a history of one or more focal or grid macular laser treatments, central foveal thickness of 250 µm or greater, and best-corrected visual acuity (BCVA) of 20/50 to 20/400 were enrolled. The primary endpoint of 15-letter improvement or better at 24 months was met by 28% of patients treated with the low-dose or high-dose implant and only 16% of patients who received sham injection. Cataract was a side effect observed in nearly all phakic patients and although increased IOP was a noted side effect, only a minority of patients — 4.8% (low-dose group) and 8.1% (high-dose group) — required incisional glaucoma surgery.

The risk of elevated IOP is a consideration prior to treatment and warrants close follow-up after therapeutic administration. Kiddee et al. demonstrated an elevation of IOP in 66% of patients treated with 0.59 fluocinolone acetonide and 79% of patients treated with 2.1 mg fluocinolone acetonide implant. Pre-existing ocular hypertension or glaucoma conferred a higher risk of elevated IOP following treatment with Iluvien. Given that the Iluvien implant is designed to provide stable dosing of fluorocinolone for 3 years, careful patient selection and possible steroid challenge may be indicated prior to starting therapy.

**FLUCINOLONE ACETONIDE 0.18 MG (YUTIQ)**

Fluocinolone acetonide 0.18 mg (Yutiq; EyePoint Pharmaceuticals, Watertown, MA) was recently FDA-approved for treatment of chronic noninfectious uveitis. Similar to Iluvien, it comes in a preloaded applicator for in-office administration. This drug delivery platform releases fluocinolone at a rate of 0.25 μg per day during a period of 3 years. Whereas the 0.59 mg fluocinolone acetonide intravitreal implant (Retisert; Bausch + Lomb, Rochester, NY) must be surgically implanted, Iluvien and Yutiq both are office-based procedures employing 25-gauge injection needles and offer increased durability compared to the dexamethasone intravitreal implant 0.7 mg (Ozurdex; Allergan, Irvine, CA), which lasts for 3 to 6 months.

Jaffe et al. demonstrated that the rate of uveitis recurrence was significantly lower in patients treated with Yutiq (19%) compared to individuals who received sham injection (40%). This study also found that rates of cataract and ocular hypertension were significantly higher in the treatment arm. In clinical practice, Yutiq offers an effective and safe treatment option for chronic noninfectious uveitis. As with other intravitreally administered corticosteroid, the risks and benefits must be weighed for each particular patient in regard to cataract and ocular hypertension.

Two hundred eighty-one patients with posterior segment involving uveitis of 1 or more years of involvement in two multicenter trials were randomized to 0.18 mg fluocinolone acetonide insert (FAi) or sham injections. At 12 months, recurrence rates observed were 97% sham versus 38% injected eyes and 71% sham versus 37% injected eyes in the two trials, demonstrating clinical efficacy in reducing recurrence in this patient population. At 12 months, glaucoma surgical procedures were performed in 4.8% of injected eyes versus 3.4% in sham eyes, and 1% of injected eyes versus 0% of sham eyes in the two studies.

**RANIBIZUMAB PORT DELIVERY SYSTEM**

The Ladder Trial, a phase 2, multicenter, randomized, treatment-controlled clinical trial, is currently underway to investigate the utility of a refillable ranibizumab (Lucentis; Genentech, South San Francisco, CA) implant for the treatment of neovascular age-related macular degeneration (nAMD). Two hundred twenty patients were randomized to receive port delivery system with either 10 mg/mL, 40 mg/mL, or 100 mg/mL and were compared to those who received monthly 0.5 mg of ranibizumab. Time to first implant refill, improvement in best-corrected visual acuity (BCVA), and central foveal thickness (CFT) were used to monitor improvement.

Patients with the 100 mg/mL implant were found to have the longest time from implant to first refill (15 months). BCVA gain was higher in the 100 mg/mL implant compared to the lower-dose implants and similar to monthly ranibizumab (5 ETDRS letters compared to 3.9). The CFT at 9 months was similar in the 100 mg/mL implant compared to monthly ranibizumab patients. This study is continuing to show that 100 mg/mL ranibizumab is well-tolerated and investigators have demonstrated the feasibility and safety of the reservoir refill procedure.

These findings suggest potential for the refillable ranibizumab implant to supply a stable dose of medication for nAMD patients and decrease follow-up burden. Patients with nAMD would require...
surgical device implantation but may benefit from up to 15 months of therapy without the need for a device refill. The phase 3 ARCHWAY trial, which is currently underway, is designed to compare the 100 mg/mL group to monthly intravitreal ranibizumab.

SUPRACHOROIDAL DRUG DELIVERY

Suprachoroidal drug delivery is emerging as a potential treatment modality for macular edema secondary to noninfectious uveitis and DME. The suprachoroidal drug delivery platform uses a 30-gauge hollow microneedle less than 1 mm in length, and the medication is administered either posterior to or within the pars plana. Pharmacokinetic studies in animal models have demonstrated higher bioavailability within the retina and choroid when compared to intravitreal therapeutics. Given lower drug dose exposure to the anterior segment and potential compartmentalization of the drug, the potential for a reduction in adverse effects associated with corticosteroid to the anterior segment makes the suprachoroidal space an attractive site for drug delivery.7,8

Five active clinical trials have evaluated the clinical efficacy and safety of suprachoroidal administration of XIPERE (ie, CLS-TA, a proprietary, preservative-free triamcinolone acetonide formulation; Clearside Biomedical, Alpharetta, GA) for macular edema associated with noninfectious uveitis. PEACHTREE is a randomized, sham-controlled phase 3 trial in which 160 patients were randomized in a 3:2 ratio to suprachoroidal administered triamcinolone acetonide or sham control at baseline and 12 weeks. The primary efficacy endpoint of a 3-line or greater BCVA gain was met by 47% of patients who received suprachoroidal corticosteroid and only 16% of controls (P < .001).9 Patients receiving suprachoroidal corticosteroid also experienced a 147-µm reduction of macular edema, consistent with the visual acuity (VA) improvement. IOP elevation rates and cataract progression or development rates were favorable compared to controls (ie, elevated IOP in 12% of treated vs. 16% of controls; cataract progression in 7% of treated vs. 6% in controls).

In the phase 2 TYBEE trial, 71 patients with DME were randomized to aflibercept (Eylea; Regeneron, Tarrytown, NY) alone or suprachoroidal triamcinolone acetonide with aflibercept. Both arms showed VA gain (ie, 13.5 letters in the aflibercept arm compared to 12.3 letters in the combination arm); however, patients in the combination arm required fewer intravitreal aflibercept injections (10) when compared to the aflibercept monotherapy arm (23) in the as-needed treatment stage.9

CONCLUSION

In summary, a number of emerging drug delivery platforms are under investigation for diseases of the posterior segment and are needed for both retina and uveitis specialists. Although intravitreal injection remains a mainstay of therapy, there is an unmet need for improved durability while balancing efficacy and safety. Among the most recent FDA-approved long-acting steroid injections are Iluvien and Yutiq, whereas the ranibizumab port delivery system and XIPERE are promising modalities being investigated to improve our ability to treat posterior segment disease and potentially reduce treatment burden for patients.

REFERENCES


David Levine, MD, can be reached at the Department of Ophthalmology, Emory Eye Center, Emory University School of Medicine, Atlanta, Georgia; email: david.alexander.levine@emory.edu.

Thomas A. Albini, MD, can be reached at Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, Miami, Florida; email: TAlbini@med.miami.edu.

Howard F. Fine, MD, MHSc, can be reached at can be reached at Rutgers Robert Wood Johnson Medical School; New Jersey Retina, 10 Plum Street, Suite 600, New Brunswick, NJ 08901; email: hfine@njretina.com.

Steven Yeh, MD, can be reached at the Department of Ophthalmology, Emory University School of Medicine, 1365B Clifton Road NE, Atlanta, GA 30322; email: steven.yeh@emory.edu.

Disclosures: Dr. Yeh is a consultant for Santen and Clearside Biomedical outside the submitted work. Dr. Fine is a consultant and/or speaker for Alimera, Allergan, Genentech, Regeneron, and Spark Therapeutics and has equity/patent interests in Auris Surgical Robotics. The remaining authors report no relevant financial disclosures.

This manuscript was supported by an unrestricted departmental grant from Research to Prevent Blindness, Inc. (New York, NY), NIH/NEI grant P30-EY06360 (Department of Ophthalmology, Emory University School of Medicine), NIH/NEI grant RO1 EY029594, and the Bayer Global Ophthalmology Awards Program.