OPHTHALMIC DRUG DELIVERY:

HISTORY, STATUS, AND TRENDS FOR THE FUTURE

It's been a long road, and there is much farther to go.

BY MICHAEL J. O'ROURKE

It seems there has been interest in the sustained release of drugs for the eye quite literally for millennia. If we believe the story, Cleopatra used belladonna plasters on her eyes in the first century BCE. Much later, surgeons in the 19th century sought ways of achieving sustained delivery of cocaine for ocular anesthesia.

The interest continues today, with increasing levels of research and investment into novel drug delivery technologies. Despite the long history, sustained ocular delivery is still an embryonic market with huge opportunities for advances. Multiple companies are engaged in development efforts for sustained delivery of drugs to both the anterior and posterior segments. I have had the good fortune to be involved in the launch of several technologies for sustained delivery of ophthalmic drugs over the past 2 decades, and, in this article, I hope to provide some historical perspective and to preview what may become a reality in the coming years.

LOOKING BACK

The first company to launch a drug delivery device for the eye was the Alza Corporation in the 1970s. Ocusert was an implant placed in the conjunctival sac for delivery of pilocarpine over a period of approximately 1 week. Ocusert was ultimately unsuccessful because it caused patient discomfort; however, it was the first effort in the modern era to develop a long-lasting drug delivery product for the eye.

It wasn't until 20 years later, in 1995, that Chiron Vision launched Vitrasert, the world's first intraocular drug delivery implant. Vitrasert (no longer available) delivered ganciclovir to the back of the eye to treat the orphan disease cytomegalovirus retinitis, an opportunistic infection associated with HIV.

This was the first time surgeons could put an implant into the posterior segment of the eye that could deliver a drug for 4 to 6 months, a major breakthrough for patients. The product was launched with a price of $4,500—a shock at the time—but the price was accepted given the fact that the device could deliver drug for such a length of time for this unmet medical need.

It was almost another 10 years before the next intraocular implant appeared. In 2005, Bausch + Lomb launched Retisert (fluocinolone acetonide 0.59 mg). The company had acquired Chiron Vision's technology, and Retisert used the same technology as Vitrasert but was smaller. It was labeled by the FDA for the treatment of the orphan disease noninfectious posterior uveitis, and it could deliver treatment for more than 32 months.

With the appearance of this second product, companies began to recognize the potential of developing implants as vehicles for drug delivery to the back of the eye. In 2009, Allergan launched Ozurdex (dexamethasone implant 0.7 mg), which was different from the preceding implants in that it did not require a trip to the OR. This was another breakthrough, the first time a drug delivery implant could be injected in the clinic. Ozurdex is now indicated for the treatment of macular edema secondary to retinal vein occlusion, noninfectious posterior uveitis, and diabetic macular edema (DME), and it releases dexamethasone for roughly 6 months.

In 2011, Alimera Sciences launched Iluvien (fluocinolone acetonide implant 0.19 mg), containing the same steroid as Retisert but even smaller and able to be injected rather than implanted. Iluvien is indicated for treatment of DME.

The posterior segment pharmacologic landscape changed dramatically in 2006 with the introduction of the anti-VEGF drug ranibizumab (Lucentis, Genentech). This large-molecule biologic drug is indicated for treatment of neovascular age-related macular degeneration, DME, and macular edema following retinal vein occlusion. A second novel large-molecule anti-VEGF biologic, aflibercept (Eylea, Regeneron), was introduced a few years later.

AN EMERGING NEED

The introduction of anti-VEGF drugs was a significant advance in the management of patients with wet age-related macular degeneration. The downside is that they require frequent intravitreal injections. There is an emerging need today, therefore, for sustained-release delivery of these large-molecule antibody products.

Genentech is developing the Port Delivery System, a refillable implant for sustained delivery of ranibizumab. This device has been evaluated in phase 2 clinical trials,[1] and phase 3 trials are underway. Some companies are now making progress in extending formulations up to 12 weeks. New therapeutics in development may have a 12-week label; but, the ultimate goal would be to provide sustained drug delivery for up to 6 months. Another company working to develop sustained-release delivery systems for biologic products is Re-Vana Therapeutics. Its EyeLief photo-crosslinked technology is aimed at achieving delivery for 4 to 6 months.

ANTERIOR SEGMENT DEVELOPMENTS

Although glaucoma is a disease that affects the optic nerve, we continue to view glaucoma as an anterior segment disease. Pharmacologic treatment for

BIMATOPROST SR

A first-in-class, sustained-release, investigational, biodegradable implant for the treatment of patients with open-angle glaucoma or ocular hypertension.

BY JAI G. PAREKH, MD, MBA, FAAO; AND MICHAEL R. ROBINSON, MD

Nonadherence to treatment regimens is endemic in glaucoma. Up to 80% of patients with glaucoma may not use topical medication as prescribed.[1] Poor adherence is associated with worsening vision and higher overall health care costs.[2] Because barriers to adherence include patient forgetfulness, difficulty administering eye drops, and the burden of dosing frequency,[1] there is an unmet need for glaucoma therapy that does not require daily eye drop instillation.

A biodegradable bimatoprost sustained-release implant (Bimatoprost SR, Allergan), currently in development for the treatment of open-angle glaucoma and ocular hypertension, could be one way to address the problem of nonadherence in glaucoma by providing long-term IOP lowering without the need for eye drops.[3] The solid, rod-shaped implant consists of the prostaglandin analogue (PGA) bimatoprost within the company's Novadur platform for drug delivery.

After a prefilled, single-use applicator is used to place the implant intracamerally in the eye (Figure), the implant slowly releases the drug as the copolymer matrix biodegrades. The implant was designed to lower IOP for at least 4 months.

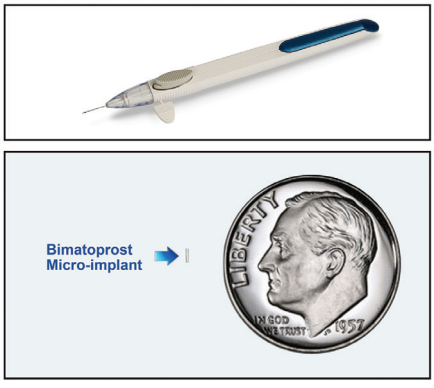

Figure. Bimatoprost SR single-use applicator (top). Implant positioned next to a dime for size comparison (bottom).

"BIMATOPROST SR HAS THE POTENTIAL TO REPRESENT A REAL PARADIGM SHIFT IN OUR OPTIONS TO PROVIDE CONTINUOUS LOWERING OF EYE PRESSURE IN PATIENTS WITH GLAUCOMA."

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STUDY RESULTS

The first clinical trial of the implant in humans was a dose-ranging, phase 1/2 study that enrolled 75 patients with open-angle glaucoma. Each dosing strength that was tested effectively lowered IOP in a dose-dependent manner over the first 16 weeks of the study, with efficacy similar to that of a topical PGA.[3] An extended duration of effect was seen in some patients; a single administration of Bimatoprost SR controlled IOP for up to 2 years without rescue or retreatment in 28% of patients.[4] The product's safety profile was favorable, and some adverse events associated with use of topical PGAs, such as eyelash growth and iris pigmentation, did not occur in eyes that received an implant.

Two 20-month, phase 3 randomized studies have enrolled 1,122 patients with glaucoma or ocular hypertension and are ongoing. Both studies compare two dosage strengths of Bimatoprost SR, administered at day 1, week 16, and week 32, to twice-daily topical timolol. Topline 3-month results have been reported, and most patients have tolerated the study treatment.[5,6] In both studies, Bimatoprost SR has reduced IOP by about 30% over 12 weeks and met the primary endpoint of noninferiority to timolol in IOP lowering through week 12. Initial long-term data from these studies suggest that a majority of patients will require no other IOP-lowering treatment for 1 year after receiving the last implant. Additional safety and efficacy data will be reported at study completion.

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glaucoma is carried out exclusively through the anterior segment route. A multitude of companies are investigating sustained-release technologies for glaucoma management. This is a highly valuable unmet medical need because of the burden placed on patients by the regimen of daily topical drop administration.

In this arena, the most notable activity at present in the development of sustained-release modalities is Allergan's Bimatoprost SR implant. This sustained-release bioerodible implant containing bimatoprost is injected into the anterior segment as an in-office procedure or at an ambulatory surgery center. In phase 2 trials, it showed favorable safety and efficacy through 6 months.[2] Phase 3 trials are underway. (For more information, see the accompanying sidebar, *Bimatoprost SR*.)

A similar unmet need lies in the treatment of dry eye disease (DED), which also requires frequent instillation of eye drops. DED is a multibillion dollar market, and several companies are exploring sustained-release technologies in this space. A technology commercialization group called C20/20 from McMaster University in Hamilton, Ontario, Canada, is developing a micelle technology for DED based on mucoadhesion. If this venture is successful, patients could administer eye drops perhaps once or twice a week, rather than several times per day.

Micelles are nano-sized structures built from polymeric molecules. Micelle is not a true sustained-release technology, but it provides a sustained effect in the eye. A number of applications for extended drug delivery in the anterior segment use micelle technology.

RECENT LAUNCHES

Two of the most recent introductions in the area of sustained-release technologies—one for the anterior segment and one for the posterior segment—have come from EyePoint

DROP THE DROPS

An intracanalicular insert delivers a corticosteroid to the ocular surface after surgery.

BY SYDNEY TYSON, MD, MPH

Cataract surgery can provide patients with excellent visual acuity, but poor adherence with the postoperative eye drop regimen can negatively affect outcomes. This is a particular problem among patients with comorbidities for whom the addition of postoperative medications expands the complexity of their drug regimen. These concerns have driven efforts to simplify the postoperative routine.

In late 2018, Dextenza (dexamethasone ophthalmic insert 0.4 mg, Ocular Therapeutix) was approved by the FDA to treat ocular pain following ophthalmic surgery. The preservative-free insert replaces topical medications with a consistent and tapered dose of drug delivered to the ocular surface for up to 30 days.

The intracanalicular insert is introduced through the punctum and into the canaliculus. After delivering dexamethasone for 30 days, the insert softens, resorbs, and exits through the nasolacrimal system. The insert is conjugated with fluorescein, facilitating its visualization under blue light with a yellow filter. If a patient develops a steroid response, the surgeon can remove the insert either with saline irrigation or manual expression.

Dextenza can replace about 70 corticosteroid drops a patient would have taken in 30 days.[1,2] The phase 3 FDA-approval data[3,4] were robust: A statistically significantly higher incidence of treated patients reported being pain free 8 days after cataract surgery compared to the vehicle control group. The insert was safe, and patients rated it as comfortable.[5]

Ocular Therapeutix is looking to expand Dextenza's current indication to include ocular inflammation after ophthalmic surgery. The FDA has set a Prescription Drug User Fee Act target action date of November 10 for its review of the supplemental new drug application. In supporting data, the insert demonstrated statistically significant superiority compared to the control vehicle in terms of absence of ocular pain at day 8 and absence of inflammation at day 14. Also at day 14, significantly more treated patients did not exhibit anterior chamber cell death compared with patients who received the placebo (52.3% vs 31.1%).

The study also demonstrated a quick onset of action, with 73% (n = 157) of patients reporting no pain on postoperative day 1. IOP elevation occurred in only one of 538 patients across all three phase 3 studies; the increase was related to the insert. Ocular Therapeutix applied for transitional pass-through payment status and a J-code with the CMS and recently announced receipt of a preliminary recommendation for a J-code that would take effect in January 2020.

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Pharmaceuticals. In 2018, the FDA approved both Dexycu (dexamethasone intraocular suspension 9%) and Yutiq (fluocinolone acetonide intravitreal implant 0.18 mg).

Yutiq, indicated for treatment of noninfectious posterior uveitis, is based on the Durasert technology developed by pSivida, similar technology to that used in Iluvien.

Dexycu, indicated for postcataract inflammation, is one of the first true anterior segment sustained-release products to come onto the market. It uses the company's Verisome technology, which supplies sustained release of small molecules in suspension.

Also in 2018, Ocular Therapeutix announced the FDA approval of Dextenza (dexamethasone ophthalmic insert 0.4 mg) to treat ocular pain following ophthalmic surgery. The intracanalicular insert delivers drug to the ocular surface for up to 30 days. (For more information on Dextenza, see the accompanying sidebar, *Drop the Drops*.)

MORE TO COME

To review, in the almost 25 years since 1995, we have seen the launches of only seven sustained-release ophthalmic products: Vitrasert, Retisert, Ozurdex, Iluvien, Dexycu, Yutiq, and Dextenza. There is a notable trend among these products: All of them dispense familiar or generic drugs. These are (or were) novel devices, but they did not carry novel drugs. It's quite a different task to take a novel drug and make it work with a new delivery technology. This is something we most likely will see more of in coming years.

Today, sustained drug delivery is still an embryonic area with incredible opportunities going forward. I believe the single biggest opportunity will be for sustained-release biologics, but there is certainly also a need for glaucoma and DED products.

Sustained-release delivery of biologic drugs for periods of 4 to 6 months will not be easy to achieve because proteins can become denatured fairly quickly. Additionally, the devices must have the drug-loading capacity to deliver the right dose of these large-molecule drugs at therapeutic levels for the desired period. Some of the new technologies under development are set to overcome these challenges.

Where else can ophthalmic drug delivery go? Obviously the emerging areas of gene and stem cell therapies will see continued development. Will sustained-release technologies have a role in these products going forward? Any product that can prolong duration of effect—whether for a small molecule, a large molecule, gene therapy, or cell therapy—is a potential advance.

The great opportunity and challenge will lie in combining novel therapeutics with sustained-release technologies at early stages of product development: that is, in phase 1 or phase 2 clinical trials. I believe we will see more of these approaches from major companies with novel therapeutics. Rather than wait for product approval and then consider drug delivery vehicles, they will tackle both, together, from the outset.

This will present heightened challenges to get products approved. Not only will companies have to get the drug right, but they will also have to get the delivery technology right, plus, they will have to successfully match the former with the latter. It will be fascinating to see efforts play out, and I hope the developments of the next 25 years match and exceed the developments we have seen in the preceding period. ■

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