

The Promise of *Implantable* Drug Delivery Systems

Humans are clumsy, forgetful, imprecise and undependable. High-tech drug pellets are not. And that is why the delivery of medications through tiny, sustained-release devices may be the future of ophthalmology.

BY ANNIE STUART,
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Enormous sums of research and money go into the approval and marketing of ophthalmic drugs, but the sad fact is that many of these medications don't reliably reach your patients' eyeballs. Therapeutic levels, minimum inhibitory concentrations, pharmacokinetics, the blood-brain barrier and patient adherence are just some of the obstacles associated with the traditional topical and systemic administrations of medicine. Even intravitreal injections, long favored for posterior segment disease, fall short. Molecules injected into the vitreous have a brief intraocular half-life, said Uday B. Kompella, PhD, professor of pharmaceutical sciences at the University of Colorado in Denver. "If it's a small molecule, most of it will disappear within a few hours. If it's a large molecule, most of it will disappear within a few days."

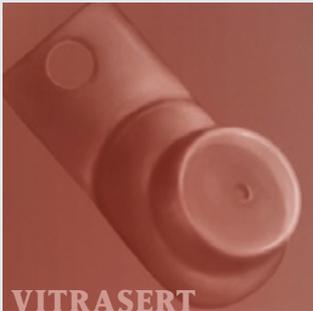
Enter the implant. Medication implant technology can achieve longer-lasting, highly localized drug delivery with more accurate concentrations and fewer side effects than any other avenue of administration. Implants have already proven themselves in inflammatory diseases. In fact, a wide array of chronic illnesses stand to gain from implant delivery, which is fortunate, given the aging population of most societies and the scores of age-related ills that will present themselves to ophthalmologists.

Following is a bird's-eye view of what is currently available in ocular medication implants and what is winding its way through the research pipeline.

RESERVOIR IMPLANTS

Although reservoir implants require surgical placement or replacement, simplicity, longevity and steady-state pharmacokinetics are their big benefits. “The primary lesson learned over the decade is to keep things simple,” said Paul Ashton, PhD, president and CEO of pSivida Corporation in Watertown, Mass. “In the beginning, there’s always a tendency to overcomplicate things from an engineering perspective.” Dr. Ashton helped develop some of the reservoir implants now on the market or under study, including Vitrasert, Retisert and Iluvien.

Vitrasert. Approved in early 1996 for the treatment of AIDS-related cytomegalovirus retinitis, this implantable form of ganciclovir was a trailblazer in the field, said Baruch D. Kuppermann, MD, PhD, professor of ophthalmology and chief of the retina service at the University of California, Irvine. With Vitrasert, he said, “There were limited ocular complications and the efficacy far exceeded the standard of care, which



was the same drug, ganciclovir, administered intravenously. The implant was completely nontoxic to the eye and worked beautifully,” said Dr. Kuppermann.

Surgically implanted through a 5.5-mm pars plana incision, Vitrasert lasts five to eight months. At the time of Vitrasert’s introduction, Dr. Kupperman said, the typical patient with AIDS-associated CMV retinitis had an expected lifespan of eight to 12 months. “So it was an implant that was well suited for controlling the disease within the context of the patient’s expected survival.”

With the advent of more potent combination therapies for HIV infection, however, opportunistic infections were more easily controlled or prevented, and so the need for Vitrasert waned, said James P. Dunn Jr., MD, associate professor of ophthalmology at Johns Hopkins University and director of ocular immunology at the Wilmer Eye Institute. At one time, Dr. Dunn implanted Vitrasert 15 or 20 times annually, but currently he does so only once or twice a year.

Retisert. The next generation of implant, Retisert, achieved even better targeted delivery and duration. Sutured to the sclera after surgical implantation through a 3.5-mm pars plana incision, Retisert releases fluocinolone acetonide and lasts about 30 months. But that duration comes with a downside: ocular side effects. Although FDA-approved in 2005 for noninfectious uveitis after achieving dramatically reduced recurrence of uveitis, the toxicities were considered too much for patients with diabetic macular edema. “Studies suggest that the risk of cataract is upward of 90 percent with Retisert,” said Dr. Dunn, adding that steroid-induced

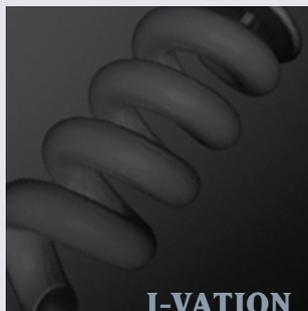
glaucoma is another significant concern. “The risk of glaucoma is about 50 percent with a Retisert implant, and about a third of those patients end up needing surgery because the glaucoma can’t be controlled with medication alone.”

A large, five-year study of Retisert, the Multicenter Uveitis Steroid Treatment trial, will likely shed some needed light on the effectiveness of Retisert compared with conventional oral corticosteroids in the management of severe cases of uveitis. “Is the Retisert more effective, less effective or comparable to the systemic therapy?” asked Dr. Dunn. “That was a major question three years ago. It’s still a major question today.”

Iluvien. pSivida is also studying the delivery of fluocinolone acetonide in a nonerodable intravitreal implant injected through a 25-gauge needle during an office procedure, allowing for a self-healing wound. With two release rates—0.5 µg/day for 18 months or 0.2 µg/day for 36 months—it floats in the vitreous cavity for the treatment of DME. A trial of 37 patients on Iluvien showed that the high-dose group had better visual acuity than the low-dose arm, but also suffered higher rates of glaucoma. Iluvien is licensed to Alimera, which will be seeking FDA approval of the implant by the third quarter of this year, following the conclusion of the FAME (Fluocinolone Acetonide in Diabetic Macular Edema) study. Alimera is also studying Iluvien for both wet and dry AMD as well as for retinal vein occlusion.



I-Vation. Taking a slightly different twist on treatment of DME, I-Vation, developed by SurModics, is an implantable titanium screw coated with triamcinolone acetonide. Requiring conjunctival dissection, it is implanted through a 25-gauge needle and self-anchors in the sclera, delivering the drug for up to two years. The implant’s helical coil increases the surface area for drug delivery and uses a polymer coating that’s commonly used for cardiac stents. “Theoretically, you can coat it with almost any drug you want,” said Dr. Dunn, who added that its design offers a lot of appeal. And although it involves a conjunctival cut-down in an operating room, the 0.5-mm needlestick makes it less invasive than Vitrasert or Retisert, which require larger incisions.



I-Vation’s safety and effectiveness are still under study, although a phase 1 trial of 30 patients showed a reduction of DME at 24 months. However, a phase 2b clinical trial was suspended in 2008 when laser treatment appeared to be better than intravitreal injections of triamcinolone, said Dr. Kuppermann.

BIODEGRADABLE IMPLANTS

Although biodegradable implants are newer, they offer the prospect of certain benefits over reservoir systems, such as no need for removal and less potential for ocular toxicity. “Because reservoir implants last longer, they risk more ocular complications of the drug,” said Dr. Kuppermann. “And, although we think the reservoir hardware we leave behind is benign, we haven’t really answered that question yet.” Biodegradable implants are more easily tailored by modifying polymer chemistry to change release rates and accommodate different drugs, he said.

The first sustained-release biodegradable steroid implant, Surodex, was a device placed behind the iris for postoperative inflammation after cataract surgeries. A market did not materialize, however, because Medicare wouldn’t reimburse for its placement during cataract surgery.

Ozurdex. Inserted surgically in the operating room or with a special injector, this device secured FDA approval for Allergan in June of 2009 for macular edema caused by vein occlusion. Called Posurdex during testing, the FDA required a name change for the version distributed in the United States. Now called Ozurdex, this implant is a biodegradable copolymer in pellet form that hydrolyzes to lactic and glycolic acids, releasing either

700 or 350 µg of dexamethasone over six months. Now under way is a combination study of Ozurdex and ranibizumab (Lucentis) to see if ranibizumab dosing can be reduced.

In the meantime, said Dr. Dunn, Ozurdex will likely be used off-label for

certain types of uveitis. “Because it’s a more water-soluble steroid than triamcinolone or fluocinolone acetonide, it may be able to control disease without causing as many ocular complications,” said Dr. Kuppermann, adding that this could be compelling enough for many ophthalmologists to make the switch. “With a global pharmaeconomic analysis taking into account the differing rates of cataract and glaucoma in each of the technologies, it is possible that Ozurdex may be less expensive in this context than injections,” he said, “especially if the risks for glaucoma and cataract were significantly less.”

Dr. Dunn cautioned that although preliminary data show a lower rate of glaucoma than was associated with Retisert, the devices have not undergone a head-to-head comparison. “Many glaucoma cases don’t show up in the first six months,” he said. “It might be that the data will show patients who get repeated Ozurdex injections experience an equally high glaucoma rate.”

INNOVATION ON TAP

What’s on the horizon for implant technology? Here’s a sampling of devices in preclinical studies.

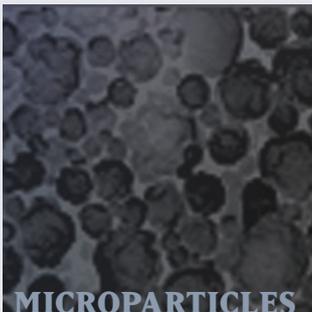
Lucentis in a new vehicle. Last October, SurModics provided Genentech, a member of the Roche group, an exclusive license to use its proprietary biodegradable microparticles drug-delivery system to develop a sustained-release formulation of ranibizumab.

BioSilicon Technology. pSivida is developing a nanostructured porous silicon, which Dr. Ashton said is fully bioerodible, can accommodate various molecule sizes and stabilizes the drug within the device, thereby overcoming issues of long-term delivery of peptides and proteins.

Replenish Mini Pump. The Replenish Mini Pump is a microelectromechanical system that delivers continuous or bolus-targeted drugs to both the anterior and posterior segments. The electronically activated device consists of a refillable drug reservoir, flexible cannula and check valve with a 30-gauge needle used to refill the reservoir transconjunctivally in the clinic. Most of the device resides outside the eye, with only a portion of the cannula inside. This makes it easy to implant and remove, said Mark S. Humayun, MD, PhD, codeveloper of the device and professor of ophthalmology and biomedical engineering at the University of Southern California in Los Angeles. “This is basically a reverse-drainage glaucoma device,” said Dr. Humayun. “Glaucoma devices drain fluid from the eye to lower pressure, but this pumps drugs into the eye.” Its novelty, he said, is its ability to be refilled. Another feature is its programmability: A wireless remote control can customize delivery and adapt to the changing environment in the eye. “We think this device also has major applications for retinal disease and certain inflammatory diseases,” he said.

Encapsulated Cell Technology (ECT). Developed by Neurotech Pharmaceuticals, ECT can potentially solve the problems of delivering large molecular weight compounds to the retina and storing complex proteins at 37 degrees centigrade for prolonged periods without significant molecular degradation, said Dr. Kuppermann.

In principle, ECT involves the genetic engineering of human retinal pigment epithelium cells in a process called plasmid transfection. The plasmids encode a therapeutic protein, which is then incorporated into the cell’s genome. The engineered cells are loaded into a polymer membrane capsule and surgically inserted into the vitreous body during an outpatient procedure. There they continuously produce the therapeutic protein, which then diffuses out of the implant at the target site. Encapsulated cells are nourished by the influx of nutrients yet simultaneously protected from direct contact with the immune system. “ECT is unique because there is no need for long-term drug storage—it essentially makes the bread fresh daily,” said Dr. Kuppermann. “It’s capable of programming



cells to produce a wide range of compounds. Durability of the current implant is about 18 months, maybe longer.”

Neurotech’s current ECT iteration is NT-501, which secretes ciliary neurotrophic factor for the treatment of retinal degeneration. In March of 2009, Neurotech announced positive results from the high-dose group of its NT-501 phase 2 study of dry AMD. At 12 months, 96.3 percent of treated patients lost fewer than three lines of vision compared with 75 percent of patients in the control group. The company plans to test ECT with several other applications.

LESSONS FOR THE FUTURE

Still in its youth, implantable drug delivery is nevertheless beginning to offer up a few pearls of wisdom.

Location, location, location. Where an implant

resides in the globe may have great bearing on drug concentrations. For example, moving an implant 4 mm farther into the vitreous increases macular drug levels fourfold compared with implants placed at the eye wall, said Dr. Kuppermann.

Location might increase or decrease side effects, as well, said Dr. Ashton. “But unfortunately there are no human data to substantiate the mathematical projections.” For example, he said those projections predict that “if you move the Retisert device 5 or 6 mm posteriorly, you’d have a dramatic reduction in the concentration of the drug in the aqueous humor. This could possibly cause a concomitant reduction in IOP elevation.”

With respect to tumors, implant location would require careful consideration, especially in the vitreous, said Dr.

IMPLANTABLE DRUG DELIVERY ON THE MARKET, IN THE PIPELINE

IMPLANT	TRIALS/FDA APPROVAL	DELIVERY	DRUG/DOSE	DURATION
Reservoir Implants				
Vitrasert (<i>pSivida</i> , licensed to <i>Bausch & Lomb</i>)	1996 FDA approval for CMV retinitis	Surgical implantation into pos- terior segment through 5.5-mm pars plana incision.	Ganciclovir 0.45 mg	5 to 8 months
Retisert (<i>pSivida</i> , licensed to <i>Bausch & Lomb</i>)	2005 FDA approval for chronic noninfectious uveitis	Surgical implantation into pos- terior segment through 3.5-mm pars plana incision.	Fluocinolone acetonide 0.59 mg	30 months
Iluvien, previously Medidur (<i>pSivida</i> , licensed to <i>Alimera</i>)	Awaiting results of FAME trial for DME	Injection of 3-mm-long cylindri- cal tube via pars plana inci- sion. In-office procedure using 25-gauge needle.	Fluocinolone acetonide 0.5 µg/day or 0.2 µg/day	Larger dose for 18 months or smaller dose for 36 months
I-Vation (<i>SurModics</i>)	Phase 1 trial for treatment of DME	Surgical implantation through a 25-gauge needle with conjuncti- val cut-down.	Triamcinolone acetonide 1 µg/day or 3 µg/day	Up to 2 years
Biodegradable Implants				
Ozurdex, previously Posurdex (<i>Allergan</i>)	2009 FDA approval for macular edema due to vein occlusion	Surgical implantation through 20-gauge incision or 22-gauge injection.	Dexamethasone 350 or 700 µg	6 months
New Approaches				
Lucentis in microparticles (<i>SurModics</i> , licensed to <i>Genentech</i>)	In development	Biodegradable microparticles.	Not yet determined	Not yet determined
BioSilicon Technology (<i>pSivida</i>)	In development	Nano-structured porous silicon.	Not yet determined	Long-term; to be determined
Replenish Mini Pump (<i>Replenish</i>)	In development	Electronically activated, refill- able drug reservoir with flexible cannula and valve with 30-gauge needle.	Not yet determined	Not yet determined
NT-501 (<i>Neurotech Pharmaceuticals</i>)	Phase 2 study of dry AMD	Genetically engineered human retinal pigment epithelium cells with transfected plasmids encod- ing a therapeutic protein; cells are loaded into a polymer mem- brane capsule.	Ciliary neurotrophic factor. High dose: 203,000 cells released at 800 ng per 1 x 10 ⁶ cells/day	Up to 18 months

Kompella. "Once you invade the intraocular space, there is the possibility that you could spread tumor cells around. But if you're in the periocular space, as opposed to invading intraocular tissues, you may be okay."

Timing and dosing. A high initial release of medication and rapid elimination is one of the problems with traditional injection systems, said Dr. Dunn. So a critical advantage of a sustained-release system is that it provides a consistent level of drug concentration. Even given that advantage, a drug's molecular size and characteristics can affect the longevity of a system. And it may be preferable in some instances, said Dr. Dunn, to aim for pulsatile delivery, allowing for a drug holiday to avoid effects such as elevated IOP. In other situations, it may be preferable to maintain a low but steady dose to prevent side effects yet still achieve therapeutic levels. Combination drug delivery systems also hold appeal, especially for inflammatory diseases. Co-administering drugs may mitigate complications, for example, by perhaps minimizing the effects of an anti-VEGF with a neuroprotectant.

The drug that delivers itself. The most elegant solution might be a completely vehicle-free system made entirely of drugs conjugated to themselves, said Dr. Ashton. In the end, ease of administration will largely determine which systems prevail. "If you have something administered in an office visit, I'm not sure it really matters if it is a lump, a bump or a solution—as long as the darn thing works."



MEET THE EXPERTS

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