Sustained Drug-delivery for Retinal Disease

Current technologies include implanted and injected devices.

BY GLENN J. JAFFE, MD

Sustained delivery of drugs to the posterior segment of the eye has increasingly become a therapeutic option in ophthalmology. Before the development of delivery systems for sustained drug delivery to the posterior segment, methods to deliver pharmacotherapy to the back of the eye were limited. Chronic, sight-threatening conditions, such as infectious and noninfectious uveitis, often required systemic treatment, with the concomitant risk of systemic side effects, or repeated intravitreal injections, with the risk of local complications. Topical drug delivery for posterior segment disease faced the challenge of penetrating through many layers of the eye to reach its target, while systemic delivery had to cross the blood-ocular barrier to achieve an effect.

One of the first successful devices for sustained drug delivery to the posterior segment was developed in response to the AIDS crisis in the 1980s and '90s. The ganciclovir implant was developed to provide controlled antiviral release in the eyes of people with AIDS-related cytomegalovirus (CMV) retinitis.[1] The implant delivered ganciclovir over a period of 5 to 8 months and relieved patients with CMV retinitis of the need to undergo intravenous treatment with ganciclovir.

The technology for the ganciclovir implant, which is currently marketed by Bausch + Lomb as Vitrasert, was developed by co-invented by Paul Ashton, P. Andrew Pearson, and Thomas Smith at the University of Kentucky. Dr. Ashton later moved to Boston, where he helped to found Control Delivery Systems (CDS), a start-up company that was acquired by the Australian company pSivida Ltd. in 2006 and renamed pSivida Inc. CDS also developed, and pSivida now owns, the technology for the Retisert fluocinolone acetonide (FA) intravitreal implant, marketed by Bausch + Lomb and currently approved for treatment of chronic noninfectious uveitis affecting the posterior segment; and the Medidur implant technology, licensed to Alimera Sciences and used in the Iluvien injectable FA intravitreal insert.

This article reviews some of the steps in the development of these sustained-delivery technologies and implications for future therapeutic options.

TREATMENT FOR UVEITIS

After the development of the ganciclovir implant, as CDS was investigating other delivery system options, my colleagues and I at Duke University were looking for more effective and efficient ways to treat posterior uveitis, with an interest in sustained delivery. Using preclinical animal models of uveitis, we tested several prototype implant devices developed by CDS, including cyclosporine, dexamethasone, and a number of configurations of FA implants.

The FA implant that would eventually become the basis for Retisert was modeled on the design of the ganciclovir implant. The device consisted of a suture strut connected to a polymer/drug pellet, designed to be sutured to the eye wall during a vitrectomy procedure. Like the ganciclovir implant, the pellet contained a solid drug core surrounded by polymer, but both the polymer and drug components were different; the ganciclovir implant had used an ethylene vinyl acetate and polyvinyl alcohol polymer, while the new FA implant used a silicone-polyvinyl alcohol combination.

We first tested the dexamethasone implant in an animal model of severe uveitis and found that it worked well to control inflammation. Subsequently, the FA implant underwent pharmacodynamic studies and safety studies in animals,[2] but it was not tested in an animal model of uveitis before it was used in humans. Knowing that the dexamethasone implant had been so effective in the animal model of uveitis, and having studied the pharmacodynamics and safety of FA, we thought the implant was likely to perform well.

FIRST HUMAN USE

The first human use of the FA implant was in a patient with severe uveitis refractory to other treatments. This

patient, under the care of the uveitis specialist at the Wilmer Eye Institute of Johns Hopkins University in Baltimore, did not tolerate immunosuppressant medications and had received multiple intravitreal injections of a corticosteroid—well over 100 injections in total.

We thought this patient would be an ideal candidate for the FA implant. At the time we became aware of the patient, however, the implant had not yet undergone the safety testing mentioned above. Therefore, over the next year the patient was maintained on steroid injections while safety and pharmacokinetic studies were performed.[2] When we were satisfied that the implant would be safe and would release the drug over a reasonable time frame, we applied to the US Food and Drug Administration (FDA) for an Emergency Use Investigational New Drug (IND) approval. We requested the emergency IND because the frequency of the patient's inflammatory episodes were accelerating; the time between recurrence became shorter and shorter, and caused additional retinal damage with each recurrence. We were concerned that if we waited to obtain a standard IND, the patient would likely suffer additional permanent vision loss.

The implant worked well in this patient, and we obtained IND approval to treat other patients at our center with no viable treatment alternatives—patients who did not tolerate immune-suppressing medications or steroid injections or both, or in whom these treatments were not working. Based on our experience with these patients, we believed that the FA implant was a promising new therapy for the treatment of severe uveitis that deserved to be evaluated in a randomized study in a larger group of patients.[3]

CLINICAL TRIALS

At that point we embarked on an individual investigator pilot study of the implant using two doses of FA.[4] As this trial progressed, officials at Bausch + Lomb became aware of our work and were enthusiastic enough about the results to fund phase 3 studies of the implant in people with noninfectious uveitis.

It is notable that the rationale for this study was based on the safety study in rabbits and a handful of patients from a preliminary pilot study. It is highly unusual in my experience that a company would be willing to invest in a new technology without much more patient data. The quiet eyes of our uveitis patients must have presented compelling evidence.

Two 34-week randomized prospective clinical trials were undertaken, one in 278 patients at 26 US centers and one center in Singapore,[5] and a second confirmatory study in 239 patients at 19 centers in Canada, the United States, Europe, Asia, and the Pacific Rim.[6]

The implant significantly reduced uveitis recurrence, improved visual acuity, and decreased the need for adjunctive therapy in the patients in these trials. The most common side effects included increased intraocular pressure (IOP) and cataract progression. In 3-year follow-up of pooled data from phase 2b/3 clinical trials, 74.8% of patients required ocular hypotensive medications, and 36.6% required IOP-lowering surgery.[7]

In 2003, Bausch + Lomb assumed all responsibility for clinical development and regulatory activities related to the FA implant from Control Delivery Systems.[6] The Retisert implant received FDA approval in April 2005 based on the results of those two pivotal trials.

INJECTABLE PLATFORM

Results with the sutured-in FA implant showed that this paradigm of drug delivery was effective, but the safety profile left room for improvement. From the clinician's point of view, a smaller, less-invasive implant that could potentially be injected in an office procedure was desirable and might result in less elevation of IOP. This was the impetus behind development of the Medidur drug delivery system, the platform now used in the Iluvien insert. Rather than being secured to the eye wall with sutures, this nonbiodegradable insert could be injected into the vitreous cavity, where the drug would be released over a prolonged period of time.

We tested this injectable FA device in the rabbit model of severe uveitis, the same one used to evaluate the dexamethasone implant, and found it to be effective.[8] However, it was first brought to humans not in patients with uveitis, but rather in patients with diabetic macular edema (DME). The FDA was willing to allow the use of this next-generation FA implant in patients with DME before it had been tested fully in animals because the earlier FA insert had been evaluated in patients with DME before those efforts were curtailed to concentrate on the uveitis trials.[6]

These intravitreal FA inserts have now been evaluated in clinical trials in patients with DME. One-year results of a phase 2 clinical trial in 37 patients with DME were recently published online,[9] and 2-year results of two large phase 3 trials were presented at a meeting earlier this year.[10]

The Fluocinolone Acetonide in Macular Edema (FAME) phase 3 study consisted of two controlled randomized clinical trials at 101 centers in the US, Canada, Europe, and India, enrolling a total of 953 patients in two identical protocols. Patients were randomly assigned to one of three groups in a 2:2:1 randomization. One group received a high dose of FA (approximately 0.45 µg per day initially), a second received a low dose (approxi-

mately 0.23 µg per day initially), and a control group received sham treatment.

At 2 years, 26.8% to 30.6% of patients receiving the low dose demonstrated improvement in best corrected visual acuity (BCVA) of at least 15 letters from baseline, and 26.0% to 31.2% of those receiving the high dose demonstrated that level of improvement. In the control group, 14.7% to 17.8% of patients demonstrated BCVA improvement of at least 15 letters from baseline.

Regarding safety, increases in IOP of 30 mm Hg or more were seen in 16.3% of patients receiving the low dose and 21.6% of patients receiving the high dose. Trabeculectomy was performed in 2.1% of patients receiving the low dose and 5.1% receiving the high dose.

CHALLENGES FACED, CHALLENGES REMAIN

Engineers and researchers overcame several technological challenges in the development of the existing nonbiodegradable FA implants. One challenge was the selection of inert materials appropriate for long-term residence in the eye. In the case of the sutured-in FA implant, the silicone-based polymer was similar to the familiar materials used for many decades in foldable silicone intraocular lenses (IOLs). The polyimide material chosen for the nonsutured insert is in the same chemical family as some IOL haptics that have likewise stood the test of time in the eye. For both implants, engineers faced the challenge of achieving drug release at a constant rate, and this was accomplished fairly readily.

Another engineering challenge with the sutured-in FA implant was securing it to the eye wall. In some of the prototypes we investigated, the drug/polymer pellet separated from the suture strut over time. With improvements in the bond between the strut and the pellet, that occurs rarely today.

For the nonsutured FA insert, engineers faced the challenge of providing an injection system that is convenient to use in the clinic and as comfortable for the patient as possible. The 25-gauge needle used for injection is considerably larger than the 32-needle we currently use for intravitreal antiangiogenic injections, but the wound is self-sealing. From the surgeon's perspective, there is a short learning curve to be overcome for administering the device, but from the patients' perspective the procedure seems to be well tolerated.

To date there is not much experience with use of the nonsutured insert in vitrectomized eyes, so it remains to be seen how it will perform in that scenario: Will it move around, and will that cause problems? Patients who had previously undergone vitrectomy were excluded from the FAME study, and so we do not have data from that trial to address implant performance in vitrectomized eyes. The sutured-in implant is secured to the eye wall, so the absence of vitreous is not an issue for implant mobility. In a nonvitrectomized eye, the nonsutured insert is held by the vitreous or in the vitreous base and tends not move around. Experience will show what happens without the support of the vitreous.

The positive results of the FAME study bode well for regulatory approval of the Iluvien FA insert, but to date it has not been approved for general use.

A pilot study (FAVOR: Fluocinolone Acetonide for Vein Occlusion in Retina) is under way investigating the use of this device in patients with macular edema secondary to retinal vein occlusion.

An individual investigator study of the sutured-in FA implant for patients with macular edema secondary to retinal vein occlusion is ongoing at Duke University. We are investigating use of the device in patients with chronic macular edema that has not responded to other types of treatment.

Sustained drug delivery to the posterior segment already has a significant history as a therapeutic option in ophthalmology. Current experience suggests that use of these devices will increase with time and that these technologies will continually improve. It is hoped that patients with chronic inflammatory diseases will derive benefit from these technologies for many years to come. ■

Glenn J. Jaffe, MD, is a Professor of Ophthalmology in the Vitreoretinal Service at Duke University Eye Center, Durham, NC. He reports that he has no financial relationships to disclose in relation to this article. Dr. Jaffe may be reached at jaffe001@mc.duke.edu.

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