

Implants Can Deliver Corticosteroids, Pharmacologic Agents

Although intravitreal injections are very successful, the frequency with which they have to be used is a concern.

BY BARUCH D. KUPPERMANN, MD, PhD

The concept of local delivery of pharmacologic agents to the eye has been important for some time. The presence of the blood-retinal barrier renders systemic therapy relatively ineffective. Fortunately, we have an effective posterior drug delivery system available to us—intravitreal injection—and we have been successful with this technique.

Now with the current era of effective pharmacotherapy, however, we are being a bit overwhelmed with the frequency with which we have to give intravitreal injections. Therefore, we are interested in looking at longer-term drug delivery systems. Two of these have already been licensed, both by Bausch & Lomb (Rochester, NY), have been approved by the US Food and Drug Administration, and are extremely effective: Ganciclovir implant for cytomegalovirus retinitis and a fluocinolone acetonide reservoir implant for uveitis. A smaller version of the fluocinolone reservoir implant (Medidur; Alimera Sciences, Alpharetta, GA) is in phase 3 clinical trials. Allergan (Irvine, CA) has a biodegradable dexamethasone implant in phase 3 trials, and a helical coil containing triamcinolone (SurModics, Eden Prairie, MN) is in phase 1 trials. Another new technology is an encapsulated cell implant (Neurotech, Lincoln, RI) that is in phase 1 trial.

RESERVOIR STYLE IMPLANTS: RETISERT AND MEDIDUR

Retisert. Bausch & Lomb's Retisert reservoir-style implant for fluocinolone is quite remarkable; it is designed to last approximately 1,000 days (Figure 1). The implant contains a total of 0.59 mg of drug, and it delivers a 0.5 µg per day of fluocinolone with a terrific benefit. But we also see, unfortunately, some significant ocular side effects. The concept that such a small amount of drug can be effective, however, highlights the efficacy of drug delivery systems.

There have been uveitis and diabetic macular edema (DME) trials with the Retisert technology, but currently the label indication is for uveitis only. While a benefit is

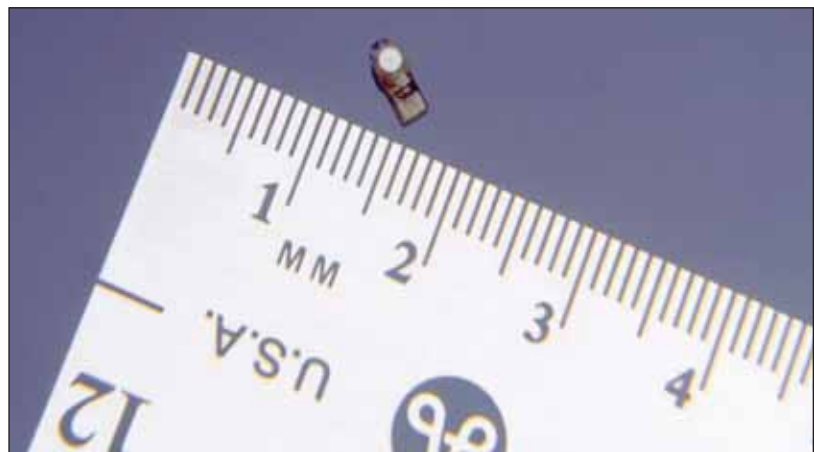


Figure 1. Bausch & Lomb's Retisert reservoir-style implant for fluocinolone is designed to last approximately 1,000 days.

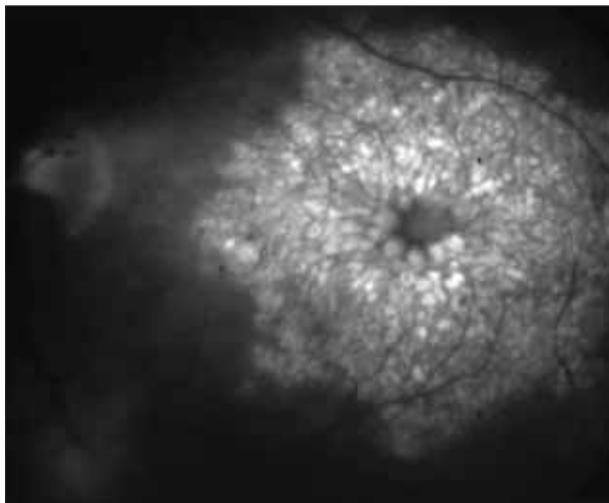


Figure 2. A case of DME with an extensive cystoid component.

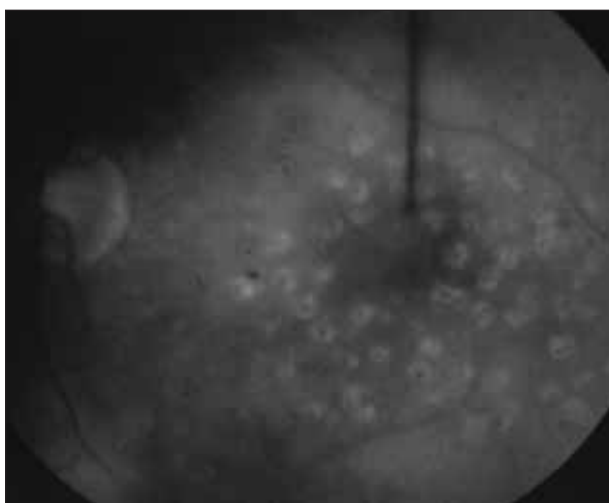


Figure 3. Complete resolution of the fluid was seen 6 weeks later and the preexisting laser spots that were previously invisible in the face of edema were visible.

seen in both conditions, the ocular side effects were significant enough that the indication was limited to uveitis.

The type of efficacy we see is not near misses or close calls: 1-year postimplant the recurrence rate for uveitis was 5.4% compared with 46% in the fellow eye. At 3 years that curve begins to close together, but it is still statistically significant. In this case of DME with an extensive cystoid component (Figure 2), complete resolution of the fluid was seen 6 weeks later and the preexisting laser spots that were previously invisible in the face of edema were visible (Figure 3).

The trouble is the ocular side effects of steroids, and the question of whether all steroids behave the same. In our series we saw almost a 50% rate of glaucoma—a significant trade off which seems acceptable in uveitis



Figure 4. Comparison of the sizes of the Medidur, Retisert, and Vitrasert implants.

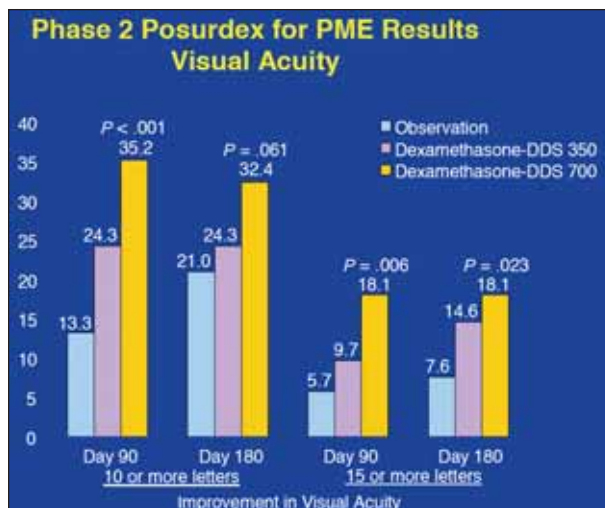
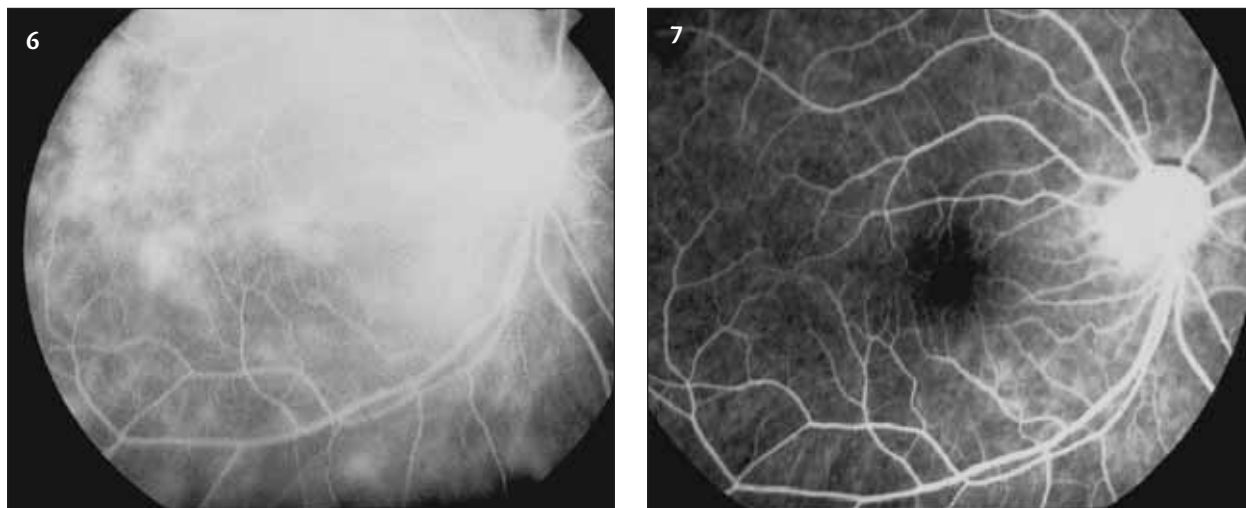


Figure 5. In a large study of patients with persistent macular edema, 18% of eyes had a three-line improvement in vision out to 180 days.

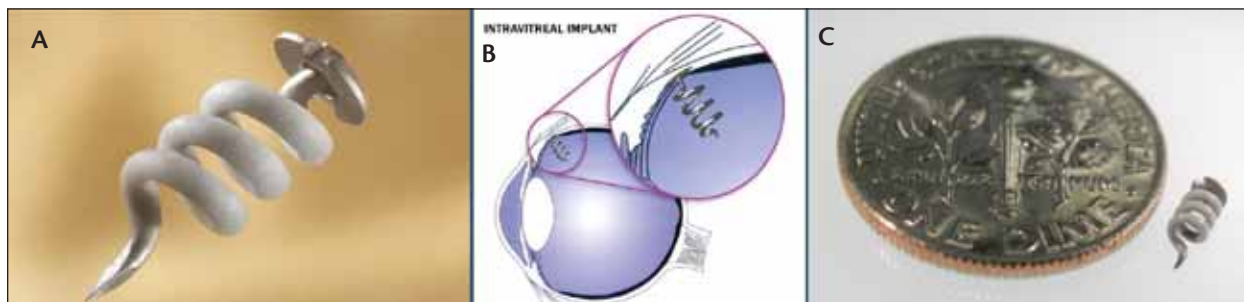
patients, but not in DME patients.

Additionally, cataracts are almost ubiquitous by the time you get to 3 years in the study: 93% of eyes needed cataract surgery compared to 20% in the control group.

Medidur. The Medidur (Alimera) implant also contains fluorocinolone, but it is much smaller (Figure 4). The implant is a surgical cut down that must be performed through a 3.5-mm incision in the operating room with a 25-ga needle. It is a reservoir implant, but it is not sutured to the eye wall, and it is allowed to float freely in the vitreous space. A phase 3 trial is underway with some limited safety data on 20 patients; 900 patients will be enrolled in a larger phase 3 trial of DME.



Figures 6 and 7. A patient before treatment (left) and then again 2 1/2 months after treatment (right).



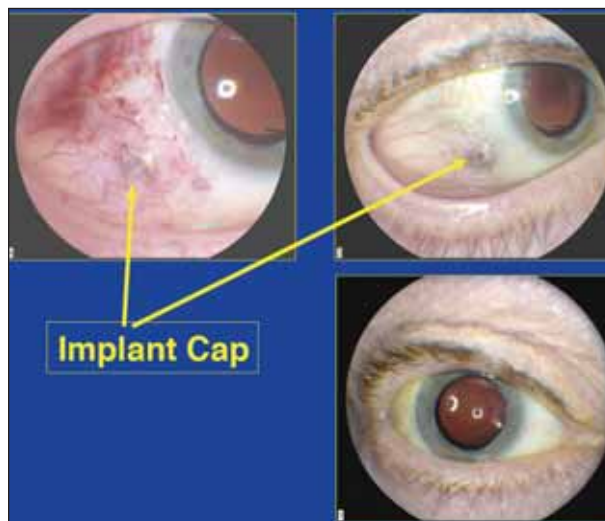
Figures 8 and 9. I-vation technology from SurModics consists of a helical coil with an eluting polymer containing triamcinolone (A through C above). It is implanted through a 25-ga needlestick and it is self-anchoring within the sclera (Figure 9, right).

POSDUREX BIODEGRADABLE IMPLANT

The Posurdex biodegradable dexamethasone implant (Allergan) is a different concept. It's biodegradable system is not reservoir based, it uses polymer and drug mixed together and the drug releases over time. As the polymer degrades the drug is released, so finally all that is left is the polymer which completely degrades.

Phase 2 trials tested a version of this implant through a 20-ga incision, surgically inserted in the operating room. The version being tested in phase 2b and 3 trial is inserted in the office setting with no surgical cut down and a 20-ga biplanar pass; it is also longer and thinner than the original version.

We have seen strong efficacy with this technology as well. In a large study of patients with persistent macular edema, 18% of eyes had a three-line improvement in vision out to 180 days (Figure 5). This study, in press with *Archives of Ophthalmology*, included eyes that had



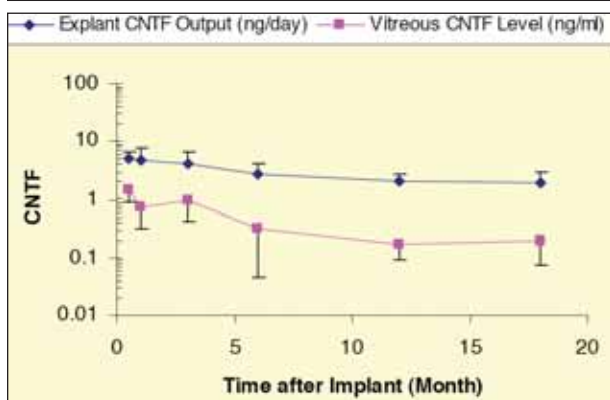
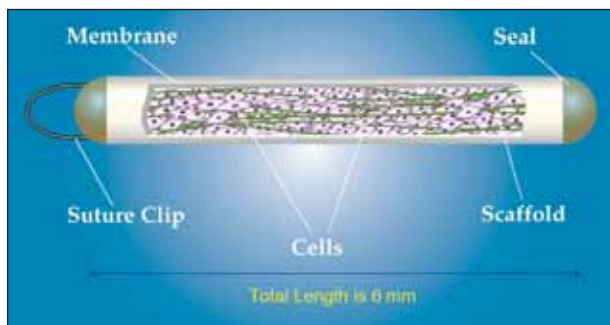
failed all prior therapy. Figure 6 and Figure 7 show a patient before treatment and then again 2 1/2 months after treatment.

EFFECTIVE

These therapies work, and we have found that sequestering the drug into the eye is very effective. The concern with the fluorocinolone implant—and we are looking at

COVER STORY

ADVANCES IN
DRUG DELIVERY



Figures 10 through 12. The Encapsulated Cell Technology implant is 6-mm long and is surgically placed inside the eye (top). The CNTF elutes over time (middle), and the explants continue to secrete CNTF (bottom).

this very carefully with the Posurdex implant—is the increase in intraocular pressure (IOP) and the incidence of cataract. So far with 6-month follow-up, we are seeing some evidence of an increase in IOP with the fluorocinolone implant, but to a lesser degree than with triamcinolone. In the current phase 3 trials patients received repeated injections for up to 3 years, therefore we will be getting data to understand the long-term consequence of this technology.

NOVEL HELICAL DESIGN

The I-vation technology from SurModics (Eden Prairie, MN) consists of a helical coil with an eluting polymer containing triamcinolone. This system pro-

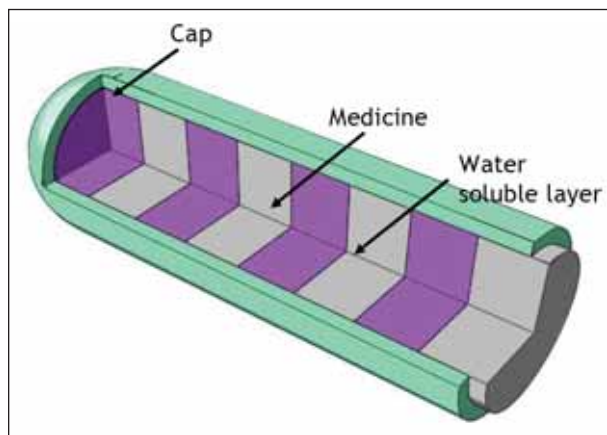


Figure 13. The Ocular Drug Delivery Group at the University of California, Irvine, is working on the Micromachined Drug Delivery System.

vides a way of obtaining a controlled release of triamcinolone, the steroid that we are most familiar with and have used most commonly. It is implanted through a 25-gauge needlestick and it is self-anchoring within the sclera (Figure 8 and Figure 9). A prospective, randomized, double-masked multicenter trial is underway with this technology, using two formulations in 30 patients with DME. Enrollment is complete, and this trial will have a 3-year follow-up.

Encapsulated Cell Technology ophthalmic implant is controversial. This technology uses ARPE-19 cells, a human RPE cell line retinal cell biologists use in their labs.

ENCAPSULATED CELL TECHNOLOGY

Encapsulated Cell Technology (Neurotech, Lincoln, RI) ophthalmic implant is different and exciting, but also controversial. This technology uses ARPE-19 cells, a human retinal pigment epithelium (RPE) cell line retinal cell biologists use in their lab. These cells are commercially available and have been modified to produce ciliary neurotrophic factor (CNTF). They can be designed to produce almost any growth factor. Neurotech claims, for example, the cells can produce rhuFab V2, a ranibizumab-like (Lucentis; Genentech, San Francisco) compound. The controversy is that these RPE cells produce other compounds as well and the question is whether these are being disproportionately stimulated. Of course, RPE cells in our own eyes produce growth factors all the time as well.

The Encapsulated Cell Technology implant is 6 mm long and is surgically placed inside the eye (Figure 10). The CNTF elutes over time (Figure 11), and the explants continue to secrete CNTF (Figure 12). Postexplant the cells still appear viable. In this solution to the problem, how can complex proteins remain stable at 37° Centigrade for a prolonged period of time inside the eye, they are “baked fresh daily,” so to speak.

MICROMACHINED DRUG DELIVERY SYSTEM

Our Ocular Drug Delivery Group at the University of California, Irvine is working on the Micromachined Drug Delivery System (Figure 13). The goal of this project is to use micromachining technology to build a passive, programmable, pulsatile drug delivery system, with many pulses, yet small enough for ocular implants. There are null zones in our polymer and then zones loaded with drug, this enables drug levels to cycle up and down in a preprogrammed fashion, also allowing native expression of endogenous cytokines and growth factors.

CONCLUSION

There are two fundamental approaches and philosophies with regard to ocular drug delivery. One is the longer-acting reservoir implants that offer good long-term control of disease but with potential for drug or suppressive side effects from chronic suppression of growth factors. The other option provides for shorter-acting biodegradable inserts that potentially expose the eye to less drug or suppressive side effects but may not control disease as well. Depending on what drug you pick for this method, however, we might get such good suppression of the cytokine cascade that the eyes can then have a prolonged drug holiday with a slow mounting of the cytokine cascade before clinical disease is manifested—we would treat at that point.

The hope is that all of these technologies will see the light of day and that different approaches will have preferential usage in different diseases or with different drugs. ■

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Kuppermann BD. Implant delivery of corticosteroids and other pharmacologic agents. Presented at Retina 2006: Emerging New Concepts. Held in conjunction with the American Academy of Ophthalmology 2006 annual meeting. Nov 10-11, 2006. Las Vegas.

TRANSSCLERAL UPTAKE, DIFFUSION OF BEVACIZUMAB AND RANIBIZUMAB

REVIEWED BY LENNART C. BERGLIN, MD

Transscleral drug delivery of bevacizumab (Avastin; Genentech, San Francisco) and ranibizumab (Lucentis, Genentech), possibly with a sustained release, may be a viable alternative to intravitreal drug injection.

Lennart C. Berglin, MD, and colleagues from the St. Erik's Eye Hospital and Karolinska Institute, Stockholm, undertook an experiment that explored in vitro and in vivo transscleral-retinal pigment epithelium (RPE) uptake and diffusion of bevacizumab, ranibizumab, and structurally related immunoglobulins.

According to an abstract the group will present at the upcoming Association for Research in Vision and Ophthalmology meeting, human scleral donor tissues were perfused at 15 mm Hg in a Lucite block system for 24 hours with 200 μ L FITC conjugated IgG, FITC conjugated Fab Fragment, bevacizumab, or ranibizumab. After perfusion, the drugs were tagged with a FITC or CY3 conjugated Goat Anti-Human Fab2 fragment specific IgG. The investigators analyzed the perfusate and scleral washout for protein content. Transscleral-RPE uptake and diffusion of bevacizumab and ranibizumab were analyzed in both living and euthanized mice and Dutch belted rabbits up to 24 hours after subconjunctival injection.

Dr. Berglin's group found that human scleral tissue was permeable to all immunoglobulins studied, often with a visible intrascleral fluorescent gradient. After 2 hours, washout for the agents was maximal. They found that human sclera also showed uptake of bevacizumab and ranibizumab when exposed on the episcleral surface. The live mice had levels of bevacizumab and ranibizumab detectable in the sclera and retina after 1 hour with increasing intensity after 3 hours. The drugs were minimally visible after 24 hours. In situ rabbit sclera also showed a progressive uptake of both bevacizumab and ranibizumab at 24 hours from a 50 μ L subconjunctival injection.

The group concluded that human and rabbit sclera are permeable to these agents and that transscleral drug delivery could be a viable alternative to intravitreal injection. ■

Lennart C. Berglin, MD, is from the Karolinska Institutet and St. Erik's Eye Hospital, Stockholm. Dr. Berglin disclosed that he has no financial interest in the products or companies mentioned. He may be reached at lennart.berglin@sankterik.se.

Berglin LC, Bergman L, Kim ES, et al. Transscleral uptake and diffusion of bevacizumab (Avastin) and ranibizumab (Lucentis). To be presented at the Association for Research in Vision and Ophthalmology 2007 annual meeting. May 10, 2007. Fort Lauderdale, Fla.