

A Novel Sustained-release Intravitreal Drug Delivery System for Retinal Vascular Disease

Results with a liquid containing triamcinolone were promising in phase 1 trial in RVO.

BY ANNE E. FUNG, MD

The past decade has seen the introduction of numerous pharmacologic treatments for retinal diseases. The prime example of this was seen with therapies for choroidal neovascularization secondary to age-related macular degeneration (AMD); first, photodynamic therapy with or without intravitreal triamcinolone,¹ followed shortly by intravitreal injection of vascular endothelial growth factor (VEGF) inhibitors,²⁻⁴ improved the prognosis for patients with this heretofore blinding degenerative condition. Now AMD patients may reasonably hope to maintain and even improve visual acuity. This improvement in outcomes has come at a cost, however, as patients, retina specialists, and health care systems are challenged with managing frequent visits and potential risks of repeated intravitreal injections.

Retinal vein occlusion (RVO), one of the most common retinal vascular disorders, second in prevalence only to diabetic retinopathy, may be the next disease to be affected by the retina pharmacologic revolution. Clinical trials of an anti-VEGF agent for treatment of central and branch RVO have shown clinically and statistically significant improvements in visual acuity.^{5,6} Again, however, there is the potential for the same treatment burden as with AMD: The improved vision results in the trial were achieved with monthly intravitreal injections.

Considering this current trend, it is clear that a sustained-release drug delivery method for treatment of retinal diseases is an unmet clinical need. An injectable, biodegradable, sustained-release system could reduce the

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treatment burden for patients and physicians.

To answer this need, Icon Biosciences, Inc. (Sunnyvale, CA) is developing a promising drug delivery technology called Verisome, a delivery system that can be injected into the vitreous as a liquid via a standard 30-gauge needle. When the Verisome-based product is injected into the vitreous, it coalesces into a single spherule that settles in the inferior vitreous. The biodegradable vehicle provides controlled, extended drug release; the shrinkage of the Verisome spherule over time reflects the simultaneous degradation of the delivery system and release of drug.

This article presents some of the science behind this delivery system and summarizes results of a recent clinical trial.

THE SCIENCE

The Verisome technology is a robust drug-delivery system that, according to its manufacturer, can potentially be used to release a broad range of pharmaceutical agents, including small molecules, peptides, proteins, and

monoclonal antibodies. The basic technology is highly versatile and can be formulated into numerous products, as a biodegradable solid, gel, or liquid that can provide drug release in a controlled manner over weeks to a year for ocular, systemic, or topical applications.⁷ Ophthalmic applications are focused on its ability to create an injectable liquid or slightly viscous gel.

The drug delivery system degrades as the active agent is released over the intended time duration. In ophthalmology, this mode of delivery offers clinical advantages because the physician can easily assess the status of therapy by observing the drug-containing system in place in the eye. When the spherule is no longer visible, all the drug has been released, and no vehicle remains in the eye. The ability to observe the drug's progress facilitates planning for additional dosing.

In the future, the flexibility of the system, along with this ability to observe its status directly, may allow physicians to tailor the duration of drug delivery to individual patients, potentially leading to cost efficiencies and better clinical results. Rather than having therapy dictated by the design of the delivery vehicle, physicians may be able to administer drugs with what they deem to be the appropriate duration and intensity of treatment for each patient.

For its first clinical trial, the Verisome technology was formulated as an injectable intraocular sustained-release product for delivery of triamcinolone acetonide. The injected gel forms a spherule in the posterior chamber after injection (Figure 1), which gradually degrades and disappears as the drug is released. This liquid-gel formulation was designed to last for up to 1 year, with duration determined by the volume injected.

CLINICAL EVALUATION

A phase 1 multicenter open-label study that assessed the safety and evidence of efficacy of a drug referred to as IBI-20089 (triamcinolone acetonide formulated with the Verisome technology) in patients with chronic cystoid macular edema (CME) due to RVO has been completed.⁸ Ten patients with CME secondary to RVO received one of two doses of the drug and were followed for 1 year. The primary endpoint of the study was safety and tolerability of IBI-20089 at day 60. Secondary

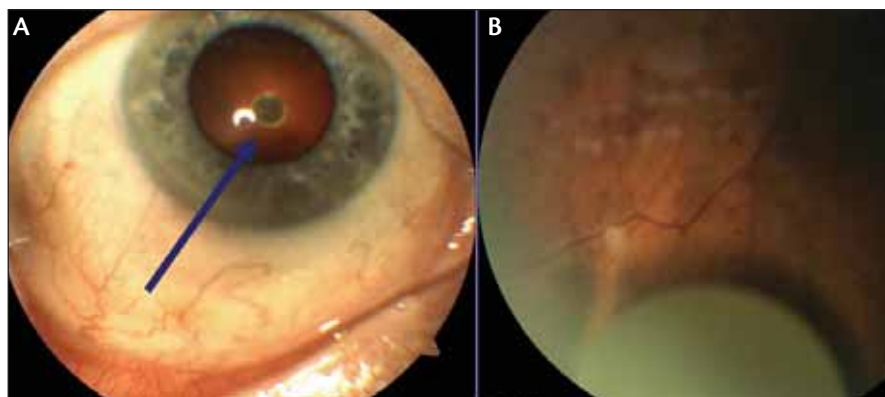


Figure 1. Slit lamp photo of the Verisome immediately after injection before it has settled down in the vitreous (A). Fundus photo of the Verisome inside the eye, sitting below the visual axis (B).

endpoints included visual acuity and retinal thickness as measured by optical coherence tomography (OCT) to serve as efficacy surrogates.

In brief, subjects included had macular edema due either to RVO or to pseudophakia. Known steroid responders or glaucoma patients were excluded.

Intravitreal injections were given with standard 30-gauge needles. The five patients in cohort 1 received the lower dose, 6.9 mg triamcinolone in 25 μ L. Once all five patients cleared the safety endpoint at day 60, a second cohort of five patients received longer-term delivery of 13.8 mg triamcinolone in 50 μ L. Patients were examined at baseline, days 1 and 7, and months 1, 2, 4, 6, 9, and 12.

Of the 10 patients enrolled at three sites, nine were women. Average age was 73 years. Four patients had branch RVOs and six had central RVOs. The average baseline visual acuity in patients selected for cohort 1 (the first-in-human-eyes phase 1 study) was 20/400. Mean baseline retinal thickness in cohort 1 was 499 μ m and in cohort 2 was 518.2 μ m.

For the primary outcome of safety, no cases of uveitis, endophthalmitis or injection-related adverse events were observed during the study. Two eyes developed neovascularization and required intraocular pressure control with glaucoma surgery and panretinal photocoagulation with topical therapy. One death from congestive heart failure occurred after the 6-month mark and was judged to be unrelated to the study medication.

A biologic effect was evident as early as day 7 and was maintained through day 180. Following day 180 there was increased thickness in one patient, while the other four remained stable.

The investigators concluded that this Verisome formulation was well tolerated by patients without any

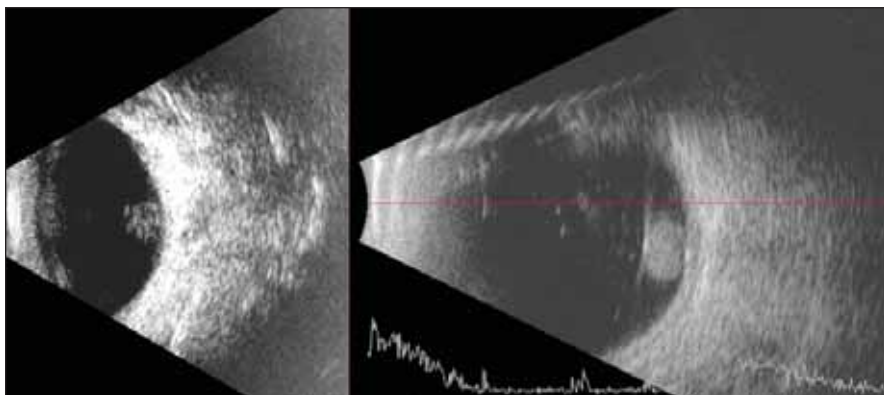


Figure 2. On ultrasound imaging, the Verisome is visible in the vitreous cavity of a rabbit model (left) and in our patient (right).

drug-related adverse events and demonstrated evidence of controlled release efficacy for a low dose of triamcinolone in eyes with CME due to RVO. The larger dose showed more evidence of efficacy than the smaller dose.

CASE EXAMPLES

Case examples can illustrate patient responses to Verisome delivery of triamcinolone in this phase 1 trial.

In one patient in the higher-dose group, the spherule can be seen in the eye after injection (Figure 1). It appears whitish due to the triamcinolone content. The Verisome is injected in a single slow motion to form the single spherule. Initially in this patient a small bubble floated up into the pupil but then settled and coalesced with the main bolus of drug in the inferior vitreous. Ultrasound showed the presence of the spherule sitting inferiorly in the retina (Figure 2). OCT demonstrated reduction of the macular edema from day 1 through day 120, and visual acuity improved from 20/320 to 20/125 from baseline to day 120.

In another case courtesy of Jennifer I. Lim, MD, again the spherule is seen posterior to the lens, and reduction of retinal thickness is seen at 1 week and 1 month. Color photos show that the extensive retinal exudates at baseline were significantly reduced by month 12.

CONCLUSION

In this phase 1 study,⁸ Verisome extended release of triamcinolone was well tolerated and showed drug efficacy in patients with CME secondary to RVO. No injection-related adverse events or safety signals were observed during the trial. Controlled-release biologic efficacy was also observed on sequential OCTs over 1 year. A phase 2-3 pivotal clinical study of the compound is anticipated to begin later this year.

The delivery system is elegant and simple to use, with no need for special hardware or equipment. A biodegradable, sustained-release drug delivery system is particularly important for chronic retinal diseases such as AMD or diabetic retinopathy due to the relatively small surface area of the conjunctiva and sclera and the delicate nature of both tissues. AMD patients who develop the disease in their sixth or seventh decade of life may live for 30 or more years with the disease. Implants that

last only 3 to 12 months would require many repeat implant and explant procedures, potentially scarring the conjunctiva and opening scleral fistulas. Reservoir-style implants present the challenge of old drug being mixed with new at each refill. The field of sustained ocular drug delivery is gaining momentum, and promising approaches are rapidly maturing. ■

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1. Visudyne in Minimally Classic Choroidal Neovascularization Study Group. Verteporfin therapy of subfoveal minimally classic choroidal neovascularization in age-related macular degeneration. 2-year results of a randomized clinical trial. *Arch Ophthalmol*. 2005;123:448-457.
2. Gragoudas ES, Adamis AP, Cunningham ET Jr, Feinsod M, Guyer DR. VEGF Inhibition Study in Ocular Neovascularization Clinical Trial Group. Pegaptanib for neovascular age-related macular degeneration. *N Engl J Med*. 2004;351(27):2805-2816.
3. Rosenfeld PJ, Brown DM, Heier JS, et al. Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med*. 2006;355(14):1419-31.
4. Brown DM, Kaiser PK, Michels M, et al; ANCHOR Study Group. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. *N Engl J Med*. 2006;355(14):1432-44.
5. Campochiaro PA. Safety and efficacy of intravitreal ranibizumab (Lucentis) in patients with macular edema secondary to branch retinal vein occlusion: The BRAVO Study. Paper presented at: Retina Congress 2009; October 4, 2009; New York, NY.
6. Brown DM. Safety and efficacy of intravitreal ranibizumab (Lucentis) in patients with macular edema secondary to central retinal vein occlusion: The CRUISE Study. Paper presented at: Retina Congress 2009; October 4, 2009; New York, NY.
7. Verisome Technology Overview. Icon Bioscience Inc. Web site. <http://iconbioscience.com/Technology-Overview.html>. Accessed April 2, 2010.
8. Fung AE. One-year safety and efficacy of an injectable, sustained-delivery, liquid steroid for treatment of macular edema due to retinal vein occlusion. Paper presented at: Angiogenesis 2010; February 20, 2010; Miami, FL.

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