Ocular Drug Delivery Systems for the Posterior Segment: A Review

BY NORIYUKI KUNO, PHD, AND SHINOBU FUJII

Editor's note: To follow is a review of ocular drug delivery systems for the posterior segment currently in development. Because of the sheer volume of technologies, we chose to narrow this review by eliminating discussion of those that have US Food and Drug Administration or European Union approval for at least 1 indication. Figure 1 and Table 1 provide supplementary information for this article.

NONBIODEGRADABLE POLYMERIC DRUG DELIVERY SYSTEMS

• **I-vation.** Sustained delivery of triamcinolone acetonide (TA) to the vitreous using I-vation (Surmodics Inc.) is in development for diabetic macular edema (DME). The I-vation intravitreal implant is a titanium helical coil coated with TA (925 µg) and the nonbiodegradable polymers poly(methyl methacrylate) and ethylene-vinyl acetate. It is predicted that this implant will have an in vivo sustained delivery of at least 2 years. A phase 1 clinical trial in patients with DME has been completed and 24-month interim results have been reported.[1] At 24 months, 25 of 31 patients remained in the study; 11 patients (11 eyes) in the slow-release group, 14 patients (14 eyes) in the fast-release group. The proportion of patients demonstrating improved visual acuity (greater than 0 ETDRS letter gain from baseline) was 64% in the slow-release group and 72% in the fast-release group; 28.6% of patients in the fast-release group gained greater than 15 letters. The mean macular thickness, measured by optical coherence tomography (OCT), decreased in the slow group from 529 µm at baseline to 328 µm, and in the fast-release group from 376 µm at baseline to 268 µm. No further clinical trial has commenced.[2]

• **Renexus.** Encapsulated cell technology provides extracellular delivery of ciliary neurotrophic factor (CNTF) with long-term and stable intraocular release at constant doses through a device (Renexus [formerly NT-501], Neurotech) implanted in the vitreous. It contains human cell line of retinal pigment epithelium (RPE), NTC-200, genetically modified to secrete recombinant human CNTF. Renexus consists of a sealed semipermeable hollow fiber membrane capsule surrounding a scaffold of 6 strands of polyethylene terephthalate yarn, which can be loaded with cells. The device is surgically implanted in the vitreous through a tiny scleral incision and is anchored by a single suture through a titanium loop at one end of the device. The semipermeable hollow fiber membrane allows the outward diffusion of CNTF and other cellular metabolites and the inward diffusion of nutrients necessary to support the cell survival in the vitreous cavity while protecting the contents from host cellular immunologic attack.

Data from a phase 1 clinical trial showed that Renexus was well tolerated in patients with late-stage retinitis pigmentosa (RP) for 6 months.[3] A phase 2 study in patients with geographic atrophy (GA) associated with atrophic age-related macular degeneration (AMD) randomized patients in a 2:1:1 ratio to receive high- (20 ng/day) or low-dose (5 ng/day) Renexus, or to sham surgery, respectively. Among eyes with baseline BCVA of 20/63, the mean BCVA in the high dose group was 10.5 and 10.0 letters greater than the low dose/sham group at 12 months (P = .03) and 18 months, respectively.[4,5] Stabilized visual acuity was accompanied

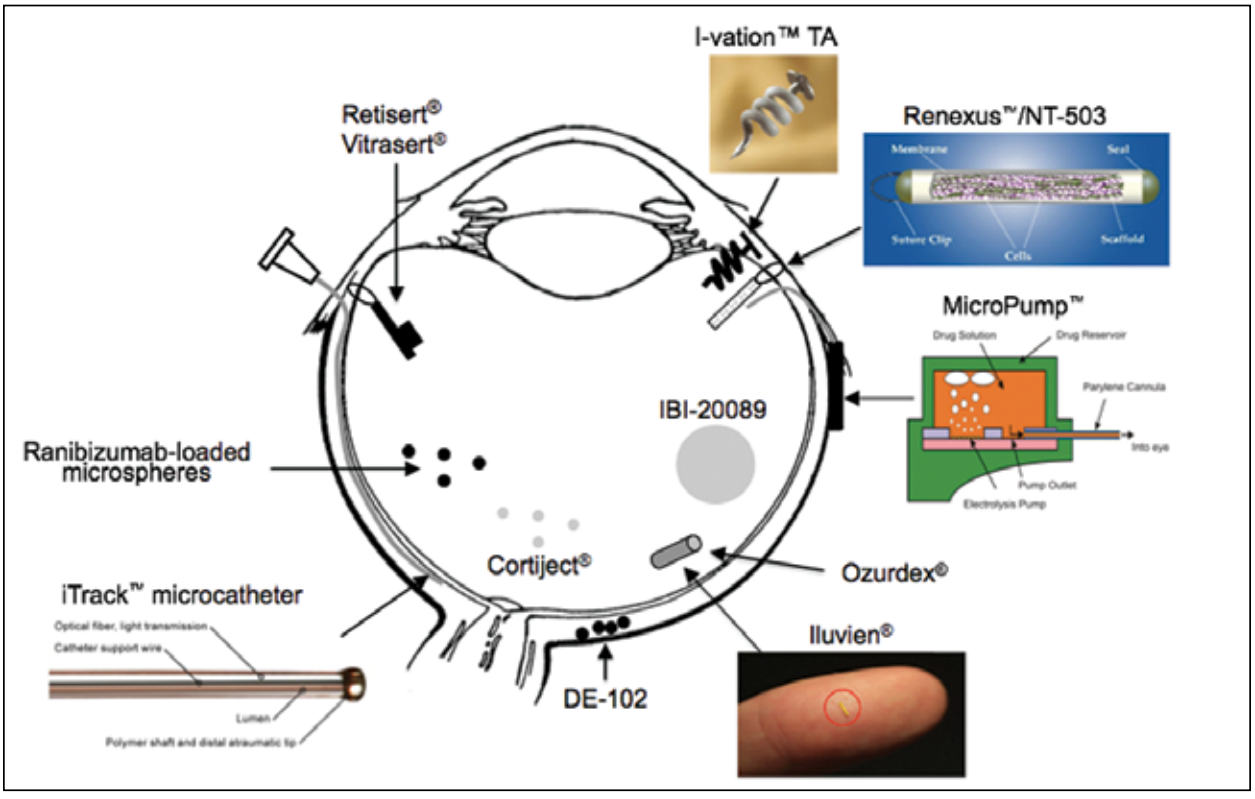

Figure 1. Examples of drug delivery systems for posterior segment.

by corresponding structural changes that were dose dependent ($P < .001$). The growth rate of GA area was reduced in treated eyes compared with fellow eyes at 12 and 18 months. In addition, Renexus prevented secondary cone degeneration in patients with RP.[6] At present, a phase 2 clinical trial for early-stage RP or Usher syndrome (type 2 or 3) and a phase 1 study for macular telangiectasia are under way.

• **NT-503.** Neurotech has been developing another device (NT-503) encapsulating VEGF receptor Fc-fusion protein (VEGFR-Fc)-releasing cells.[7] This VEGFR-Fc is 20-fold more efficient in neutralizing VEGF compared with ranibizumab. NT-503 is confirmed to release VEGFR-Fc constantly up to 1 year in the rabbit vitreous. A phase 1 clinical trial of NT-503 for neovascular AMD is ongoing outside of the United States.[8]

• **ODTx.** The injectable, biocompatible, nonresorbable device (ODTx, On Demand Therapeutics) contains reservoirs designed for drug release in optimized doses for laser activation.[9,10] The reservoirs are capable of storing small- or large-molecule drugs that can be released via a standard, noninvasive laser activation procedure. The multiple reservoir system allows ophthalmologists to control drug delivery by activating specific reservoirs, while unactivated reservoirs remain intact. Unfortunately, clinical trials of ODTx have not commenced.

BIODEGRADABLE POLYMERIC DRUG DELIVERY SYSTEMS

• **Brimonidine intravitreal implant.** Brimonidine is an alpha-2 adrenergic agonist that can release various neurotrophins, including BDNF, CNTF,[11] and b-FGF.[12] These neurotrophins have potential to prevent apoptosis of photoreceptors and/or retinal pigment epithelium.[13,14] A phase 2/3 clinical trial of a biodegradable, rod-shaped poly(lactide-co-glycolide) intravitreal implant containing brimonidine tartrate in patients with retinitis pigmentosa has been completed, and a phase 2 clinical study in atrophic AMD[15] is now being conducted by Allergan.

• **Thethadur.** Thethadur (pSivida) is a honeycomb-like nanostructured porous silicon (biosilicon), which is both biocompatible and biodegradable. Thethadur can load a variety of drugs including small chemical entities, peptides, proteins, and other molecules and can provide sustained drug release.[16] Further details regarding Thethadur have not been disclosed by the company.

• **DE-102.** In Japan, a randomized, multicenter, controlled, phase 2/3 clinical trial for sub-Tenon injection of biodegradable microspheres with betamethasone

TABLE 1. DRUG DELIVERY SYSTEMS FOR CHORIORETINAL DISEASES IN THE MARKET AND UNDER CLINICAL TRIALS

Active ingredient	Brand name	Dosage form	Release-controlling excipient	Target indication	Developmental stage
Ganciclovir	Vitrasert	IVT, implant	EVA/PVA	CMV retinitis	Launched
Fluocinolone acetonide	Retisert	IVT, implant	Silicone/PVA	Posterior uveitis DME CRVO	Launched P2/3 Unknown
Fluocinolone acetonide	Iluvien	IVT, implant	Polyimide/PVA	DME Atrophic AMD RVO	Approved in Austria, UK, and Portugual P2 P2
Triamcinolone acetonide	I-vation TA	IVT, implant	PMMA/EVA	DME	P2, terminated
CNTF (NT-501)	Renexus	IVT, implant	Semipermeable hollow fiber membrane/NTC-200	RP Atrophic AMD MacTel	P2/3 P2 P1
VEGFR-Fc (NT-503)	-	IVT, implant	Semipermeable hollow fiber membrane/NTC-200	Neovascular AMD	P1
Dexamethasone	Ozurdex	IVT, implant	PLGA	CRVO BRVO Posterior uveitis DME	Launched Launched Launched P3
Brimonidine tartrate	-	IVT, implant	PLGA	Atrophic AMD RP	P2 P1/2, completed
Betamethasone (DE-102)	-	S-T, injection	Not disclosed	DME BRVO	P2/3 P2/3
Verteporfin	Visudyne	IV, injection	Liposome	CNV	Launched
Difluprednate	Durezol	Eye drops	Emulsion	DME	Off label
Triamcinolone acetonide (IBI-20089)	-	IVT, injection	Benzyl benzoate	Neovascular AMD (w/Lucentis)	P2
Dexamethasone prodrug (NOVA-63035)	Cortiject	IVT, injection	Emulsion	DME	P1, completed
Aganirsen (GS-101)	-	Eye drops	Emulsion	Neovascular AMD	Unknown
CNTO 2476	-	SR, injection	iTrack 275 microcatheter as injector	Atrophic AMD	P1/2
Ranibizumab	-	Not disclosed	Refillable port drug delivery system	Neovascular AMD	P1

AMD: age-related macular degeneration, BRVO: branch retinal vein occlusion, CMV: cytomegalovirus, CNTF: ciliary neurotrophic factor, CNV: choroidal neovascularization, CRVO: central retinal vein occlusion, DME: diabetic macular edema, EVA: ethylene-vinyl acetate copolymer, IV: intravenous, IVT: intravitreal, MacTel: macular telangiectasia, NTC-200: cell line of human retinal pigment epithelium, P: phase, PLGA: poly(lactide-co-glycolide), PMMA: poly(methyl methacrylate), PVA: poly(vinyl alcohol), RP: retinitis pigmentosa, RVO: retinal vein occlusion, SR: subretinal, S-T: sub-Tenon, UK: United Kingdom, VEGFR-Fc: vascular endothelial growth factor receptor-Fc fusion protein.

(DE-102, Santen Pharmaceutical Co. Ltd.) designed to sustained release has been conducted for the treatment of DME[17] and for branch retinal vein occlusion.[18]

• **Ranibizumab-loaded microspheres.** Despite the remarkable effectiveness of ranibizumab (Lucentis, Genentech) for treating neovascular AMD and other retinal diseases, patients and physicians have been hoping for an alternative to frequent intravitreal injections. SurModics Inc. and Genentech have been developing biodegradable microparticles that incorporate ranibizumab, which are currently in preclinical stage.[19] It is hoped that ranibizumab-loaded microparticles can deliver the agent over a period of approximately 4 to 6 months.

OIL/LIPID-BASED DRUG DELIVERY SYSTEMS

• **IBI-20089.** Icon Bioscience Inc. is developing IBI-20089 containing TA using the Verisome drug delivery platform technology. The Verisome is a translucent liquid. When IBI-20089 mixes with saline, the solution becomes a milky, slightly opaque color and forms a gel. According to Icon's patent,[20] IBI-20089 might be a solution of TA in benzyl benzoate. IBI-20089 is designed to last up to 1 year with a single intravitreal injection. An open-label, phase 1 study for cystoid macular edema associated with branch retinal vein occlusion or central retinal vein occlusion has been completed, and the results have been published.[21] Five patients received an intravitreal injection of 6.9 µg TA in 25 µL, and another 5 patients received 13.8 µg TA in 50 µL using a 30-gauge needle. For the 6.9 µg cohort, mean central subfield thickness decreased from 477 µm at baseline to 369 µm at day 1 ($P < .06$); 387 µm at day 30 ($P = .18$), and 251 µm ($P = .46$) at day 360. For the 13.8 µg cohort, mean central subfield OCT thickness decreased from 518 µm at baseline to 404 µm at day 1 ($P = .134$); 289 µm at day 30 ($P = .003$), 207 µm at day 180 ($P = .004$), and 278 µm ($P = .009$) at day 360. The reported side effects include intraocular pressure (IOP) elevation, which occurred in 3 eyes, 2 of which had neovascular glaucoma.

IBI-20089 adjunctively with 0.5 mg of ranibizumab is now being tested in a phase 2 clinical study for neovascular AMD.[22] Lim et al[23] have demonstrated the safety and efficacy of a combination therapy of IBI-20089 and ranibizumab in 8 patients (3 patients; treatment-naive, 5 patients previously received ranibizumab injections) with neovascular AMD. Patients received intravitreal IBI-20089 followed by intravitreal ranibizumab. At 30 days, 2 of 8 patients required reinjection of ranibizumab. At 60 (n=7) and 90 days (n=6), no patients required ranibizumab reinjections. At 120 days 3 of 6 patients, and at 180 days, 1 of 5 patients required repeated injections of ranibizumab. The results show that IBI-20089 may decrease the frequency of as-needed ranibizumab treatment.

• **Cortiject.** Cortiject (NOVA63035, Novagali Pharma SA, acquired by Santen Pharmaceutical Co. Ltd.) is a preservative-free emulsion composed of oily carrier and phospholipid as surfactant, encapsulating a target tissue-activated dexamethasone prodrug.[24] Released dexamathasone prodrug is de-esterified by a retina-specific esterase, and activated to become dexamethasone. A single intravitreal injection provides sustained release over 6 to 9 months. An open-label, phase 1 study for DME is currently under way.[25] According to an interim report,[26] mean foveal thickness decreased after an intravitreal injection and continued lower at the last available follow-up time. However, further results of this trial have not been reported since 2009.

• **Aganirsen.** Eye drops of aganirsen (GS-101, GeneSignal International SA), an antisense oligonucleotide inhibiting insulin receptor substrate-1 expression, have been evaluated in a phase 3 clinical trial for the treatment of corneal angiogenesis associated with corneal transplantation.[27] Recently, Cloutier et al[28] evaluated emulsion-based eye drops of aganirsen applied in a laser-induced choroidal neovascularization (CNV) monkey model. A single topical application of aganirsen as an emulsion led to its dose-dependent accumulation in the retina within 90 minutes in monkeys. The incidence of high-grade CNV lesions decreased from 20.5% in vehicle-treated animals to 1.7% ($P < .05$) at an 86-µg dose. Importantly, all doses of aganirsen led to a sustained concentration of the compound in the monkey retina up to 8 hours, and the concentration achieved in the retina was within the range of the effective concentration of aganirsen shown to prevent VEGF-induced capillary tube formation in human endothelial cells.

INJECTION DEVICES

• **iTrack microcatheter.** The iTrack microcatheter (iScience Interventional) was originally designed for canaloplasty, a new treatment for glaucoma.[29,30] The iTrack microcatheter includes an optical fiber to allow transmission of light to the microcannula tip for surgical illumination and guidance. The iTrack microcatheter has been evaluated for suprachoroidal drug delivery in animals. The pharmacokinetic study of suprachoroidal delivery of TA in pigs has shown that TA remained in the ocular tissues for at least 120 days, and systemic exposure was very low.[31] In contrast, a study to compare the pharmacokinetics of bevacizumab (Avastin, Genentech) between intravitreal and suprachoroidal injections in pigs[32] reported that the profile of intravitreal injec-

tions of bevacizumab was more sustained than that of suprachoroidal injections at the same dosage level. Intravitreally injected bevacizumab distributed more to the inner retina, whereas suprachoroidally injected bevacizumab distributed primarily to the choroid, RPE, and photoreceptor outer segments.

Tetz et al[33] have reported the safety of suprachoroidal delivery of a combination of 4.0 mg bevacizumab and 4.0 mg TA via iTrack 400 microcatheter in 21 eyes of 21 advanced neovascular AMD patients who had been unresponsive to at least 3 prior other therapies including laser photocoagulation, photodynamic therapy, intravitreal pegaptanib (Macugen, Eyetech), bevacizumab, and ranibizumab. No serious intraoperative or postoperative complications including suprachoroidal hemorrhages were observed. One eye had a transient IOP elevation at 3 months after administration, which was medically controlled, and 2 eyes (10.5%) had apparent progression of nuclear sclerotic cataracts. Rizzo et al[34] evaluated the safety and efficacy of suprachoroidal delivery of a combination of 1.25 mg bevacizumab and 4.0 mg TA via iTrack 400 microcatheter in 6 eyes with chronic macular edema with severe subfoveal hard exudates secondary to retinal vasculopathies including DME and RVO. BCVA improved by 2 lines or greater in 4 eyes and remained stable in 2 eyes. At 1 to 2 months after administration, hard exudates were almost completely resolved in all eyes, and macular edema was significantly reduced. There were no surgical or postoperative complications during 12 months of follow-up.

Recently, the iTrack microcatheter was used for cell transplantation into the subretinal space. A phase 1/2 clinical trial of human umbilical tissue-derived cells (CNTO 2476, Janssen Biotech Inc.) was conducted for atrophic AMD.[35] A suspension of CNTO 2476 was delivered into the subretinal space near the macular geographic atrophy through a sclerotomy and choroidotomy via iTrack 275 microcatheter.[36] In addition, de Smet et al[37] evaluated the safety of repeated cell transplantation into the subretinal space in pigs via iTrack 275 microcatheter. Cells were successfully injected at the same or adjacent sites on the initial and the second dosing occasion without significant surgical trauma or adverse consequences in pigs.

• **Microneedles.** Microneedles, with lengths of 800 to 1000 µm, have successfully injected micro- and nanoparticles into the suprachoroidal space without surgery in rabbit, pig and human ex vivo eyes.[38] The technology has promise for reducing the frequency of injection for treating retinal disease, and reducing exposure of potentially toxic compounds such as corticosteroid to the lens and other anterior segment structures of the eye.

Edelhauser et al[38] performed a pharmacokinetic study of suprachoroidal injection of 2 mg TA in 100 µL into rabbit eyes in vivo, compared with intravitreal injection of the same dose.[39] At 1 week after each injection, about 80% of TA was remained in both groups. However, in the intravitreal injection group, 63% was in the vitreous and more than 10% in the lens and anterior segment, whereas in the suprachoroidal injection group 77% remained in the choroid and negligible amounts reached the lens and anterior segment. At 2 months after each injection, approximately 30% of TA remained in the suprachoroidal injection group vs about 5% in the intravitreal injection group. In suprachoroidal injection of bevacizumab (1.25 mg/50 µL) using a microneedle 700-800 µm long, quick distribution of bevacizumab into the choroid was achieved (15 minutes; 76%), but choroidal levels declined very rapidly (2 days; 0.5%).[40]

Clearside Biomedical Inc. has been developing the lead product (CLS1001) for the treatment of macular edema.[41]

REFILLABLE DEVICES

• **MicroPump.** A microelectromechanical systems (MEMS) drug delivery device is being investigated for the treatment of chronic and refractory ocular diseases.[42,43] The MEMS device can be refilled with drug solution to provide long-term drug therapy while avoiding repeated surgeries. The first generation of MEMS is a manually controlled system limited by variations in the drug-release duration and force applied for depressing of the reservoir. To resolve this problem, the next generation device consists of an electrolysis chamber with electrolysis actuation to precisely delivery the desired dosage volume, a drug reservoir with refill port, battery and electronics. Biocompatible and flexible parylene is used to construct the MEMS. Battery and wireless inductive power transfer can be used to drive electrolysis. Electrolysis is a low power process in which the electrochemically induced phase change of water to hydrogen and oxygen gas generates pressure in the reservoir forcing the drug through the cannula.[43] The reservoir is implanted in the subconjunctival space, and the flexible cannula is inserted through an incision into the anterior or posterior segment. Gonzalez-Soto et al[44] have demonstrated that a slower prolonged infusion of the same volume and concentration of intravitreal ranibizumab is equivalent to a bolus intravitreal injection of ranibizumab in a human VEGF-induced retinal hyperpermeability model in rabbits.

Replenish Inc. plans to begin clinical trials for a refillable and programmable pump that would be implanted in the eye to deliver medicine for glaucoma or AMD. The Replenish device can last more than 5 years before

needing replacement, much longer than current treatments.[45]

• **Port drug delivery system.** Genentech is also in collaboration with ForSight Vision 4 Inc., which is the fourth company to spin out of the ophthalmic incubator ForSight Labs, LLC, to develop a refillable port drug delivery system (PDS) designed to release ranibizumab over a period of months.[46] Phase 1 studies of PDS have been conducted for the treatment of neovascular AMD by the company.[47]

SUMMARY

Most chorioretinal and vitreoretinal diseases are chronic, progressive and refractory retinal degenerative diseases, and induced by complex pathophysiological conditions. It is necessary to consider further the most efficacious combinations of optimal drugs, doses, routes, and drug-release patterns (sustained-release, pulsatile-release, or controlled-release responding to a trigger) based on the pathophysiology and progressive courses of the targeted diseases. ■

Noriyuki Kuno, PhD; and Shinobu Fujii are with the Research and Development Center at Santen Pharmaceutical Co. Ltd., in Nara, Japan. Dr. Kuno may be reached at +81 743 79 4508; fax: +81 743 79 4518; or via email at noriyuki.kuno@gmail.com.

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