

A Peek Down the Pipeline: Emerging Drug Delivery Options for Retinal Disease

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The range of intravitreal therapeutics available to the retinal specialist for the treatment of chronic retinal disease including age-related macular degeneration (AMD), retinal vein occlusion (RVO), diabetic macular edema (DME), and posterior uveitis has continued to expand significantly, providing excellent options for improved visual acuity and quality-of-life outcomes.¹⁻⁴ With multiple medications targeting VEGF (ranibizumab [Lucentis, Genentech], bevacizumab [Avastin, Genentech], and aflibercept [Eylea, Regeneron]) available in the United States for AMD, RVO, DME, and with the intravitreal sustained-release corticosteroid dexamethasone formulation (0.7 mg; Ozurdex, Allergan) approved by the US Food and Drug Administration (FDA) for RVO, DME, and posterior uveitis, a major compelling arena of discussion for both patients and providers involves the future of drug delivery to improve patient care from a treatment burden standpoint.

Two major questions arise in considering drug delivery to the posterior segment: (1) Can the drug delivery system provide sustained release or prolonged therapeutic levels of medication for the specific disease process? And (2) Does the drug delivery system provide therapeutic levels to appropriate ocular tissue compartments in which the disease process is implicated (ie, vitreous, retina, retinal pigment epithelium, suprachoroidal space) as opposed to anterior segment structures?

This article summarizes some of the promising methods of drug delivery in development, which provide future options for retinal disease therapy (Table).

AVAILABLE IMMEDIATELY OR NEARLY IMMEDIATELY

Although AMD, RVO, and DME are the major retinal diseases cared for by vitreoretinal providers, posterior uveitis was the initial disease condition whereby strides in sustained-release drug delivery were made. The parallel among these disease processes is in their chronicity, thus mandating long-term therapy. It was in this context that the Retisert implant (fluocinolone acetonide, Bausch + Lomb) was designed and eventually FDA-approved for the treatment of posterior uveitis.⁵⁻⁷ The Retisert implant is a corticosteroid-eluting, surgically implanted device that releases medication for 3 years and has demonstrated efficacy for decreasing inflammation and improving visual acuity and quality-of-life metrics. However, the need for cataract surgery (90%) and incidence of glaucoma requiring filtration surgery (25–40%) is a concern that is integral to every patient-physician discussion about efficacy and long-term side effects.⁵⁻⁷

The Ozurdex implant (DEX) is a sustained-release intravitreal injectable therapeutic, which lasted from 4 to 6 months in clinical trials.⁸⁻¹⁰ It is injected in the clinic, avoiding the need for a surgical procedure. The DEX implant has been FDA-approved for RVO, posterior uveitis, and, recently, for DME in pseudophakic patients and phakic patients scheduled for cataract surgery.⁸⁻¹⁰ Boyer et al recently reported the 3-year outcomes of 2 randomized, multicenter, sham-controlled phase 3 trials on the DEX intravitreal implant for patients with DME.¹⁰ In 1048 patients with DME, the percentage of patients with 15-letter or greater improvement was 22%

and 18% in 0.7 mg and 0.35 mg DEX implant groups, respectively, compared with 12% in the sham control group ($P \leq .018$). Patients receiving the DEX implant also demonstrated greater improvements in central retinal thickness measured with optical coherence tomography (OCT), with greater than 100- μm improvement in both treatment groups, compared with a reduction of 40 μm in sham ($P < .001$). Rates of cataract-related changes were 67%, 64%, and 20% in the DEX 0.7 mg, 0.35 mg, and sham groups ($P < .001$), respectively, while intraocular pressure elevations were controlled medically or without therapy.¹⁰ Prior clinical trials have also demonstrated the efficacy of the DEX implant for posterior uveitis and RVO, and this device has received FDA approval for both indications.⁸⁻⁹

Iluvien is an intravitreally injected fluocinolone acetonide implant (190 mg; Alimera Sciences) that is delivered via a proprietary 25-gauge injector system. In 2 parallel, prospective, randomized, sham-controlled multicenter clinical trials, patients with DME were randomized in a 1:2:2 ratio to sham injection ($n = 185$), low-dose insert ($n = 375$), or high-dose insert ($n = 393$). Twenty-eight percent of eyes receiving either a low- or high-dose fluocinolone acetonide implant achieved improvement in their ETDRS visual acuity by 15 letters or more compared with 16% in the sham group ($P = .002$ for both comparisons). Cataract surgery was more frequent in eyes receiving the implants compared with control patients, and glaucoma occurred in 3.7%, 7.6%, and 0.5% of low-dose, high-dose, and sham groups, respectively. Notably, although both the high-dose and low-dose groups benefited from the insert, the risk-benefit ratio favored the low-dose insert.¹¹⁻¹² The Iluvien implant has received approval for marketing in a number of European countries including Austria, France, Germany, Italy, Portugal, Spain, and the United Kingdom; the company is currently seeking FDA approval for the drug in the United States.

SUPRACHOROIDAL DRUG DELIVERY

Topical application and periocular and intravitreal injections of anti-VEGF medications and corticosteroids are currently a mainstay of therapy for posterior segment disease. However, the development of cataract and glaucoma with corticosteroid delivery associated with these methods of delivery remains an ongoing concern, particularly with repeated injections.¹³ In addition, the inherent risks (even if they are minimal) and bioavailability limitations with intravitreal injections place suprachoroidal drug delivery at the forefront of current research.

Options studied for suprachoroidal delivery include the surgical catheterization of the suprachoroidal space

with a microcatheter and the use of hollow microneedles for suprachoroidal drug delivery.

Suprachoroidal Drug Delivery Via a Microcatheter

In a primate and porcine animal study, Olsen et al evaluated the surgical technique, safety profile, and pharmacokinetics of triamcinolone acetonide introduced via surgical microcatheter cannulation of the suprachoroidal space.¹⁴ To access the suprachoroidal space, a conjunctival peritomy and radial incision was made 3 to 4 mm posterior to the limbus to expose bare choroid. Healon (Abbott Medical Optics) was used to viscodissect the choroid from bare sclera; following this, the posterior drug delivery system (PDS) was introduced. A light pipe was inserted through a second sclerotomy to visualize the beacon probe tip. Once the beacon probe tip was in position posterior to the area centralis—or the porcine foveal equivalent—the drug was injected.

In this study in 94 animals, successful and reproducible suprachoroidal cannulation was performed in 93 of 94 animals with a low incidence of complications. Postoperative inflammation (6/94 animals) was infrequently observed; endophthalmitis and wound abscess were notably rare (1/94). The pharmacokinetics of a 3-mg dose of suprachoroidal triamcinolone demonstrated sustained levels for up to 120 days at study termination (compared with approximately a 3-month duration of effect of 4-mg triamcinolone acetonide injection). Based on this initial study of this anatomic space for drug delivery, further clinical studies were recommended for the role of suprachoroidal drug delivery.¹⁴

More recently, prospective studies in patients with the microcatheter suprachoroidal drug delivery system (iTrack 400, iScience Interventional Corporation) have shown encouraging results, albeit in small series at this point. This microcatheter, commercially available for the delivery of fluid infusion and aspiration in ophthalmic microsurgery, features a 370- μm diameter width and has an illuminating and atraumatic tip for suprachoroidal drug delivery and a lumen for drug/fluid administration. Similar to the technique described by Olsen et al, a conjunctival peritomy and scleral cutdown are performed to expose bare choroid. A Sinskey hook is then used for dissection of deeper scleral lamellae, followed by viscoelastic hydrodissection to expand the sclera and choroid. As the microcatheter is marked at 5-mm intervals, its subsequent correct anatomic localization within the suprachoroidal space and underneath the area of regard (ie, the fovea in initial studies) is then monitored through the operating microscope via direct visualization of the illuminated tip of the microcatheter. Successful drug delivery can then be verified once the microcatheter is in its correct position.¹⁵

In a prospective, interventional pilot study using this technique, Rizzo et al evaluated 6 eyes of 6 patients with retinal vascular disease (ie, central or branch RVO or DME) with massive refractory subfoveal hard exudates who received combination bevacizumab and triamcinolone using suprachoroidal drug delivery.¹⁵ Successful anatomic insertion was achieved in all eyes, and no intra-operative or postoperative complications were seen in any eye. Moreover, mean visual acuity improved by 2 or more lines in 4 eyes and mean OCT macular thickness decreased from 603 μ m to 276 μ m at final follow-up. These findings were suggestive that suprachoroidal infusion of bevacizumab and triamcinolone was feasible and potentially beneficial in patients with massive hard exudates in patients with retinal vascular disease.¹⁵⁻¹⁶

Hollow Microneedles for Suprachoroidal Drug Delivery

To avoid the need for a surgical procedure, suprachoroidal injection of drugs using hollow microneedles has been studied in vitro, as well as in recent clinical studies in humans. Patel et al evaluated a minimally invasive method of microparticle and nanoparticle injection into the suprachoroidal space in whole rabbit, pig, and ex vivo human eyes.¹⁷ In their study, microneedles fabricated from borosilicate micropipette tubes (Sutter Instrument) were placed into a custom, pen-like device with a threaded cap to position the microneedle and ensure precise length measurement. Microneedles were introduced perpendicular to the sclera at 5 to 7 mm posterior from the limbus, and the infusion solution was introduced into the suprachoroidal space. Following the initial introduction of red-fluorescent sulforhodamine B, the solution was noted to spread within the suprachoroidal space from the initial injection site. Up to 35 μ L could be injected without leakage (compared with 50 μ L of many intravitreal medications). Patel et al also showed that particles up to 1000 nm in diameter could be introduced into the suprachoroidal space, suggesting the possibility that drug-loaded biodegradable particles could be introduced into this compartment for sustained release over a period of weeks to months. Factors that influenced the delivery of particles to the suprachoroidal space warranting future consideration for its clinical use included infusion pressure (ie, pressure at which drug was infused following placement of microneedle), microneedle length, increasing intraocular pressure, and particle size.¹⁷

Since this study, further research in rabbit models has shown that suprachoroidal administration of bevacizumab, fluorescein, and fluorescently tagged dextrans could yield drug levels 10-fold higher in posterior segment tissues (ie, choroid and retina) compared with anterior

segment structures. The achieved levels (ie, chorioretinal selectivity) of suprachoroidal delivery of sodium fluorescein was an order of magnitude greater when compared with levels achieved by intravitreal injection.¹⁸ Further work in a porcine model of uveitis showed that suprachoroidal injection of triamcinolone was feasible and effective in reducing inflammation with no significant procedural or drug toxicity in the animals studied.¹⁹ A phase 1/2 study is ongoing evaluating the suprachoroidal delivery of triamcinolone acetonide (Triesence, Alcon) to treat noninfectious intermediate, posterior, and panuveitis (clinicaltrials.gov identifier NCT01789320).

INTRAVITREAL INJECTIONS: NANOMEDICINE, VERISOME, AND OTHERS

Although the number of therapeutics and indications for intravitreal injections is continuing to expand, the treatment burden and limitations of intravitreal therapeutic delivery also present opportunities for improvement in drug delivery. The 2 main mechanisms of drug clearance from the vitreous cavity are the anterior elimination pathway via bulk flow of aqueous humor and the posterior elimination pathway via retinochoroidal bulk flow. Transcellular carrier-mediated transporters in the retinal pigment epithelium (RPE) comprise another mechanism of drug elimination.²⁰ The elimination half-life of drugs that are cleared through both the aqueous humor and retina (eg, small lipophilic drugs) tends to be shorter than for drugs eliminated through the anterior route alone (eg, large hydrophilic drugs). Other factors include the molecular weight of the drug (larger molecular weight > 70 000 kD demonstrate longer half-lives), lipophilicity, ionic charge, solubility, volume of distribution, bioavailability, and duration of action.²¹ In this context, the vehicle for drugs administered via intravitreal injection warrants consideration.

A number of drug delivery technologies including nanotechnology and the Verisome drug delivery platform (Icon Bioscience) have been studied utilizing some of the properties for sustained release of intravitreal therapeutics. Nanotechnology, which refers to substances of nanometer scale, has received attention because of the potential of various nanoparticles for drug penetration, controlled release, and drug targeting for ophthalmic indications.²² Broadly, drug classes of nanocarriers of drug that have been studied for ophthalmic indications include liposomes, micro/nanospheres, emulsions, and dendrimers.

Liposomes

Liposomes are small, closed lipid vesicles composed of a phospholipid bilayer; water-soluble drugs may be

TABLE. SUMMARY OF DRUG DELIVERY PLATFORMS DISCUSSED IN THE THIS ARTICLE.

Product (manufacturer)	Status in pipeline	Comments
Retisert (fluocinolone acetonide 0.59 mg implant; Bausch + Lomb)	FDA approved for treatment of posterior uveitis	Surgically implanted device elutes drug for up to 3 years; demonstrated efficacy for decreasing inflammation, improving VA and QoL. May be associated with need for cataract surgery (90%) and incidence of glaucoma (25–40%)
Ozurdex (dexamethasone implant 0.7 mg; Allergan)	FDA approved for treatment of RVO, posterior uveitis, and DME	Demonstrated efficacy in reducing inflammation with duration of about 4 months. Indicated for use in DME among patients who are pseudophakic or who are scheduled for cataract surgery. May be associated with cataract formation and ocular hypertension in some patients
Iluvien (fluocinolone acetonide 190 mg; Alimera Sciences)	Not approved in the United States Approved for marketing in several European countries	Studies in patients with DME indicate higher rate of 15-letter gains versus sham. May be associated with need for cataract surgery. Product is currently being reviewed by the FDA
Suprachoroidal cannulation	Several studies in animal models have been performed	Animal models suggest a longer duration of action compared with injection. Studies in small series using a microcatheter drug delivery system (iTrack 400, iScience Interventional Corporation) have shown encouraging results
Suprachoroidal drug delivery via microneedle	Several studies in animal models complete; phase 1/2 trial in posterior uveitis.	Studies indicate plausibility of delivering both small- and large-molecules via microneedle to the suprachoroidal space
Nanocarriers • Liposomes • Micro- and nanospheres • Microemulsions/dendrimers	Several preclinical and animal model studies have been performed by various developers	Liposomes may be attractive due to ability to control its lipid composition, size, and electrical charge, and thus, its ability for targeted delivery. Micro- and nanospheres employ synthetic biodegradable polymers that erode over time to affect sustained drug delivery. Early work with microemulsions and dendrimers is intriguing but needs further verification
Verisome (Icon Biosciences)	Phase 1/2 study ongoing for AMD	Verisome is a proprietary technology designed for sustained drug delivery (up to 1 year) and has been studied with small molecules, proteins, and monoclonal antibodies
Encapsulated cell technology (Neurotech) • NT-501 (Renexus) • NT-503	2 phase 3 trials are investigating NT-501 for early- and late-stage RP. Phase 2 study of NT-501 in GA secondary to AMD recently completed. NT-501 also being studied in other disease states. Phase 1 trial recently completed with NT-503	NT-501 is an encapsulated cell technology platform that secretes ciliary neurotrophic factor, which retards photoreceptor loss and may protect against further degeneration. NT-503 is an encapsulated cell technology platform that secretes VEGF receptor Fc-fusion protein
Refillable implants • MicroPump (Replenish) • Port Delivery System (PDS; ForSight Vision4)	Anterior MicroPump under investigation for glaucoma; Posterior MicroPump being studied for various retinal applications. PDS in-licensed by Genentech; phase 1 trial in AMD and phase 1/2 for uveitis underway	MicroPump system uses a pumping mechanism based on electrolysis and a drug refill port for controlling drug delivery. PDS is a proprietary refillable device designed to release medication over several months
Abbreviations: FDA, US Food and Drug Administration; VA, visual acuity; QoL, quality of life; RVO, retinal vein occlusion; DME, diabetic macular edema; AMD, age-related macular degeneration; RP, retinitis pigmentosa; GA, geographic atrophy		

incorporated into their aqueous phase, whereas lipid-soluble drugs may be incorporated into their lipid phase. One property of a liposome that gives it an advantage as a drug carrier lies in its noncovalent nature; specifically, its lipid composition, size, and electric charge may be controlled, thereby facilitating drug targeting.²² A study by Abrishami et al showed that liposomal bevacizumab concentrations were 5-fold higher at day 42 when compared with eyes receiving soluble intravitreal bevacizumab.²³ Potential risks of liposomes include blurred vision after the injection of the liposomal suspension into the vitreous body, storage conditions required depending on the composition of the drug and liposome, and potential proinflammatory effects.

Microspheres/Nanospheres

Microspheres are spherical preparations with diameters ranging from 1 μm to several hundred microns. Particles with smaller diameters are considered nanospheres. Drugs may be encapsulated in synthetic and natural polymers, permitting sustained-release delivery of medication and drug targeting. Polylactic acid (PLA), polyglycolic acid (PGA), and a copolymer, poly(lactic-co-glycolic acid), or PLGA, are the most common substrate vehicles for drug delivery. Studies have demonstrated that PLA and PLGA may be inserted with no evidence of histologic or functional toxicity to the retina.²⁴⁻²⁵ The Ozurdex implant is a PLGA device, and it is biodegradable. PLA, PGA, and PLGA are widely used as suture materials, bone screws, vascular grafts, and surgical scaffolds for tissue regenerative medicines, and all are FDA-approved for drug delivery.²⁵

Microemulsions and Dendrimers

A microemulsion is a dispersion system consisting of 2 liquid types. Micelles (diameters ≤ 100 nm) are transparent or semitransparent and are composed of water, oil, and surfactant. Their tissue permeability is favorable because of their size, and the instillation of a dexamethasone-containing microemulsion in rabbit eyes has demonstrated enhanced permeability following topical delivery.²⁶ However, microemulsions, unlike microspheres and liposomes, are unsuitable for sustained-release drug delivery.

Dendrimers are repetitive single molecules with a branched structure composed of a central core and side chain moieties, or dendrons. Hydrophobic substances can be incorporated within the core of a dendrimer and their structure may be modified at the molecular level for their development as drug carriers. An *in vitro* study showed that an intravitreally administered sense oligonucleotide (ODN-1) could inhibit expression of VEGF.²⁷

However, the safety of these molecules when compared with liposomes and microspheres is unknown.

Verisome

Verisome is a proprietary drug delivery technology designed for controlled-release drug delivery for up to 1 year.²⁸ Small molecules, proteins, and monoclonal antibodies may be delivered using this technology. Ophthalmic indications being targeted by this technology include macular edema, glaucoma, retinoblastoma, AMD, and cataract surgery.

Lim et al reported the results of a phase 1 clinical trial evaluating the drug delivery system with a single intravitreal injection of the investigational drug IBI-20089 for cystoid macular edema due to RVO.²⁸ Five patients were administered 6.9 mg triamcinolone acetonide in 25 μL and 5 patients received 13.8 mg triamcinolone acetonide in 50 μL using a 30-gauge needle. They found that their drug delivery technology was able to deliver controlled and sustained delivery of medication with a longer sustained effect in the 13.8 mg triamcinolone group (up to 1 year). The intraocular pressure was elevated in 3 eyes, although 2 of these elevations were attributed to neovascular glaucoma.

A phase 1/2 study is ongoing assessing the safety and tolerability of the investigational drug IBI-20089 triamcinolone acetonide (6.9 mg or 13.8 mg) used in combination with ranibizumab 0.5 mg for subfoveal neovascular AMD. Following the initial administration of either 6.9 mg or 13.8 mg IBI-20089/ranibizumab, patients will receive monthly ranibizumab as needed based on clinical and OCT outcomes.

IBI-10090, a drug that employs the Verisome technology, provides a sustained-release formulation of dexamethasone in the anterior chamber through a single injection administered immediately following cataract surgery to avert the need for postoperative topical medications. In a phase 2 study of IBI-10090 in cataract surgery (NCT01214174), eyes treated with IBI-10090 at the time of cataract surgery demonstrated an anterior chamber cell count of 0 in 31%, 25%, and 46% of eyes receiving 513 μg , 776 μg , and 1046 μg dosages of IBI-10090, respectively. A phase 3 study of IBI-10090 for postcataract-surgery inflammation recently completed enrollment of 390 patients and will compare a low dose and medium dose of IBI-10090 with placebo (NCT02006888).

ENCAPSULATED CELL TECHNOLOGY

NT-501

Ciliary neurotrophic factor (CNTF) is a neurotrophic factor that retards photoreceptor cell loss during retinal degeneration and has been shown to protect

photoreceptors in animal models of photoreceptor degeneration. The NT-501 implant (Renexus, Neurotech) contains a human cell line of RPE encapsulated within a semipermeable polymer capsule that secretes recombinant CNTF into the vitreous.

A phase 2 study of NT-501 for geographic atrophy due to macular degeneration showed a dose-dependent increase in retinal thickness by 4 months after implantation, which was maintained through 12 months of study. Visual acuity stabilization (loss of fewer than 15 letters) was achieved with greater frequency in the high-dose group (20 ng/day) when compared with low-dose (5 ng/day) and sham surgery groups. Specifically, loss of fewer than 15 letters was observed in 96.3%, 83.3%, and 75% in the high-dose, low-dose, and sham surgery groups, respectively.²⁹ NT-501 is also in current trials for macular telangiectasia and achromatopsia.

In 2 phase 3, multicenter studies of the CNTF implant for early-stage and late-stage retinitis pigmentosa (CNTF4 [n = 68] and CNTF3 [n = 65]), patients with late-stage retinitis pigmentosa tolerated the implant well. However, a therapeutic benefit in the primary outcome (ie, change in BCVA) was not observed in either study.³⁰

NT-503

A similar technology using the encapsulated cellular delivery system (NT-503, Neurotech) utilizes cells releasing VEGF receptor Fc-fusion protein. In a phase 1, single-arm, multicenter open-label study, 13 patients with choroidal neovascularization secondary to AMD were evaluated. Early reports showed that the implant could be safely performed.³¹ The design of next-generation encapsulated cell technology for the delivery of VEGF antagonist is currently ongoing to increase the dosage of VEGF antagonist via increased numbers of encapsulated cells, thereby improving cell viability and protein expression efficiency.³²

SUSTAINED-RELEASE REFILLABLE OPTIONS

MicroPump

Using microelectromechanical systems (MEMS) engineering, a novel mini drug pump for sustained-release drug delivery is under investigation. Features of this drug delivery device include a pumping mechanism based on electrolysis and a drug refill port and pressure check valve to control drug delivery. Utilizing surgical principles similar to glaucoma aqueous drainage devices, the mini drug pump was successfully implanted in 4 rabbits with no evidence of device extrusion or infection, and no filtering blebs were observed.³³

Anterior MicroPump and Posterior MicroPump platforms (both by Replenish) are under investigation for patients with glaucoma and retinal disease, respectively.³⁴

Port Delivery System

The PDS (ForSight Vision4) is a refillable drug delivery device designed to release medication over several months. In December 2010, Genentech and Roche entered into an agreement to develop and commercialize anti-VEGF-A targeted therapies.³⁵ A phase 1 clinical trial evaluating the efficacy and safety of the device is ongoing in patients with wet AMD (NCT01186432). A phase 1/2 study evaluating the PDS for patients with chronic noninfectious uveitis is also currently ongoing (NCT02125266).

SUMMARY

The innovative approaches of these emerging ophthalmic devices and pharmaceuticals offer promising options for drug delivery that will likely strengthen the vitreoretinal specialist's armamentarium for patients with AMD, RVO, DME, and posterior uveitis in the future. Intravitreal implants with refillable reservoirs and suprachoroidal delivery via microcatheter delivery or hollow microneedles represent a few of the potential routes whereby sustained-release drug delivery may be achieved. In addition, the vehicles (Verisome technology, nanotechnology, others) by which medications are administered via intravitreal injections may also offer longer-term options to reduce the treatment burden of frequent injections and clinic visits. As evidenced by intravitreal implant options previously studied, the ophthalmic benefit-risk ratio, as well as the cost of these medications, will be critical to their implementation and widespread acceptance in the clinical setting. However, patients with retinal disease will likely have additional therapeutic options in the future as these promising drug delivery platforms move forward in development. ■

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