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## Advances in Drug Delivery to the Posterior Segment

William Pearce, MD<sup>1</sup>, Jason Hsu, MD<sup>2</sup>, and Steven Yeh, MD<sup>1</sup>

<sup>1</sup>Emory Eye Center, Emory University School of Medicine, Atlanta, GA

<sup>2</sup>Retina Service of Wills Eye Hospital, Mid Atlantic Retina, Philadelphia, PA

### Abstract

**Purpose**—Emerging developments and research for drug delivery to the posterior segment offer a promising future for the treatment of vitreoretinal disease. As new technologies enter the market, clinicians should be aware of new indications and ongoing clinical trials.

**Recent Findings**—This review summarizes the advantages and shortcomings of the most commonly used drug delivery methods including vitreous dynamics, physician sustainability and patient preferences. Currently available intravitreal corticosteroid-release devices offer surgical and in-office management of retinal vascular disease and posterior uveitis. The suprachoroidal space offers a new anatomic location for the delivery of lower dose medications directly to the target tissue. Implantable drug reservoirs would potentially allow for less frequent intravitreal injections reducing treatment burdens and associated risks. Newer innovations in encapsulated cell technology offer promising results in early clinical trials.

**Summary**—While pars plana intravitreal injection remains the mainstay of therapy for many vitreoretinal diseases, targeted delivery and implantable eluting devices are rapidly demonstrating safety and efficacy. These therapeutic modalities offer promising options for the vitreoretinal therapeutic landscape.

### Keywords

drug delivery; suprachoroidal; encapsulated cell technology; posterior uveitis

### Introduction

Intravitreal delivery of pharmacologic agents is the key method of drug delivery for posterior segment disease including retinal vascular disorders and posterior uveitis. While intravitreal administration of therapeutics increases concentration in the area of diseased tissue (i.e. retina, choroid, retinal pigment epithelium), while reducing systemic side effects, other drug delivery options reviewed in this manuscript offer promise for posterior segment

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**Corresponding Author** Steven Yeh, MD, 1365B Clifton Rd. NE, Atlanta, GA 30322, steven.yeh@emory.edu, Phone no: 404-778-5070, Fax no: 404-778-4380.

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conditions. Such drug delivery options may reduce treatment burden and minimize injection risk via sustained-release delivery (e.g. corticosteroid implants, refillable reservoirs), introduce medication in the suprachoroidal space (e.g. hollow microneedles, suprachoroidal cannulation), or potentially circumvent repeated injections altogether (e.g. encapsulated cell technology).

### **Intravitreal injections: historical perspective**

Intravitreal therapy began as pioneering German ophthalmologists injected air into the vitreous in the first pneumatic retinopexies in the early twentieth century.[1] Several decades later, penicillin was injected into a vitreous abscess that developed after extracapsular cataract extraction with good results.[2] In the 1970s, triamcinolone acetonide was accidentally injected into the vitreous cavity with a dermatologic applicator.[3] Since the development of vascular endothelial growth factor (VEGF) inhibitors, treatment of neovascular and exudative retinal disease has exponentially increased.[4] However, intravitreal injections are limited by ocular pharmacokinetics and the frequent need for retreatment.[5\*] This need for repetitive therapy increases costs, risk profiles, and patient discomfort. Moreover, the rapid growth of intravitreal therapy also creates an issue of sustainability as the volume of patients requiring chronic, ongoing intravitreal therapies for retinal disease continues to rise.

### **Current Trends**

Age-related macular degeneration (AMD), retinal vein occlusion (RVO), diabetic eye disease, and posterior uveitis continue to remain at the forefront as targets for ocular therapeutics and drug delivery methodology. Currently, United States Federal Drug Administration (FDA) approved anti-VEGF medications for intraocular indications include ranibizumab (Lucentis, Genentech, San Francisco, CA) and aflibercept (Eylea, Regeneron, Tarrytown, NY), for NVAMD, RVO, and diabetic macular edema (DME). Aflibercept, which is a VEGF-trap molecule, was a promising development as its theoretical longer duration of action offers a potentially less frequent retreatment option for neovascular AMD. [6-7\*\*]. Bevacizumab (Avastin, Genentech, San Francisco, CA) has demonstrated comparable results to ranibizumab, although it has not yet been approved for intraocular use by the FDA.[8] Triamcinolone acetonide (Triesence, Alcon, Fort Worth, TX) has been FDA approved for posterior uveitis, but has also demonstrated efficacy for macular edema due to retinal vein occlusion and diabetes. Each of these therapies has provided a marked improvement in visual outcomes and quality of life for patients. However, less invasive, more durable and targeted treatments that reduce adverse side effects (e.g. cataract and glaucoma associated with intravitreal corticosteroid) are increasingly desirable.

Studies have shown that VEGF suppression after intravitreal injection ranges from 26 to 69 days, and may be attributed to variable responses to therapy observed among different patients.[5\*] Ocular volume and lens status do not significantly contribute to variability in vitreous pharmacokinetics. Drug elimination from the vitreous is more likely determined by anterior bulk flow of aqueous humor, posterior elimination via retinochoroidal flow, and transcellular transportation mediated by specific carrier proteins in the retinal pigment epithelial cell membranes.[9] Molecular weight, lipophilicity, hydrophilicity and ionic

charge affect diffusion through the vitreous cavity as well as blood-ocular barriers, further altering the elimination rates of drugs delivered to the posterior segment.[10] Because of these drug elimination kinetics, multiple studies have demonstrated the importance of monthly and bimonthly injections for maintaining and improving vision during the treatment of AMD, RVO and DME.[6,8,11-12] Due to patient discomfort and risks (e.g., endophthalmitis) as well as physician sustainability issues, pro re nata and treat-and-extend protocols have been investigated to reduce the burden of intravitreal therapy on both parties. [8, 13] Technology that can deliver sufficient medication concentrations to the appropriate anatomic regions via novel drug delivery mechanisms represents an area of active interest in the ophthalmology community. Table 1 summarizes the mechanism of drug delivery, FDA-approved indications, and ongoing clinical trials for the platforms discussed in this review.

### **Sustained-Release Corticosteroid Implants**

Some of the initial strides in sustained-release intravitreal drug delivery were developed for posterior uveitis, a condition often defined by chronicity and the necessity for long-term therapy. The use of sustained-release corticosteroid implants has also been studied for retinal vascular disease including macular edema associated with retinal vein occlusion and diabetic macular edema.

#### **Retisert intravitreal implant (Fluocinolone acetonide, Bausch and Lomb, Bridgewater, NJ)**

The Retisert implant is a surgically implanted steroid-eluting device that releases fluocinolone acetonide into the vitreous cavity for up to three years.[14-16] In the Multicenter Uveitis Steroid Treatment (MUST) Trial, the Retisert implant was compared to systemic corticosteroids plus immunosuppression for noninfectious uveitis. The visual acuity improved over the 24-month study period in patients who received the Retisert implant and in patients who received systemic therapy with neither approach superior within the study's power. However, patients who received the Retisert implant had a greater likelihood of cataract surgery (80%) and glaucoma (17%) than patients who received systemic therapy. On the other hand, patients receiving systemic immunosuppression had more prescription-requiring infections than patients who received the implant. Overall, systemic adverse outcomes were uncommon in both groups.[16]

Sangwan et al. recently reported three-year results from a randomized clinical trial for the treatment of non-infectious uveitis with the Retisert implant. Of the 239 eyes that were implanted, recurrence rates decreased from 42.3% in the year prior to intervention to 25.9% (P=0.0003) during the three years after implantation.[17] Moreover, a statistically significant number of implanted eyes gained three or more lines of best-corrected visual acuity (BCVA) compared to the non-implanted fellow eyes and required less adjunctive systemic immunosuppression. These findings were consistent with the results from a prior original 3-year clinical trial.[15]

#### **Ozurdex (dexamethasone 0.7 mg, Allergan, Inc. Irvine, CA)**

The Ozurdex insert is a sustained-release dexamethasone intravitreal insert that has received FDA approval for posterior uveitis, RVO, and DME.[17-19\*\*] Several studies have demonstrated its efficacy for intermediate and posterior uveitis in children and adults when

topical, periocular or systemic corticosteroids fail or cannot be tolerated secondary to side effects.[20-21\*] When used to treat cystoid macular edema after RVO, the Ozurdex 0.7 mg implant allowed 30% of 412 eyes receiving treatment to gain at least 15 letters in BCVA after 60 days. In addition, 29.8% of 302 phakic eyes demonstrated cataract progression after receiving two implants.[18] More recently, a randomized, controlled trial of Ozurdex for diabetic macular edema demonstrated that 22% of treated eyes versus 12% of sham control eyes achieved at least a 15 letter increase in BCVA, while central retinal thickness decreased by 100  $\mu\text{m}$  or more in the treatment group compared to 40  $\mu\text{m}$  in the sham group.[19\*\*]

Recently, the Ozurdex implant was described to migrate into the anterior chamber from its original posterior segment insertion site in aphakic and pseudophakic patients with an open posterior capsule. In a review of eighteen cases of Ozurdex implant migration into the anterior chamber, fourteen (71%) developed corneal edema necessitating corneal transplantation in six cases. The average time from injection to migration was thirteen days. Previous pars plana vitrectomy and absence of lens capsule were found to be significant risk factors.[22] Because of these recent reports, careful patient selection and counseling are necessary to avoid this potential complication.

### **Iluvien injectable insert (fluocinolone acetonide, Alimera Sciences Inc., Alpharetta, GA)**

Most recently added to the market after FDA approval in September 2014 is the Iluvien injectable insert. Iluvien is indicated for the treatment of DME in patients who have demonstrated a lack of steroid responsive intraocular pressure elevation. Recently, a multicenter, randomized, controlled trial compared a low and high dose implant to sham treatment and demonstrated that the low dose implants resulted in similar levels of significant visual improvement as the higher dose cohort with a lower rate of side effects. Among 953 patients, 28.7% (0.2 $\mu\text{g}/\text{d}$ ) and 27.8% (0.5 $\mu\text{g}/\text{d}$ ) achieved a gain of at least 15 letters in BCVA compared to 18.9% in the sham group (P=0.018). Patients with DME for longer than three years at the onset of treatment experienced almost a doubling of treatment effect compared to sham groups in a preplanned subgroup analysis. Necessity for cataract surgery occurred in nearly all phakic patients, while only 4.8% and 8.1% of the low and high dose groups respectively, required glaucoma surgery after three years.[23]

With multiple steroid-eluting devices on the market, several studies have now sought to investigate the differences among various therapeutic systems. Kiddee et al. compared the intraocular pressure elevation after injection of a 4 mg triamcinolone acetonide suspension, a 0.59 and 2.1 mg fluocinolone implant and a 0.35 and 0.7 mg dexamethasone implant. This meta-analysis showed that ocular hypertension developed after steroid injection in 32% of triamcinolone treated eyes, 66% and 79% in low and high-dose fluocinolone implanted eyes, and 11% and 15% of low and high-dose dexamethasone inserted eyes. Risk factors for developing steroid responsive ocular hypertension were pre-existing glaucoma or ocular hypertension, younger age and uveitis. This study concluded that the dexamethasone insert resulted in the lowest rate of ocular hypertension, while the fluocinolone implant conferred the highest risk of needing incisional glaucoma surgery.[24]

An additional study sought to compare pharmacokinetics of the two fluocinolone acetonide delivery vehicles. Campochiaro et al. sampled aqueous steroid concentrations in two

different prospective, interventional trial groups demonstrating that mean aqueous flucinolone acetonide levels were comparable at one and three month intervals in the low (2.17ng/mL) and high-dose (3.03ng/mL) insert groups, but higher in the implant (6.12ng/mL) group. This study also demonstrated steady state trough levels remained stable up to three years in all groups.[25]

### **Implantable Reservoirs**

In contrast to drug-impregnated devices that elute medication for a predetermined interval, drug filled reservoirs with micropumps that have a capacity for minimally invasive refill have gained interest. The Replenish MicroPump (Replenish, Pasadena, CA) is a surgically implantable drug reservoir with a pump designed to release nanoliter doses at a programmed interval. Implanted into the eye similar to a glaucoma drainage device, the anterograde flow into the eye delivers continuous dosing while a readily accessible reservoir can be refilled via transconjunctival injection. Anterior and posterior platforms are in development for cannulation and targeting of both ocular segments.[26-27]

Alternatively, the Port Delivery System (PDS, ForSight VISION4, Inc.) is a refillable drug delivery device that is in phase 1 and phase 2 trials for preliminary safety and efficacy for neovascular AMD and non-infectious uveitis. ([www.ClinicalTrials.gov](http://www.ClinicalTrials.gov): NCT01186432 and NCT02125266).

### **Suprachoroidal Drug Delivery**

Another promising approach to drug delivery has involved accessing the suprachoroidal space for the delivery of therapeutics. Delivering medication to this potential space has the proposed advantage of higher concentrations of medication to target tissues (retina, choroid) and lower concentration of medication to anterior segment structures. This benefit has been demonstrated in detailed anatomic studies of medication concentrations following suprachoroidal drug delivery.[28]

### **Suprachoroidal drug delivery via microsurgical cannula**

Olsen and colleagues studied an approach to posterior segment drug delivery by cannulating the suprachoroidal space via a novel microsurgical technique. In a primate and porcine-based study, Olsen et al. demonstrated safety, tolerability and effective pharmacokinetics after suprachoroidal delivery of multiple substances including triamcinolone. Successful delivery of triamcinolone to adjacent tissues was demonstrated to last at least 120 days in sacrificed animals and deleterious side effects such as ocular hypertension and cataract were not reported with suprachoroidal delivery.[29] Another porcine-based study by Olsen et al. demonstrated that certain molecules may be more susceptible to rapid clearance from the suprachoroidal space and less effective than traditional delivery routes. In this study, bevacizumab injected into the vitreous remained detectable in target tissues of the inner retina 30-60 days after injection, whereas bevacizumab delivered via cannulation of the suprachoroidal space was no longer detectable one week after delivery.[30]

### Suprachoroidal drug delivery with a hollow microneedle

Patel et al. reported their experience with suprachoroidal drug delivery with a hollow microneedle with specific dimensions allowing penetration of the sclera and termination in the suprachoroidal space via a syringe-based injection posterior to the pars plana in a rabbit model. This minimally invasive technique demonstrated safe delivery into the suprachoroidal space and no adverse effects.[27] These animal-based studies have demonstrated proof of concept and safety for suprachoroidal drug delivery and encourage future studies into selecting molecules that are best targeted for delivery via this route.

Gilger et al. demonstrated the successful suppression of acute inflammation with suprachoroidal delivery of corticosteroid in a porcine model of noninfectious posterior uveitis.[31] Specifically, using an endotoxin-induced model of uveitis, intravitreal injections of lipopolysaccharide or balanced saline solution were followed with injections of 0.2 mg or 2.0 mg of triamcinolone acetonide into the suprachoroidal space using a hollow microneedle. The lower dose injected into the suprachoroidal space was as effective as the higher dose of intravitreal triamcinolone in reducing inflammation.

Presently, two clinical trials are enrolling patients in studies to evaluate the safety and efficacy of suprachoroidal therapy delivered by a microneedle in humans. The first is a phase 2 randomized, controlled, trial seeking to evaluate suprachoroidal injection of triamcinolone acetonide with aflibercept in patients with macular edema after RVO. The second is an interventional study designed to determine safety and efficacy of triamcinolone in the suprachoroidal space for the treatment of macular edema in non-infectious uveitis. ([www.clinicaltrials.gov](http://www.clinicaltrials.gov): NCT02303184 and NCT01789320)

### Encapsulated Cell Technology

Current injectable and implant-based therapeutics are limited by the volume and concentration that can be delivered per treatment. The development of encapsulated cell lines that can produce and secrete biologically active molecules for an indefinite period may circumvent the need for repeated procedures. Encapsulated cell technology requires the genetic engineering of a cell line to constitutively produce a gene product and then subsequent encapsulation of the cell line by a collagen and hyaluronic acid-based hydrogel. The cell lines must be able to survive within the encapsulation matrix by diffusion of nutrient substances from the surrounding media and be able to produce and elute the target protein, while still remaining protected from host defense mechanisms. Recent investigators have engineered retinal pigment epithelial cell lines that produce a soluble VEGF receptor capable of suppressing endogenous VEGF activity. This proof-of-concept study showed that the cell line remained viable and the gene product remained constant for at least the fifty-day study period. Although VEGF inhibition was modest in this *in vivo* model, this delivery modality shows promise as future advances in gene product structure and secretion rates should result in improved efficacy.[32\*\*] A phase II study of an encapsulated cell line producing ciliary neurotrophic factor for geographic atrophy in macular degeneration showed a dose-dependent increase in retinal thickness up to 12 months after implantation. A loss of less than 15 letters of BCVA was achieved in 96.3%, 83.3% and 75% in high-dose (20ng/day), low-dose (5ng/day) and sham groups, respectively.[33] This technology shows

promise in other retinodegenerative diseases such as retinitis pigmentosa, macular telangiectasia and achromatopsia.[34]

## Conclusion

While intravitreal injections remain a mainstay of therapy for the management of posterior segment disease, particularly anti-VEGF agents for retinal vascular disease, intravitreal corticosteroid implants administered via office-based procedures or in the operating room offer a backdrop whereby sustained-release drug delivery has been developed. Approaches for the future of drug delivery include refillable surgical intravitreal implants, accessing the suprachoroidal space to take advantage of tissue targeting while limiting toxicity, and cell-based technologies to circumvent the need for repeated procedures.

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## Abbreviations

<b>VEGF</b>	vascular endothelial growth factor
<b>NVAMD</b>	neovascular age related macular degeneration
<b>DME</b>	diabetic macular edema
<b>RVO</b>	retinal vein occlusion
<b>FDA</b>	United States Federal Drug Administration
<b>BCVA</b>	best corrected visual acuity

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### Key Points

- Intravitreal therapeutics, particularly anti-VEGF therapies, are a mainstay of therapy for posterior segment disease, but limitations include the patient and physician burden, as well as risks associated with repeated dosing over time.
- Sustained-release intravitreal corticosteroids have demonstrated efficacy for the treatment of posterior uveitis and retinal vascular disease including retinal vein occlusion and diabetic macular edema, but their dose-limiting side effects include the development of cataract and glaucoma.
- Promising technologies for drug delivery currently under investigation include refillable surgical intravitreal implants, suprachoroidal drug delivery, and encapsulated cell technology.

**Table 1**

Summary of drug delivery platforms reviewed

Therapy	Drug delivery platform	Current FDA Indications/Ongoing Clinical Trials
Retisert (fluocinolone acetonide 0.59 mg implant; Bausch + Lomb)	Surgical intravitreal implant	Non-infectious uveitis
Ozurdex® (dexamethasone implant 0.7 mg; Allergan)	22-gauge intravitreal injection	Indications: Retinal vein occlusion, Non-infectious uveitis, Diabetic macular edema Ongoing Trials: Macular edema due to retinal vein occlusion after treatment failure with anti-VEGF; Uveitic macular edema; Diabetic macular edema treated with pars plana vitrectomy and membrane removal (OPERA Study)
Iluvien™ (fluocinolone acetonide 190 mg; Alimera Sciences, Inc.)	25-gauge intravitreal insert	Indications: Diabetic macular edema Ongoing Trials: Non-infectious uveitis; Macular edema due to retinal vein occlusion (FAVOR); geographic atrophy secondary to AMD
Suprachoroidal injection with microneedle (Clearside Biomedical, Inc.)	Proprietary microinjector for delivery into suprachoroidal space	Ongoing Trials: Combination intravitreal aflibercept and suprachoroidal triamcinolone for macular edema following RVO (TANZANITE) Dose-Ranging, Suprachoroidal triamcinolone acetonide suspension for macular edema associated with non-infectious uveitis
Encapsulated cell technology (Neurotech) Renexus® (NT-501) NT-503	Encapsulated cells genetically modified to secrete ciliary neurotrophic factor (CNTF) Encapsulated cell technology secreting VEGF-antagonist	Ongoing Trials: NT-501 for glaucoma, ischemic optic neuropathy, achromatopsia, retinitis pigmentosa, macular telangiectasia NT-503-3 for recurrent CNV due to AMD
<b>Refillable Reservoirs</b> Microelectromechanical systems (MEMS) mini drug pump (Replenish) Port Delivery System (PDS; ForSight Vision4)	Mini drug pump with pumping mechanism based on electrolysis with drug refill port and check valve to control drug delivery Proprietary refillable drug delivery system designed to release medication over a period of months	Ongoing Trials: MEMS: N/A PDS: Safety and efficacy study of PDS-1.0 for neovascular AMD