AN UPDATE ON SUSTAINED DRUG DELIVERY IN RETINA

Unique ways to address treatment burden for patients with retinal conditions.

BY DEEPAK SAMBHARA, MD, AND MARIN STOWE, BS


Anti-VEGF and steroid agents have revolutionized how we treat many retinal vascular diseases such as wet AMD, diabetic retinopathy (DR), diabetic macular edema (DME), and uveitis.[1,2] Real-world data show that patients who receive more frequent or continuous fixed dosing of these agents achieve more favorable anatomical and visual outcomes. In contrast, those who receive less frequent dosing than those in clinical trials have worse outcomes.[3] However, the high treatment burden associated with managing these diseases has underscored the need for novel treatments and sustained-release drug delivery (SRDD) platforms. Here, we examine some of the latest therapeutics in the pipeline and the evolution of SRDD platforms in the vitreoretinal space.

POLYMER-BASED SRDD

Polymer platforms can broadly be classified into bioerodible implants (BIs) and nonbioerodible implants (NBIs). Several NBIs have been FDA approved to treat retinal diseases, many of which are polyvinyl alcohol (PVA) implants made from hydrolyzed polymers of vinyl acetate. PVAs help to regulate drug diffusion and can be combined with ethylene vinyl alcohol to control the surface area of diffusion. Although PVAs are bioerodible structures, the implants are often nonbioerodible due to the reservoirs used to modulate and control drug release.

Nonbioerodible Implants

Retisert (Bausch + Lomb), an intravitreal NBI of fluocinolone acetonide, was FDA approved in 2005 for the treatment of chronic noninfectious uveitis.[4] This surgically placed implant releases fluocinolone acetonide at an initial rate of 0.6 µg/day, decreasing to a steady state of 0.3 µg/day to 0.4 µg/day over 30 months.

In 2014, Iluvien (Alimera Sciences) was the first intravitreally injected NBI to receive FDA approval for the treatment of DME. This implant releases 0.19 g fluocinolone acetonide at an average rate of 0.2 µg/day for up to 36 months.

Yutiq (Alimera Sciences) is a nearly identical NBI of fluocinolone acetonide approved by the FDA in 2018 to treat chronic noninfectious uveitis.[5] The implant is injected into the vitreous cavity and releases 0.18 g fluocinolone acetonide at 0.25 µg/day for up to 36 months.

Bioerodible Implants

Bioerodible platforms provide the additional benefit of resorption over time without leaving significant remnants of the delivery system.[6] BI platforms include polylactide acids (PLAs), polylactic-co-glycolic acids (PLGAs), and hydrogels. PLA metabolites are nontoxic, are hydrolyzed into constituent α-hydroxy acid, and can be eliminated naturally. PLA degradation depends on several factors, including molar mass, conformation, and copolymer composition.

PLGAs are bioerodible through the hydrolytic cleavage of

their polyester backbones into lactic and glycolic acids that are soluble in the vitreous cavity. Metabolism and degradation rates of PLGAs can be manipulated to control drug release based on the lactic acid-to-glycolic acid ratio. Due to pH imbalances, these nontoxic metabolites can create a locally acidic environment, which has the potential to cause damage to other structures in the eye.

Ozurdex (Abbvie) is a PLGA-based intravitreal implant of 0.7 mg dexamethasone FDA approved for the treatment of macular edema secondary to retinal vein occlusion, DME, and noninfectious uveitis with a duration of up to 6 months.[7,8] Despite the implant's ability to hydrolyze and be resorbed, persistent, nondissolving, tubular foreign bodies in the vitreous have been reported.[9,10]

Hydrogels are created with natural or synthetic biopolymers, connected by physical or chemical bonds, and crosslinked to maintain a 3D macrostructure.[11] Hydrogel platforms are often used in drug delivery due to their ability to contain significant water content, mimicking biological soft tissues. Given the ability to respond to temperature and pH shifts, drug release can be tailored to specific environmental changes. The active ingredient is dissolved or suspended within the hydrogel network during crosslinking, and drug release occurs through diffusion or dissolution of the hydrogel matrix—the drug release rate hinges on the degree of physical or covalent crosslinking of the hydrogel polymers.

The Elutyx platform (Ocular Therapeutix) consists of a preservative-free, polyethylene glycol-based triglycine hydrogel fiber that biodegrades via ester hydrolysis in the presence of water. Elutyx is customizable to release an active ingredient anywhere from days to months. Currently, it is used in Dextenza (Ocular Therapeutix), an FDA approved bioerodible intracanalicular insert that releases dexamethasone through passive diffusion to treat postoperative inflammation and allergic conjunctivitis.[12]

The Elutyx platform is also being investigated for wet AMD and DR with the OTX-TKI (Axpaxli, Ocular Therapeutix) clinical program. OTX-TKI is an SRDD BI containing the tyrosine kinase inhibitor (TKI) axitinib, which is injected into the vitreous cavity. OTX-TKI (450 µg) is being evaluated in two phase 3 registration trials (NCT06495918 and NCT06223958) for wet AMD and a phase 1 clinical trial (NCT05695417) for the treatment of DR.

Durasert E (EyePoint Pharmaceuticals) is an SRDD BI developed for the treatment of wet AMD, DR, and DME. EYP-1901 (Duravyu, EyePoint Pharmaceuticals) is an intravitreal injection using the Durasert E platform to deliver the TKI vorolanib. The implant is under investigation in two phase 3 trials, LUCIA (NCT06683742) and LUGANO (NCT06668064) for the treatment of wet AMD.[13] EYP-1901 is also in phase 2 studies for nonproliferative DR (NCT05381948) and DME (NCT06099184).

DRUG-ELUTING RESERVOIRS

In 2021, the FDA approved the port delivery system (PDS) with ranibizumab (Susvimo, Genentech/Roche) for the treatment of wet AMD based on the pivotal phase 3 clinical trial (NCT03677934).[14] Susvimo is a refillable reservoir that holds up to 200 µL of medication. Passive diffusion of ranibizumab is controlled via a titanium release control element that acts as a medium between the vitreous and the device. A self-sealing septum is located on the extraskeletal surface of the device, which allows for repeated refills with a custom refill-exchange needle. A silicone encasement sits superficial to the sclera, acting as an extraskeletal flange to anchor the device into the deep conjunctiva without the need for suture fixation.

In October 2022, Genentech/Roche voluntarily recalled the device due to concerns about septum displacement.[15] The product was relaunched in July 2024 with changes to the septum and overmold interfaces while doubling the bond strength. Lubrication was added to the refill-exchange needle to reduce injection forces during refill.[16]

The PDS is still under investigation for the treatment of DR and DME in two phase 3 clinical trials (NCT04503551 and NCT04108156).

SUPRACHOROIDAL APPROACH

The suprachoroidal space (SCS) has become a therapeutic target for retinovascular disease due to the ability to achieve higher drug concentrations, increased bioavailability, and longer duration of action with a more favorable side effect profile.[17]

Xipere (Bausch + Lomb) is an SCS injection of 4 mg triamcinolone acetonide that was FDA approved in 2021 for the treatment of macular edema secondary to noninfectious uveitis.[18] The SCS Microinjector (Clearside Biomedical) used in Xipere is a piston syringe and needle approximately 1 mm

AT A GLANCE

- The high treatment burden associated with managing retinal diseases has underscored the need for novel treatments and sustained-release drug delivery platforms.
- The suprachoroidal space has become a therapeutic target for retinovascular disease due to the ability to achieve higher drug concentrations, increased bioavailability, and longer duration of action.
- Innovation in drug delivery has led to durable, efficacious, and long-acting treatments that have the potential to decrease treatment burden and improve patient outcomes.

in length (900 µm and 1,100 µm needles).

The phase 2b ODYSSEY clinical trial (NCT05891548) evaluated CLS-AX (Clearside Biomedical), a proprietary suspension of 1.0 mg axitinib delivered by SCS injection, for the treatment of wet AMD.[19]

GENE THERAPY PLATFORMS

In gene therapy, a viral vector designed explicitly with a therapeutic gene transfects host cells, leading to endogenous expression of the therapeutic gene product. In retinovascular disease, these gene products are anti-VEGF proteins, which offer the possibility of SRDD and minimized treatment burden.

Ixoberogene soroparvovec (ixo-vec, Adverum Biotechnologies) is an intravitreal gene therapy using an AAV2.7m8 viral capsid to express aflibercept. Ixo-vec was assessed in a phase 1 trial (NCT03748784) and long-term observational study (NCT04645212) for wet AMD and continues in the phase 2 LUNA trial (NCT05536973) evaluating an intravitreal injection of two dose concentrations in conjunction with prophylactic steroids. The phase 2 trial (NCT04418427) for DME was stopped due to severe adverse events reported in patients receiving the higher dose, leading to the termination of the DME clinical program.[20]

4D Molecular Therapeutics used a process of directed evolution to help develop their R100 capsid, the backbone of their investigational product for the treatment of wet AMD, DR, and DME. 4D-150 is a single-dose intravitreal gene therapy that encodes an inhibitory RNAi targeting VEGF-C and a codon-optimized sequence of aflibercept. The gene therapy is under investigation in the phase 1/2 PRISM trial (NCT05197270) for wet AMD and the phase 2 SPECTRA trial (NCT05930561) for DME.

ABBV-RGX-314 (Regenxbio/Abbvie) is a gene therapy delivered in the subretinal space or SCS that codes for a transgene on an AAV8 vector that expresses a ranibizumab-like monoclonal antibody fragment. Two phase 2b/3 studies (NCT04704921 and NCT05407636) are investigating subretinal ABBV-RGX-314 in wet AMD, and a phase 2 study (NCT04567550) is assessing the gene therapy for moderately severe or severe nonproliferative DR or mild proliferative DR. ABBV-RGX-314 is also being investigated in a phase 2 study (NCT04514653) as an SCS injection—delivered using Clearside Biomedical's SCS Microinjector—for patients with wet AMD.

NEXT STEPS

The evolution of SRDD in the vitreoretinal space has dramatically transformed the landscape over the past three decades. Innovation in drug delivery has led to durable, efficacious, and long-acting treatments that have the potential to decrease treatment burden and improve patient outcomes. As we head into 2025, we expect to see further clinical development of investigational products with the hope of expanding our clinical armamentarium for patient care. ■

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DEEPAK SAMBHARA, MD
- Partner, Medical Director of Research, Medical Retina and Diseases of the Vitreous, Eye Clinic of Wisconsin, Wausau, Wisconsin
- sambhad@eyeclinicwi.com
- Financial disclosure: Advisor/Consultant (Genentech/Roche, iDocSocial, Ocular Therapeutix, Regeneron); Research Funding (Ocular Therapeutix, Regeneron); Speaker/Speaker's Bureau (Apellis, Astellas, Evolve Medical, Heidelberg Engineering, iDocSocial, Regeneron); Stock (Eclipse Life Sciences)

MARIN STOWE, BS
- Medical Student, Medical College of Wisconsin-Central Wisconsin, Wausau, Wisconsin
- Financial disclosure: None