ADVANCES IN OCULAR DRUG DELIVERY

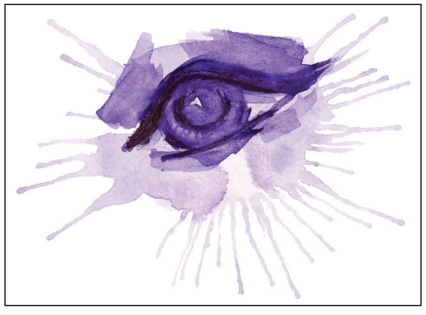
Innovative technologies mitigate side effects, reduce product waste, and enhance visual outcomes.

BY JESSICA STEEN, OD, FAAO, DIPL ABO

Developments in drug delivery for the treatment of ocular conditions continue to push the limits of biotechnology to improve durability, limit adverse effects, and provide alternative routes of administration, ultimately supporting a more individualized approach to care. Below, I discuss some of the most recent advances that may have a significant effect on our clinical practice.

OPTIMIZING TOPICAL THERAPY

Topical administration is a mainstay in the treatment of anterior segment

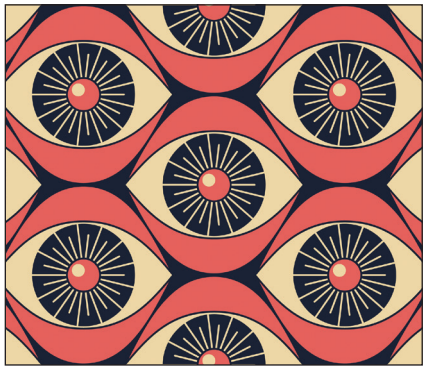


conditions due to widespread acceptance, general ease of use, and localized effect with limited systemic exposure. Although adverse effect profiles vary greatly between products, the well understood challenges related to topical ophthalmic medications, including limited corneal bioavailability and eye drop volume discrepancy with tear film capacity, can be addressed through novel approaches, such as those described below.

Tropicamide and phenylephrine hydrochloride ophthalmic spray 1%/2.5% (MydCombi, Eyenovia) received FDA approval in May for inducing mydriasis for diagnostic procedures and in conditions where short-term pupil dilation is desired. The first-in-class combination microdose formulation is administered using Eyenovia's proprietary Optejet dispenser,[1] which is held in front of the user's eye to administer a uniform microdroplet spray (approximately 6-8 µL of medication).[2,3] Use of the Optejet system is also being investigated in combination with other medications, including latanoprost, atropine, and pilocarpine, with the goal of optimizing topical ophthalmic delivery, while limiting systemic exposure and drug waste.[1-3]

The commercially available eye drop adapter Nanodropper (Nanodropper) works by attaching to a conventional topical ophthalmic medication multidose bottle and

reducing the volume of medication released by the bottle to 10.4 µL per drop.[4] In a prospective randomized trial, pediatric patients whose pupils were dilated with small-volume cyclopentolate 1%, tropicamide 1%, and phenylephrine 2.5% via Nanodropper experienced similar efficacy to those dilated using a standard drop size.[4] Statistical noninferiority was met for pupillary dilation, but was not met for cycloplegia or constriction percentage following dilation; however, the difference was not determined to be clinically significant.[4] The small volume adapter is being investigated in three clinical trials to treat patients with open-angle glaucoma and ocular hypertension.[5-7]

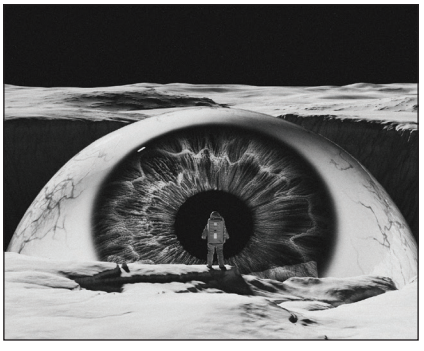


ADDRESSING CHRONIC OCULAR CONDITIONS

The challenges related to managing chronic, relatively asymptomatic ocular conditions (eg, maintaining adherence to therapy throughout the patient's life) continue to be a target for therapeutic advances. Although topically administered IOP-lowering agents tend to be the most accepted among patients, sustained-release options, including intraocular implants, aim to address the challenges of medication adherence and low corneal bioavailability of topically administered medications. One example is the FDA-approved and commercially available bimatoprost intracameral implant 10 mcg (Durysta, Allergan/AbbVie), but others are on the horizon.

A New Drug Application has been accepted by the FDA for iDose TR (Glaukos), a travoprost-releasing micro invasive intraocular implant. The device is surgically inserted and anchored to the sclera, where travoprost elutes into the anterior chamber from the reservoir of the device. Primary efficacy endpoints were met through 3 months with favorable safety and tolerability demonstrated through 12 months in clinical trials. The device is designed to be removed and replaced after complete release of travoprost. A Prescription Drug User Fee Act date has been set for December 22, 2023.[8]

Also under investigation are two biodegradable ocular implants: travoprost intracameral implant OTX-TIC (Ocular Therapeutix), which is undergoing phase 2 studies,[9] and PA5108 (PolyActiva), a latanoprost sustained-released ocular implant that is under evaluation in a phase 1 sequential dose study conducted in Australia and New Zealand for the treatment of open-angle glaucoma.



ACCESSING THE SUPRACHOROIDAL SPACE

Using the suprachoroidal space as a therapeutic reservoir in the treatment of retinal and choroidal disease provides potential advantages over use of the vitreous cavity, including high durability and high drug concentration in close physical proximity to the site of pathology due to its compartmentalized nature.[11] Previous investigations have identified that drugs injected into the suprachoroidal space result in high levels of detectable drug in the choroid, the retina, and the retinal pigment epithelium, with limited exposure to the vitreous, lens, iris, ciliary body, and anterior chamber, compared with intravitreal delivery.[11,12]

In 2021, the FDA approved triamcinolone acetonide injection suspension 40 mg/mL for use with a proprietary suprachoroidal space (SCS) Microinjector (Xipere, Bausch + Lomb/Clearside Biomedical) in the treatment of macular edema associated with uveitis. New programs are investigating the safety and efficacy of a tyrosine kinase inhibitor and a gene therapy using the SCS Microinjector to provide reliable access to the suprachoroidal space.[13-15]

The results of an extension study of the phase 1/2a OASIS trial of axitinib injectable suspension (suprachoroidal CLS-AX, Clearside Biomedical), a tyrosine kinase inhibitor of three vascular endothelial growth factor (VEGF) receptors, for patients with neovascular age-related macular degeneration (nAMD) who have had prior anti-VEGF therapy showed good durability. In the trial, 67% of participants were maintained for at least 6 months without additional treatment.[13] There were no reported serious adverse events, including intraocular inflammation, vitreous floaters, retinal detachments, and endophthalmitis.[13] Initiation of the phase 2b ODYSSEY trial evaluating CLS-AX in patients with treatment-naïve nAMD is anticipated in 2023.[13]

AAVIATE and ALTIDUDE are two phase 2 trials recruiting participants to evaluate ABB-RGX-314 gene therapy (RegenxBio) administered in the suprachoroidal space for the treatment of nAMD and diabetic retinopathy, respectively.[14,15] ABB-RGX-314 is an AAV8 vector containing a transgene that encodes for an antibody fragment that inhibits VEGF.[14,15] As an office-based, one-time procedure, the potential advantages of suprachoroidal delivery versus standard methods of delivering gene therapy products

(eg, pars plana vitrectomy, retinotomy, or subretinal injection) are significant, as is the potential durability that gene therapy may provide versus anti-VEGF agents delivered via intravitreal injection.

EARLIER INTERVENTION IN DR

With the established success of anti-VEGF agents in the treatment of late-stage complications of diabetic retinopathy (DR), including center-involved diabetic macular edema (DME) and proliferative DR (PDR), the logical next step is to understand the role of intervention on long-term visual outcomes at an earlier stage of disease. The PANORAMA study and the Diabetic Retinopathy Clinical Research Retina Network Protocol W have found that intravitreal anti-VEGF treatment reduces the development of late-stage complications of DR; however, recent Protocol W 4-year outcomes indicate that there was not a statistically or clinically meaningful improvement in visual acuity outcomes with treatment.[16,17]

Alternatively, less invasive treatment modalities under development aim to shift intervention in DR to earlier in the disease course, and to do so, will need to be met with regulatory support to most accurately identify clinically meaningful efficacy endpoints.

APX3330 (Ocuphire Pharma) is an orally administered apurinic/apyrimidinic endonuclease 1/redox effector factor-1 (APE/Ref-1) protein, referred to as Ref-1. APX3330 alters gene expression through inhibition of APE1/Ref-1, ultimately reducing downstream VEGF, TNF-alpha, interleukin 6, and other inflammatory cytokines that drive angiogenesis, oxidative stress, and inflammation.[18,19] Topline results from the phase 2 ZETA-1 clinical trial investigating the safety and efficacy of APX3330 in patients with moderately severe to severe nonproliferative DR (NPDR) or mild PDR showed that APX3330 did not meet its prespecified primary endpoint for percent of patients with a 2-step improvement in DRSS in the study eye at week 24.[18] However, a statistically significant reduction of disease progression was identified at 24 weeks with favorable safety and tolerability. APX3330 has previously been shown to result in a reversible skin rash at a dosage (720 mg) greater than the current investigative dose of 600 mg/day by oral route.[20] A pivotal trial and further development of APX3330 are planned.[18]

A topical ophthalmic selective integrin inhibitor, OTT166 (OcuTerra), is also under investigation in a phase 2 study that is actively recruiting participants for the evaluation of safety and efficacy in patients with moderately severe to severe NPDR or mild PDR who do not have center-involved DME.[21] The fluorinated molecule is proposed to penetrate the conjunctiva, sclera, and choroid to produce pharmacologic effects on retinal tissue.[22]

THE BOTTOM LINE

Innovations in drug delivery methods aimed at reducing adverse effects, maximizing effect on target tissues, and encouraging earlier treatment of disease states continue to support our clinical effort to provide a truly personalized approach to the management of ocular disease. ■

1. Eyenovia announces FDA approval of MydCombi, the first ophthalmic spray for mydriasis, which also leverages the company's proprietary Optejet device platform. [press release]. Eyenovia. May 8, 2023. Accessed May 12, 2023. eyenovia.com/eyenovia-announces-fda-approval-of-mydcombi-the-first-ophthalmic-spray-for-mydriasis-which-also-leverages-the-companys-proprietary-optejet-device-platform/
2. Ianchulev T, Weinreb R, Tsai JC, et al. High-precision piezo-ejection ocular microdosing: phase II study on local and systemic effects of topical phenylephrine. *Ther Deliv*. 2018;9(1):17-27.
3. Pasquale LR, Lin S, Weinreb RN, et al. Latanoprost with high precision, piezo-print microdose delivery for IOP lowering: clinical results of the PG21 study of 0.4 µg daily microdose. *Clin Ophthalmol*. 2018;12:2451-2457.
4. Hoppe CB, Yonamine S, Kao BW, et al. Randomized trial to evaluate the efficacy of the Nanodropper device for pupillary dilation and cycloplegia in children. *Ophthalmology*. 2023;130(3):324-330.
5. Use of Nanodropper vs. standard eyedropper in patients with glaucoma and ocular hypertension. Clinicaltrials.gov. Updated March 14, 2022. Accessed April 25, 2023. clinicaltrials.gov/ct2/show/NCT05277870
6. Efficacy of the Nanodropper device on intraocular pressure in patients with glaucoma. Clinicaltrials.gov. Updated October 13, 2022. Accessed April 25, 2023. clinicaltrials.gov/ct2/show/NCT05273385
7. Evaluation of Nanodropper-mediated microdrops vs. standard drops of 0.5% timolol maleate in glaucoma patients. Clinicaltrials.gov. Updated January 18, 2023. Accessed April 25, 2023. clinicaltrials.gov/ct2/show/NCT05181046
8. Glaukos announces FDA acceptance of NDA submission for iDose TR. [press release]. Glaukos Corporation. May 5, 2023. Accessed May 12, 2023. investors.glaukos.com/investors/news/news-details/2023/Glaukos-Announces-FDA-Acceptance-of-NDA-Submission-for-iDose-TR/default.aspx
9. A study to evaluate the efficacy and safety of OTX-TIC (travoprost) intracameral implant for patients with open-angle glaucoma (OAG) or ocular hypertension (OHT). Clinicaltrials.gov. Updated April 19, 2022. Accessed April 25, 2023. clinicaltrials.gov/ct2/show/NCT05335122
10. Open label, sequential-dose study of PA5108 latanoprost FA SR ocular implant for mild-moderate glaucoma. Clinicaltrials.gov. Updated December 27, 2023. Accessed April 25, 2023. clinicaltrials.gov/ct2/show/NCT04060758
11. Patel SR, Berezovsky DE, McCarey BE, et al. Targeted administration into the suprachoroidal space using a microneedle for drug delivery to the posterior segment of the eye. *Invest Ophthalmol Vis Sci*. 2012;53(8):4433-4441.
12. Olsen TW, Feng X, Wabner K, et al. Pharmacokinetics of pars plana intravitreal injections versus microcannula suprachoroidal injections of bevacizumab in a porcine model. *Invest Ophthalmol Vis Sci*. 2011;52(7):4749-4756.
13. Clearside biomedical announces positive 6 month results from OASIS extension study with suprachoroidal CLS-AX (axitinib injectable suspension) in wet AMD. [press release]. Clearside Biomedical. February 2, 2023. Accessed April 25, 2023. ir.clearsidebio.com/news-releases/news-release-details/clearside-biomedical-announces-positive-6-month-results-oasis
14. RGX-314 gene therapy administered in the suprachoroidal space for participants with neovascular age-related macular degeneration (nAMD) (AAVIATE). Clinicaltrials.gov. Updated October 20, 2022. Accessed April 25, 2023. clinicaltrials.gov/ct2/show/NCT04514653
15. RGX-314 gene therapy administered in the suprachoroidal space for participants with diabetic retinopathy (DR) without center involved-diabetic macular edema (CI-DME) (ALTITUDE). Clinicaltrials.gov. Updated November 21, 2023. Accessed March 21, 2023. clinicaltrials.gov/ct2/show/NCT04567550
16. Brown DM, Wykoff CC, Boyer D, et al. Evaluation of intravitreal aflibercept for the treatment of severe nonproliferative diabetic retinopathy: results from the PANORAMA randomized clinical trial. *JAMA Ophthalmol*. 2021;139(9):946-955.
17. Maturi RK, Glassman AR, Josic K, et al; the DRCR Retina Network. Four-year visual outcomes in the Protocol W randomized trial of intravitreous aflibercept for prevention of vision-threatening complications of diabetic retinopathy. *JAMA*. 2023;329(5):376-385.
18. Ocuphire announces topline results from ZETA-1 phase 2 trial of oral APX3330 in diabetic retinopathy and plans for end-of-phase 2 meeting with FDA [press release]. Ocuphire Pharma. January 25, 2023. Accessed April 25, 2023. www.ocuphire.com/news-media/press-releases/detail/395/ocuphire-announces-topline-results-from-zeta-1-phase-2
19. Hartman GD, Lambert-Cheatham NA, Kelley MR, Corson TW. Inhibition of APE1/Ref-1 for neovascular eye diseases: from biology to therapy. *Int J Mol Sci*. 2021;22(19):10279.
20. Caston RA, Gampala S, Armstrong L, Messmann RA, Fishel ML, Kelley MR. The multifunctional APE1 DNA repair-redox signaling protein as a drug target in human disease. *Drug Discov Today*. 2021;26(1):218-228.
21. OTT166 in Diabetic Retinopathy (DR). Clinicaltrials.gov. Updated April 11, 2023. Accessed April 25, 2023. www.clinicaltrials.gov/ct2/show/NCT05409235
22. Boyer DS, Kaiser PK, Magrath GN, et al. The safety and biological activity of OTT166, a novel topical selective integrin inhibitor for the treatment of diabetic eye disease: a phase 1b study. *Ophthalmic Surg Lasers Imaging Retina*. 2022;53(10):553-560.

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