TOPICAL DRUG ADMINISTRATION FOR THE POSTERIOR SEGMENT

In this article, David Bingaman, DVM, PhD, Chief Development Officer at Ora, explores the potential benefits of topical administration for diseases affecting the posterior segment of the eye.

A number of potentially game-changing innovations in retina research are currently in development, including stem cell and gene therapies, bispecific biologics and biosimilars, as well as topical eye drops that hold the potential to effectively treat posterior segment ophthalmic conditions, such as age-related macular degeneration (AMD) and diabetic eye disease. An approved topical eye drop for retinal disease would have the potential to provide a much less invasive option than the currently available management options, such as intravitreal injections and surgically implanted sustained release devices.

There are various challenges when considering the treatment of these visually debilitating retinal conditions, including limitations on how much of the drug reaches the intended tissue and the increased concentrations required for tissue penetration. If effective, such a topical drug delivery method could improve the quality of patients' lives and provide an alternative to repeated surgical procedures for retinal vascular and degenerative diseases.

CURRENT APPROVED TREATMENTS

Over the last two decades, breakthrough treatments have been approved for the treatment of retinal vascular diseases, such as wet AMD and diabetic macular oedema (DME), all requiring in-office treatments by an ophthalmologist, most of which need to be repeated frequently. Prior to intravitreal (IVT) anti-vascular endothelial growth factor (anti-VEGF) therapy, laser photocoagulation and photodynamic therapy (PDT) were the standard of care for choroidal neovascularisation (CNV).

Laser photocoagulation consists of the use of focused laser spots to treat areas of oedematous retina to prevent further retinal thickening and the resultant diseased retinal tissue. PDT involves the administration of an intravenous photosensitiser, verteporfin, after which a laser is applied to the affected area of CNV, which prevents it progressing further into the surrounding retina. Both therapies have the limitation of restricted improvements of affected vision and CNV recurrences post-therapy.[1]

Intravitreal anti-VEGF injections were a historical advancement in patient care, working to reduce pathologic vascular leakage and prevent further abnormal new vessel growth through the local administration of biologics, such as ranibizumab, bevacizumab or aflibercept, into the vitreous chamber. The most recent IVT biologic approved, faricimab, impacts both the VEGF and angiopoietin signalling pathways.

Several limitations associated with IVT injections exist, including the requirement for repeated, sometimes frequent, in-office procedures, as recommended by a patient's eye-care practitioner. These treatments can be uncomfortable, or even painful, for a patient, and visits often require family member involvement.[1] These factors may lead to substantial long-term non-compliance with frequent treatments and a resulting worsened visual prognosis.

Although rare, there are also several risks associated with IVT injections, including potentially blinding complications, such as retinal detachment or endophthalmitis. More recent advancements have focused on durable delivery platforms, with IVT

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implants becoming more popular, as they can provide sustained release drug administration – eliminating the need for repeated IVT injections. IVT implants are surgically implanted into the eye, usually under local anaesthesia and, depending on the implant, can slowly release their designated drug over a period of three months up to two-and-a-half years. There are similar risks and drawbacks to IVT anti-VEGF injections, including the risk of visually debilitating complications. Along with this, some implants are not biodegradable and therefore need to be surgically removed from the eye.[1]

To avoid frequent and invasive therapeutic options for degenerative and vascular retinal disease, there is a need for less-invasive treatment options, either replacing the currently available therapies or as a concomitant therapy to lessen the need for repeated in-office procedures. This is especially true with the advent of patient-involved disease assessments, such as home retinal imaging, and in areas where retina specialty care is difficult to obtain.

POTENTIAL BENEFITS OF TOPICAL ADMINISTRATION

Although it is rarely discussed in this context, the use of topical eye drops (Figure 1) to treat posterior segment disorders has been ongoing for quite some time as a topical therapy for lowering intraocular pressure to treat ocular hypertension and glaucoma, leading to preservation of retinal function. However, anti-hypertensive therapies are targeted to the ciliary epithelium or uveoscleral outflow system, not direct intervention at the posterior pole. Retinal indications, such as AMD and diabetic retinopathy (DR), would require pharmacodynamic activity in the outer and inner retina, respectively. Nonetheless, effective and safe topical therapy could potentially augment or replace currently available surgical therapy, or be used as a rescue method for invasive treatment.

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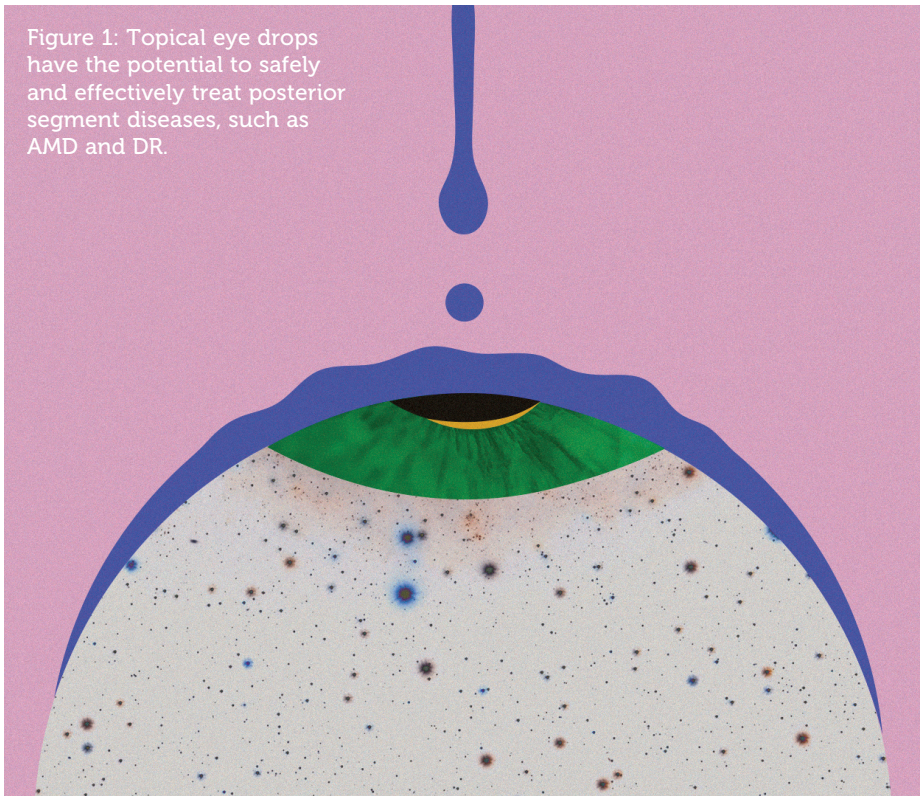

Figure 1: Topical eye drops have the potential to safely and effectively treat posterior segment diseases, such as AMD and DR.

In contrast to surgical procedures, topical eye drops have the potential to minimise the treatment burden for patients and caregivers, as fewer in-office injections may be required, which could enhance the accessibility and compliance of these treatments.[2,3] Although rare, invasive procedures like IVT injections can be painful and come with several vision-disabling risks, including ocular inflammation and infection.[1,4] These challenges, and the arduous logistics of maintaining chronic recurring visits, may cause patients to refrain from showing up to their follow-up treatments. The use of topical drops, which can be instilled anywhere and at any time, can empower patients and/or their caregivers to work more effectively with their eyecare professional.[2]

As AMD and diabetes are longstanding conditions, the use of topical drops may contribute to sustainable treatment regimens for lifelong therapy. In the future, topical drops may support a prophylactic care option for highly motivated patient populations with late-stage non-proliferative DR and intermediate AMD, potentially decreasing the risk of vision loss associated with the later stages of both diseases. As a result, this may lead to fewer in-office visits and a decreased need for patients or caregivers to take time off work – and therefore provide meaningful socioeconomical impact.

CHALLENGES OF USING TOPICAL DROPS FOR RETINAL DISEASE

Novel methods of drug delivery come with new challenges for ensuring that biologically active concentrations reach the target tissue of interest. With topical eye drops for retinal disease, numerous obstacles must be overcome to deliver effective drug concentrations to the cellular target(s) of interest. When a topical ocular drop is instilled, a blinking reflex occurs, pushing a substantial portion of the drop volume through the nasolacrimal drainage system, and possibly out of the palpebral fissure. Additionally, the tight cellular junctions of the corneal epithelium act as a barrier to drug entry.[1] Mastering the exact pharmacokinetics and distribution of an API is key to determining its ability to be delivered to the posterior segment, which includes the molecular size of the API, its lipophilicity and its pH.[5]

Since topical ocular drugs are absorbed through the conjunctiva, a portion of the drug substance or API is absorbed into the patient's systemic circulation. This systemic absorption will reduce the available API that can penetrate to the targeted retinal tissue(s), resulting in subtherapeutic treatment and/or potential systemic adverse reactions.[1] These, and other related challenges, have to be considered when selecting the specific physicochemical properties of the API and

formulating candidates. Innovative features of these molecules and/or their drug product formulations include topical drugs that travel around the peripheral ocular tissue to the posterior pole versus direct axial penetration through the cornea and ocular fluids into the central retina.[2]

ENHANCING DELIVERY OF TOPICAL DRUGS

To enhance delivery of topical ocular treatments to the posterior segment, very specific formulations have been developed, including nanotechnology, hydrogels and cell-penetrating peptides (CPPs).[6,7,8] Nanoparticle technology can be used to augment the solubility of hydrophobic drugs, administering a sustained release of a therapeutic while ensuring lower toxicity. Nanoparticles can also prolong ocular surface retention, providing sustained drug release, improving penetration through ocular tissues and achieving tissue-specific localisation.[6]

Along with nanotechnology, hydrogel carriers, which are composed of hydrophilic polymer chains for water retention, can assist with controlled release and easy delivery of liquid-gel formulations.[7]

Finally, CPPs have been investigated as penetration enhancers (PEs) for drug delivery and biodistribution to the retina and choroid. CPPs have also exhibited the capacity to carry protein therapies, nanoparticles and several other constituents to the posterior segment from a topical eye drop instillation.[8] These carriers have been evaluated for delivery of anti-VEGF therapies in neovascularised retina models and have displayed no significant difference between the topical drops and IVT anti-VEGF methods.[9]

THE FUTURE OF TOPICAL ADMINISTRATION FOR POSTERIOR SEGMENT DISEASE

The pipeline of novel treatments for retinal vascular and neurodegenerative diseases is a very active space. The unique mode of topical ocular delivery is a potential differentiator from those innovations that rely on more invasive and risky delivery platforms.

Alcon Nepafenac®

Compelling clinical research has been conducted analysing the effect of topical nepafenac, a Cox 1/2 inhibitor or non-steroidal anti-inflammatory drug (NSAID), used prophylactically to prevent macular oedema occurring following cataract surgery in patients with diabetes.[10,11] Topical nepafenac 0.3% dosed once per day may improve patient surgical outcomes and has the potential to decrease the burden patients experience with post-cataract macular oedema (PCME), including further in-office treatment, specifically for patients who are at high risk of developing PCME.

Patients at risk may include those diagnosed with diabetes and some other ocular conditions, such as AMD, uveitis and retinal vein occlusion (RVO), and patients who have a history of PCME in their other eye.[10] Although these clinical findings may be associated with reduced inflammation in the anterior and posterior chambers following nepafenac treatment, topical nepafenac has been shown to directly inhibit the posterior segment vascular complications associated with diabetes mellitus, as well as neovascularisation.[11,12]

Oculis OCS-01

Oculis OCS-01 is a topical ophthalmic drug candidate for the treatment of DME. OCS-01 incorporates dexamethasone in Oculis' (Lausanne, Switzerland) proprietary OPTIREACH solubilising nanoparticle technology, which enhances bioavailability to the posterior segment. OCS-01 has completed two Phase II clinical studies, one for the treatment of DME and the other for the treatment of inflammation and pain following cataract surgery, with both indications moving into Phase III studies.[13] For DME, the Phase II studies exhibited positive patient benefit, demonstrating that OCS-01 was more effective in decreasing central macular thickness and improving visual acuity in patients with DME versus vehicle. This drop was found to be well tolerated, with no significant adverse effects noted.[14]

OcuTerra Therapeutics OTT166

OcuTerra Therapeutics (Boston, MA, US) is developing a topical therapy called OTT166 for the treatment of moderately severe to severe non-proliferative diabetic retinopathy and mild proliferative diabetic retinopathy. OTT166 is a novel small-molecule selective integrin inhibitor that has undergone two multi-centre, randomised Phase Ib clinical trials, which exhibited safety, tolerability and proof of biological activity. The Phase II Diabetic Retinopathy: Early Active Management (DR:EAM) study is currently underway to determine efficacy, safety and best dosing for OT166.[15]

PanOptica PAN-90806

Another novel topical eye drop candidate of note is PanOptica's (Arlington, NJ, US) PAN-90806, which is intended to be a once-daily drop for the treatment of wet AMD and other neovascular eye diseases. This small molecule blocks VEGF signalling by potently inhibiting the tyrosine kinase activation of VEGF receptor two. Although other companies, such as GSK and Bayer, have attempted to develop topical ocular kinase inhibitors for retinal diseases, PanOptica's molecule has several unique physicochemical properties that provide differentiation, allowing it be absorbed by peripheral ocular blood vessels and delivered around the eye to the central choroid and retina versus via a transcorneal route.[2] PAN-90806 suspension underwent a double-masked, dose-ranging Phase I/II clinical trial for patients with wet AMD where more than 50% of treatment-naïve participants receiving PAN-90806 completed the study and did not require emergency anti-VEGF injections and 88% of these participants displayed stability or improvement. No severe adverse effects were noted.[16] Zhaoke recently announced licensing of topical ocular PAN-90806 for ophthalmic development in specific Asian jurisdictions.[17]

Mitotech Visomitin®

With no current available treatments for dry AMD, Mitotech (Luxembourg) has been innovating a potential topical ocular treatment for this vision-debilitating disease, called Visomitin (SKQ1 eye drops).[18,19] Visomitin holds a small-molecule cardiolipin peroxidation inhibitor, which transports plastoquinone, an exceedingly active antioxidant, to the mitochondria, specifically the inner leaflet of the inner mitochondrial membrane. Once delivered, it works as a target scavenger of reactive oxygen species and a cardiolipin

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protector in outer retinal tissues. Visomitin accumulation can prevent lipid degeneration, which may prevent mitochondrial dysfunction and apoptosis, as well as uncontrolled inflammation.[18] Although Visomitin has only been studied in ocular surface diseases to date, it is reported to be Phase II ready for the treatment of dry AMD.[19]

CONCLUSION

As the global population continues to age, the prevalence of degenerative and vascular retinal diseases also continues to rise. Therefore, novel drug delivery systems will be essential to ensure patient compliance and comfort with necessary chronic administration. Several therapeutic candidates in the ophthalmic development pipeline may provide an effective and safe alternative or adjunct to the monotonous, uncomfortable and sometimes anxiety-inducing invasive in-office treatments that are currently approved for use. Overcoming some of the potential anatomical barriers and compliance challenges associated with topical ocular delivery to the retina will be pivotal in bringing these novel therapies to market and providing additional benefit to patients with unmet needs.[5]

ABOUT THE COMPANY

Ora is a leading full-service ophthalmic drug and device development firm with offices in the US, UK, Australia and Asia. For over 40 years, Ora has helped clients earn more than 55 product approvals and create vision beyond what they see. The company supports a wide array of organisations, from start-ups to global pharmaceutical and device companies, to efficiently bring their new products from concept to market. Ora's preclinical and clinical models, unique methodologies and global regulatory strategies have been refined and proven across thousands of global projects. The company brings together an extensive and experienced team of ophthalmic experts, R&D professionals and operations management to maximise the value of new product initiatives.

REFERENCES

1. *Cabrera FJ et al, "Challenges and opportunities for drug delivery to the posterior of the eye". Drug Discov, 2019, Vol 24(8), pp 1679–1684.*
2. *"A new wave of innovation in Neovascular Eye Disease". Web Page, PanOptica, accessed Feb 2023.*
3. *Boyer DS, "Topical drug delivery for retinal disease management". Retina Today, 2018.*
4. *"Ocular drug delivery: Targeting the posterior segment". Ora Clinical, 2017.*
5. *Löscher M et al, "Topical drug delivery to the posterior segment of the eye". Pharmaceutics, 2022, Vol 14(1), p 134.*
6. *Meza-Rios A et al, "Therapies based on nanoparticles for Eye Drug Delivery". Ophthalmol Ther, 2020, Vol 9(3), pp 1–14.*
7. *Cooper RC, Yang H, "Hydrogel-based Ocular Drug Delivery Systems: Emerging Fabrication Strategies, applications, and bench-to-bedside manufacturing considerations". JCR, 2019, Vol 306, pp 29–39.*
8. *Thareja A et al, "Penetration enhancers for topical drug delivery to the ocular posterior segment – a systematic review". Pharmaceutics, 2021, Vol 13(2), p 276.*
9. *De Cogan F et al, "Cell-penetrating peptides as non-invasive drug delivery vehicles for ranibizumab and bevacizumab". IOVS, 2016, Vol 57, p 4037.*
10. *Yüksel B, Kartı Ö, Kusbeci T, "Topical nepafenac for prevention of post-cataract surgery macular edema in diabetic patients: patient selection and perspectives". Clin Ophthalmol, 2017, Vol 11, pp 2183–2190.*
11. *Takahashi K et al, "Topical Nepafenac Inhibits Ocular Neovascularization". IOVS, 2003, Vol 44(1), pp 409–415.*
12. *Kern TS et al, "Topical Administration of Nepafenac Inhibits Diabetes-Induced Retinal Microvascular Disease and Underlying Abnormalities of Retinal Metabolism and Physiology". Diabetes, 2007, Vol 56, pp 373–379.*
13. *"OCS-01: A potential paradigm shift in diabetic macular edema (dme) treatment". Web page, Oculis, accessed Feb 2023.*
14. *"OCULIS announces publication and presentation of phase 2 data showing topical OCS-01 improves macular thickness and visual acuity in patients with diabetic macular edema". Press Release, Oculis. Sep 6, 2022.*
15. *"Pipeline". Web Page, OcuTerra, accessed Fen 2023.*
16. *"PanOptica Anti-VEGF eye drop shows promise in treatment of neovascular (wet) AMD". Press Release, PanOptica, Oct 10, 2019.*
17. *"PanOptica Announces Licensing Agreement with Zhaoke Ophthalmology for the Treatment of Neovascular Eye Diseases in China, South Korea, and Southeast Asia". Eyewire+, June 23, 2021.*
18. *"Visomitin®: A Cardiolipin peroxidation inhibitor". Web Page, Mitotech, accessed Feb 2023.*
19. *"Clinical programs". Web Page, Mitotech, accessed Feb 2023.*

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