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THE EVOLVING GLAUCOMA THERAPY PARADIGM

MOVING TOWARD SUSTAINED DRUG DELIVERY IN GLAUCOMA MANAGEMENT

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ROBERT N. WEINREB, MD (CHAIR)

IKE K. AHMED, MD, FRCSC

E. RANDY CRAVEN, MD

This continuing medical education activity is provided by **New York Eye and Ear Infirmary of Mount Sinai.**
This educational activity was developed and implemented in collaboration with **MedEdicus LLC.**

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ACTIVITY DESCRIPTION

The traditional approach to glaucoma management begins with topical medications and progresses, as needed, to laser therapy and ultimately incisional surgery. This approach reflects the Hippocratic philosophy of minimizing harm by applying the least invasive options first, yet it necessarily relies on the patient to accept and adhere to the responsibility for daily self-dosing (often multiple times per day). Adherence to glaucoma therapy is well known to be suboptimal for numerous reasons, including forgetfulness, difficulty instilling drops, and difficulty with the medication schedule. Suboptimal adherence is associated with worse visual field defects, highlighting an important public health issue. Toward a solution to this problem, several implantable devices that release analogues of the same medications found in topical glaucoma therapies are under investigation. The desired results of this educational activity are for learners to improve their knowledge and competence regarding the potential role of sustained drug delivery systems in improving visual outcomes for patients with glaucoma who are challenged to adhere to topical therapy.

TARGET AUDIENCE

This educational activity is intended for ophthalmologists caring for patients with glaucoma.

LEARNING OBJECTIVES

Upon completion of this activity, participants will be better able to:

- Discuss the limitations of the current topical glaucoma treatment paradigm
- Describe the pharmacodynamics of topical and sustained delivery of glaucoma therapy
- Compare the relative efficacy and safety of novel drug delivery systems with topical formulations of glaucoma medications
- Identify patients who would be most likely to benefit from sustained delivery of glaucoma therapy

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FACULTY

ROBERT N. WEINREB, MD (CHAIR)

Distinguished Professor and Chair, Ophthalmology
Distinguished Professor, Bioengineering
Director, Shiley Eye Institute
Director, Hamilton Glaucoma Center
Morris Gleich, MD, Chair of Glaucoma
University of California, San Diego
La Jolla, California

IKE K. AHMED, MD, FRCSC

Professor
University of Utah
Salt Lake City, Utah
Assistant Professor
Director, Glaucoma and Advanced Anterior Segment Surgery (GAASS) Fellowship
Research Director, Kensington Eye Institute
University of Toronto
Toronto, Canada

E. RANDY CRAVEN, MD

Chief
Wilmer Eye Institute - Bethesda
Associate Professor of Ophthalmology
Johns Hopkins University School of Medicine
Bethesda, Maryland

CME REVIEWER FOR NEW YORK EYE AND EAR INFIRMARY OF MOUNT SINAI

KATEKI VINOD, MD

Assistant Professor of Ophthalmology
Icahn School of Medicine at Mount Sinai
Associate Adjunct Surgeon
New York Eye and Ear Infirmary of Mount Sinai
New York, New York

THE EVOLVING GLAUCOMA THERAPY PARADIGM

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Introduction

Topical medical therapy remains the preferred first-line therapy for newly diagnosed glaucoma. Today's medications are highly effective and safe, offering the convenience of once-daily dosing, and, in many cases, are available in inexpensive generic formulations. Topical medical therapy, however, has limitations, the most important of which is nonadherence. Most patients with glaucoma fail to adhere to their prescribed medical regimens consistently over time; this increases the risk of disease progression and vision loss. Multiple sustained drug delivery platforms are in late-stage clinical development, and 1 or more may become commercially available in the near future. These novel treatment options can offer several potential advantages over topical therapy, including better safety, less responsibility for self-dosing, better disease control, and potential improvements in quality of life. This activity will review the current status and limitations of glaucoma topical therapy, preview the sustained drug delivery platforms in late-stage clinical development, and discuss the implications of sustained drug delivery for both patients and providers.

Topical Medicine First: An Imperfect Glaucoma Treatment Paradigm

For decades, the standard clinical approach to glaucoma management began with topical eye drop medications, followed, if needed, by laser therapy, with surgical interventions reserved for those whose glaucoma proved recalcitrant to less invasive options. This approach was driven primarily by safety, reserving the least safe treatments for eyes inadequately controlled with less invasive therapies.

The medicine-first strategy has been challenged in the past. Proponents of lower intraocular pressure (IOP) as the best means of preventing progression have made the case that primary surgery—specifically trabeculectomy—is the best initial therapy to achieve low target IOP and confer the best protection against progression.[1] Two studies—Moorfields Eye Hospital's Primary Treatment Trial in the United Kingdom and CIGTS (Collaborative Initial Glaucoma Treatment Study) in the United States—were carried out to test this hypothesis.[2,3] In both studies, surgery lowered IOP significantly more than did medications, but progression rates were similar.

Advocates of laser trabeculoplasty have also argued that laser should replace medications as primary therapy. The Glaucoma Laser Trial convincingly demonstrated that initial argon laser trabeculoplasty provided superior protection against progression compared with medications, but failed to drive a paradigm shift.[4] Later, the

SLT/Med study was initiated to compare first-line selective laser trabeculoplasty (SLT) with medications, but terminated early owing to poor enrollment without achieving its objective.[5] More recently, the LiGHT (Laser in Glaucoma and Ocular Hypertension) study was successfully conducted in the United Kingdom and demonstrated superior outcomes (lower progression rates and surgical rates) with SLT vs medications in treatment-naïve patients with newly diagnosed mild to moderate primary open-angle glaucoma or high-risk ocular hypertension, and 78% of the 536 SLT-first eyes were medication-free at 3 years.[6] The effect of this very recent study on the glaucoma treatment paradigm is not yet clear.

Why is the medicine-first approach under assault? The era of prostaglandin analogues has provided the safest, most effective, and most conveniently dosed medications in the history of glaucoma pharmacology. Why should clinicians be looking elsewhere for something better?

The reality is that topical medical therapy does have limitations, and those limitations can compromise the effectiveness of treatment. The single most relevant limitation of topical medical therapy is nonadherence. Low adherence rates to chronic glaucoma medical therapy have been well documented and extensively reviewed.[7] After 3 years of therapy, only 37% of patients refilled their initial prescribed medications.[8] By 4 years, nonpersistence with therapy reached 85%.[9] Nonadherence can take many forms: doses may be missed because of forgetfulness or cost of therapy, or skipped intentionally because of a multitude of causes, including the desire to minimize adverse effects or the belief that therapy is inherently unhelpful. Glaucoma therapy is purely prophylactic—the goal of therapy is to prevent future progression—so there are no appreciable improvements in visual function associated with therapy, and thus no positive feedback to encourage adherence. Of those patients who faithfully refill their glaucoma prescriptions and take their drops as directed, approximately one-third fail to properly administer the drop into their eye when self-dosing.[10] Poor adherence to therapy has important clinical consequences: patients who are less than 80% adherent are significantly more likely to have more severe visual field defects than those who are more faithful with their drop dosing.[11]

Just as there are consequences of nonadherence, there can be costs to adherence as well. Long-term exposure to prostaglandin analogues contributes to a condition called prostaglandin-associated periorbitopathy, characterized by ptosis and a sunken appearance to the eye related to loss of orbital fat.[12,13] In addition, long-term exposure to glaucoma medications in general has a strong association with ocular surface disease (OSD). The prevalence of OSD in patients using topical glaucoma therapy is 50% to 60%,[14,15] much higher than the approximately 7% to 14% rate in the general population.[16,17] The preservative benzalkonium chloride (BAK), found in most glaucoma medications, has been implicated as contributory to OSD.[18] Manifestations of BAK-associated OSD include pain, tear film instability, conjunctival inflammation, corneal surface impairment, and even reduced success rates for subsequent glaucoma filtering surgery.[18]

Quality of Life, Glaucoma, and Topical Therapy

Quality of life is a term used to describe the full breadth of the human experience, encompassing daily functioning, emotional well-being, symptoms (of both disease and treatment), mobility, independence, and social life, among other factors.[19] These aspects of life are difficult to measure quantitatively, and various questionnaire-based instruments have been developed and validated to provide numeric estimates of quality of life. These instruments probe both objective patient-centered outcome measures and subjective patient-reported outcome measures.[19] Some, such as the Glaucoma Symptom Scale, have been developed to probe the specific effects of a single disease or condition on quality of life.[20] The value of such instruments is limited because glaucoma does not happen in a vacuum. Patients with glaucoma are older and affected by concomitant health issues related to aging that confound assessment of single-disease effects on quality of life. None of these tools adequately captures enough detail to reliably and consistently describe the status of individual patients. Instead, they are meant as research tools to assess differences in populations or differences associated with interventions or changes over time.

Glaucoma has a major effect on a person's quality of life. Studies using a variety of instruments have documented reduced quality of life in patients with glaucoma compared with age-matched subjects without glaucoma, as well as worsening quality of life with more advanced glaucoma and visual field loss.[21,22] Simply being diagnosed with glaucoma has an adverse effect on quality of life.[23-25] In CIGTS, approximately 50% of 607 newly diagnosed patients expressed at least moderate fear of blindness upon being told they had glaucoma; this number decreased to approximately 25% over the 5-year study.[25] This underscores the value of education and counseling at the time of diagnosis to provide reassurance and to reinforce the importance of adherence to therapy to prevent vision loss and blindness.

Unfortunately, glaucoma therapy also affects quality of life. In addition to adverse effects, difficulty administering eye drops and the complexity of therapeutic regimens are determinants of patient satisfaction with glaucoma therapy.[26] In a willingness-to-pay analysis, patients were willing to pay more for topical medications that did not cause blurred vision, drowsiness, stinging, or tearing, and that could be dosed once daily vs 3 times daily.[27] In a separate study, patient satisfaction with therapy was correlated with ocular irritation, conjunctival hyperemia, and ease and convenience of dosing.[28]

The OSD aggravated by glaucoma therapy also adversely affects quality of life. Symptoms of OSD, as well as exposure to BAK-preserved drops used per day, correlated well with quality of life measured with glaucoma-specific instruments.[29,30]

Evolving Glaucoma Therapy Paradigm: Sustained Drug Delivery

Preserving quality of life is the ultimate goal of glaucoma therapy.[31,32] A paradigm shift away from topical medical therapy

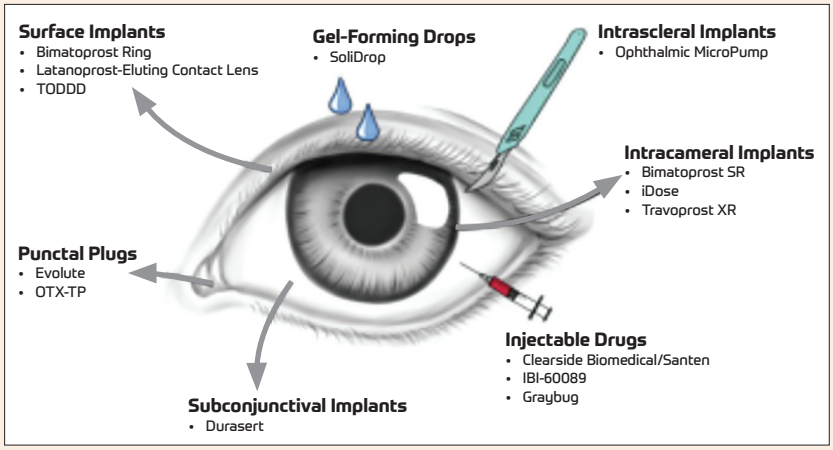

Figure 1. Array of investigational platforms for sustained delivery of glaucoma medications

Abbreviations: SR, sustained release; TODDD, topical ophthalmic drug delivery device; XR, extended release.

Figure adapted with permission of Devesh K. Varma, MD, FRCSC; and Bryn Mawr Communications. Varma DK. Sustained-release drug delivery: closer than you think! *Glaucoma Today.* May/June 2018;58-60.

as first-line treatment for glaucoma could overcome many of the limitations of topical therapy while improving patient quality of life.

A number of innovative sustained delivery platforms for glaucoma medications are in late-stage clinical development. Unlike topical therapy, which delivers pulse therapy with each dose, these systems have in common the goal of delivering a constant supply of medication over the device's lifespan. This has the effect of maintaining steady-state pharmacokinetics and pharmacodynamics, eliminating the peak and trough IOP effects seen with topical therapy as each dose wears off before the next is administered. Many of these systems are designed for intraocular use, which has the added advantage of sparing the ocular surface exposure to the active and excipient ingredients of topical formulations.[33] Such exposure—particularly to the preservatives in these formulations—can contribute to OSD,[18] an important factor in glaucoma-related quality of life.

Sustained delivery is not a new concept in ophthalmology. The pilocarpine sustained-release device dates back more than 40 years; it resides in the conjunctival fornix and delivers low-dose pilocarpine for up to a week at a time.[34] The ganciclovir intravitreal implant minimizes the frequency of intravitreal injections required to treat cytomegaloviral retinitis before the development of highly active antiretroviral therapy for human immunodeficiency virus, improving quality of life for patients and reducing the risk of needle-stick infection among eyecare providers.[35] More recently, steroid implants eluting dexamethasone[36] and fluocinolone acetonide[37,38] have been developed for the treatment of inflammatory eye diseases.

In general, the platforms under investigation for delivery of glaucoma drugs fall into 2 broad categories: (1) those delivering drug to the ocular surface and (2) those providing intraocular administration **(Figure 1)**. As always, the balance between risk and benefit is at play. Ocular surface platforms would be expected to be safer but less effective, whereas intraocular platforms would be expected to be more effective, but coming at a higher risk of complications related to both the intraocular insert and the implantation procedure itself.

Sustained Drug Delivery on the Ocular Surface

Bimatoprost Ring

The bimatoprost ring consists of a polypropylene core coated with a matrix of silicone and 13 mg of bimatoprost **(Figure 2A)**.[39] The device is preservative free and is available in diameters ranging from 24 to 29 mm. It is intended to rest on the conjunctival surface, centered on the cornea and extending to the inferior and superior fornices **(Figure 2B)**. Bimatoprost is constantly eluted in a passive, gradient-driven process from the silicone matrix to the tear film, beginning at approximately 35 µg/d at the time of insertion and dissipating to ~6 µg/d by day 180, the expected duration of action of the device. For reference, a drop of bimatoprost, 0.003%, solution contains approximately 9 µg of bimatoprost.

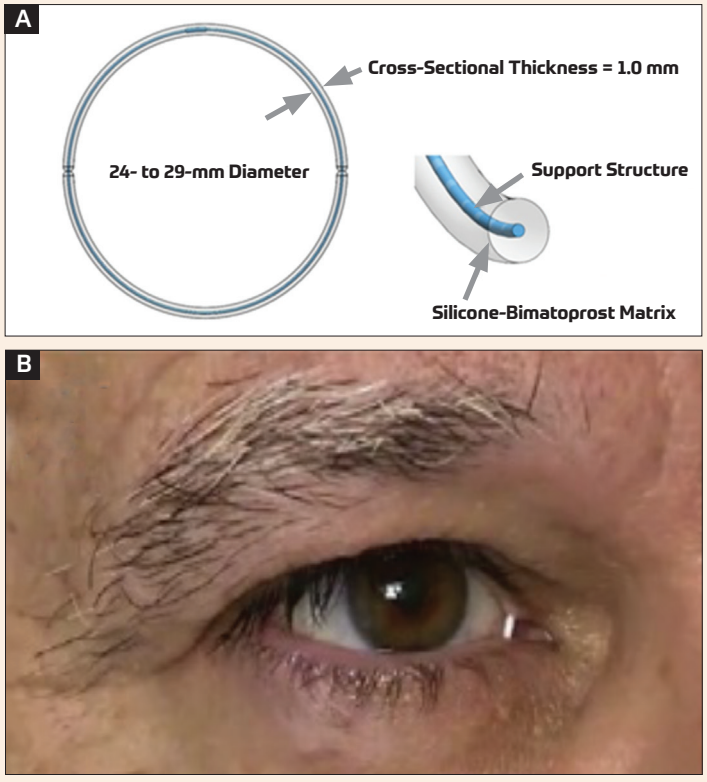

Figure 2. Bimatoprost ring schematic (A) and in situ (B)[39]

Reprinted from *Ophthalmology,* 123, Brandt JD, Sall K, DuBiner H, et al, Six-month intraocular pressure reduction with a topical bimatoprost ocular insert: results of a phase II randomized controlled study, 1685-1694, Copyright 2016, with permission from Elsevier.

In phase 1 trials, a version of the device loaded with only 4.2 mg of bimatoprost lowered IOP by 27% at 3 months, and the effect dissipated by 4 months,[40] whereas a 13-mg loaded device provided ~21% IOP reduction through 6 months.[41] The latter version was employed in phase 2 testing, which consisted of a prospective, randomized, double-masked comparison of the insert to twice-daily

timolol, 0.5%.[39] Mean IOP reductions ranged from 3.2 to 6.4 mm Hg in eyes given the bimatoprost insert and from 4.2 to 6.4 mm Hg in eyes given timolol. Criteria for noninferiority were not met, implying that timolol was more effective than the insert. The insert retention rate at 6 months was 88.5%, and adverse effects were those expected from the drugs according to prior trials with topical eye drop delivery. Ten patients discontinued use of the device for ocular (n = 8) or systemic (n = 2) adverse effects. The investigators suggested that receptor subsensitivity—arising from constant exposure to the drug compared with burst exposure with daily topical dosing—may have contributed to the lower than expected efficacy of the insert compared with the known efficacy profile of topical bimatoprost.[39,42] This theory is supported by independent observations that exposure to prostaglandin analogues in excess of 1 drop daily can lead to paradoxical elevations of IOP.[43]

One drawback of the ring insert is that there is no forniceal coverage of the device nasally as it passes the caruncle, allowing visibility of the white ring in the nasal interpalpebral region **(Figure 2B)**.[39] A potential advantage of the device, however, is that it can be loaded with other drugs, allowing for the possibility of multiple drugs for patients requiring > 1 medication for adequate IOP control.

Travoprost Punctal Plug

Travoprost has been incorporated into a polyethylene glycol–based hydrogel punctal plug embedded with poly(lactic acid) microspheres of encapsulated travoprost.[44] These microspheres slowly dissolve, releasing travoprost into the tear film over 30 days. The implant is meant to be inserted into the vertical portion of the inferior or superior canaliculus and, when inserted and exposed to tears, swells to conform to the shape of the punctum **(Figure 3)**.[45] This punctal occlusion effect may potentiate drug activity by increasing residence time within the tear film. The entire plug dissolves away over time.

A phase 1 feasibility study of 17 patients reported IOP reductions that peaked at 24% at day 10 and declined to 16% by day 30.[44] Retention was 100% at day 10, 87.5% at day 20, and 41.7% at day 30. Common adverse effects included foreign body sensation (38.5%) and itchiness (15.4%). In a phase 2 evaluation, the travoprost punctal plug was compared with twice-daily timolol, 0.5%, in a randomized, double-masked clinical trial.[46] At day 60, mean IOP reduction was 4.8 mm Hg with the travoprost punctal plug and 6.4 mm Hg with timolol. In a phase 3 evaluation, the punctal plug was compared with placebo and failed to demonstrate superior IOP reduction.[47]

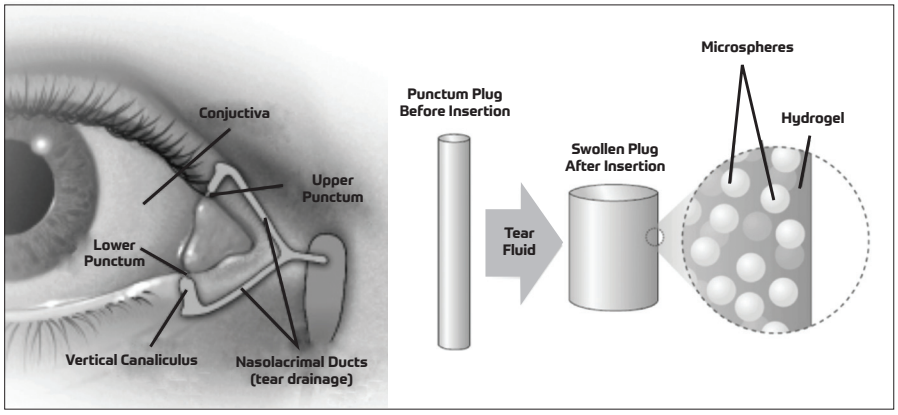

Figure 3. Punctal plugs used as sustained drug delivery systems for glaucoma therapy[45]

Latanoprost Punctal Plug

A punctal plug that elutes latanoprost has also been developed and evaluated. In phase 2 studies comparing several doses and plug location configurations, the combination of a 95-µg latanoprost plug in the lower punctum and a drug-free blank plug in the upper punctum produced IOP reductions of ~5 mm Hg at 4, 8, and 12 weeks.[48] The product was not advanced to phase 3 development.

Contact Lenses

Drug-impregnated contact lenses have been developed and evaluated. A latanoprost-based contact lens delivery system **(Figure 4)** has been described that is capable of delivering latanoprost adequately to achieve aqueous humor concentrations that are comparable to or greater than those achieved with topical latanoprost dosing for up to 30 days.[49] In glaucomatous monkeys, the latanoprost contact lens system lowered IOP significantly more than did topical latanoprost through 1 week of continuous wear.[50] This platform has the advantage of being able to correct refractive error while treating glaucoma, but its acceptance may be limited in some patients, such as those with OSD who might be contact lens intolerant.

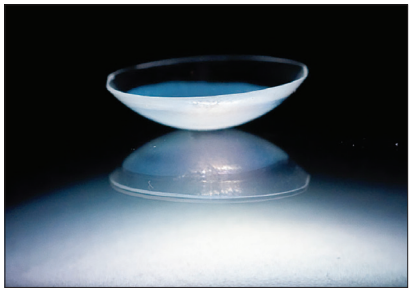

Figure 4. Attributes of a latanoprost-eluting contact lens

Image courtesy of Joseph B. Ciolino, MD, and Daniel S. Kohane, MD, PhD

Subconjunctival Depot Delivery

Just as the sub-Tenon space can serve as a repository for a depot injection of steroids, the subconjunctival/sub-Tenon space can be used to store a depot of glaucoma medication. The common limiting factor is the rate at which the drug depot dissipates. Several strategies have been developed to slow dissipation and extend drug activity.

The juxtascleral (sub-Tenon) administration of anecortave acetate has been evaluated in eyes with primary open-angle glaucoma. This cortisol derivative is classified as a cortisone and lacks anti-inflammatory and cataractogenic activity.[51] The drug itself is relatively insoluble and served as its own depot when administered in the sub-Tenon space, delivering IOP

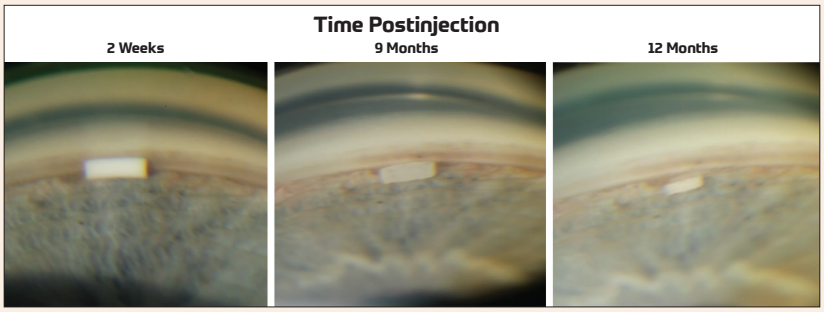

Figure 5. Appearance of the bimatoprost sustained-release implant in the anterior chamber as it dissolves over time

Images courtesy of E. Randy Craven, MD

reductions of 30% to 35% over 12 months in a pilot study.[52] These results were confirmed in follow-up studies,[53,54] but the therapy was ultimately not developed for commercialization.

For more soluble drugs, several strategies have been developed to extend their period of activity. Latanoprost has been incorporated into both collagen gels and wafer depots that can be injected into the subconjunctival space. These have been shown in vitro to deliver therapeutic concentrations of latanoprost for up to 30 days or longer.[55]

Sustained Drug Delivery With Intraocular Delivery

Bimatoprost Sustained Release

The bimatoprost sustained-release (SR) implant is a biodegradable polymer-based delivery system that slowly releases bimatoprost into the aqueous humor over 4 to 6 months **(Figure 5)**.[56] The implant is delivered via a peripheral corneal injection using an integrated delivery handpiece onto which it is preloaded. The implant is approved by the US Food and Drug Administration for the reduction of IOP in eyes with open-angle glaucoma or ocular hypertension; the indication is for a single administration.[57]

The bimatoprost implant's IOP-lowering efficacy was first evaluated in a phase 1/2 dose determination study (APOLLO).[56] Patients with open-angle glaucoma or ocular hypertension (n = 75) with untreated IOP between 22 and 36 mm Hg were enrolled; 1 eye received the bimatoprost implant in doses of 6, 10, 15, or 20 µg (the latter delivered as two 10-µg implants), and the fellow eye was treated with once-daily topical bimatoprost, 0.03%. At week 16, mean IOP reductions were 7.2, 7.4, 8.1, and 9.5 mm Hg with the 6-, 10-, 15-, and 20-µg implants, respectively, and 8.4 mm Hg in topical bimatoprost-treated fellow eyes. Overall, 91% of eyes were still controlled at 16 weeks and 71% at 6 months in the combined implant groups. Ten patients (5 each receiving the 10- and 15-µg implants) maintained IOP control through 24 months of follow-up, with IOP levels consistently comparable to those of topically treated fellow eyes over 2 years.[58] Interestingly, the rate of conjunctival hyperemia was substantially lower in the SR group than in the topical group (6.7% vs 17.3%).[56] This observation is consistent with a study in dogs demonstrating undetectable levels of bimatoprost on the ocular surface following SR intracameral implantation, though being detectable within the aqueous humor for up to 4 months.[33] Also, changes in corneal endothelial cell density were minimal in both groups in the phase 1/2 human trial (3% with bimatoprost SR and 1% for topical bimatoprost; difference was not significant).[56] Patient-reported outcomes were also collected in the phase 1/2 study. Overall, 80% of 74 patients reported the implantation procedure to be somewhat or much less burdensome than expected, 78% of 72 patients were very or extremely likely to have another implant when needed, and 83% of 72 patients were very or extremely likely to recommend the implant to others with glaucoma.

Bimatoprost SR was then evaluated in a pair of phase 3 studies (ARTEMIS 1 and 2).[59,60] These studies enrolled a combined 1122 subjects with open-angle glaucoma (approximately three-fourths) or ocular hypertension (approximately one-fourth) who received either bimatoprost SR 10 or 15 µg (dosed at day 1, week 16, and week 32) or twice-daily topical timolol, 0.5%, with a sham injection to maintain subject masking.

At the 12-week primary end point analysis, bimatoprost SR met the criteria for noninferiority to twice-daily timolol, with mean IOP reductions of 7 to 8 mm Hg in bimatoprost SR eyes and 6 to 7 mm Hg in timolol eyes.[59,60] The IOP reductions from bimatoprost SR 10 µg in ARTEMIS 1 and 2 were similar to those in APOLLO, with mean IOP reductions of 7.7 to 7.9 mm Hg and IOP reductions of 32% in all 3 studies.[56,59,60] Furthermore, the planned retreatment at weeks 16 and 32 in ARTEMIS 1 and 2 provided better long-term IOP control than the single treatment approach taken in APOLLO, with 80% vs 36% of eyes surviving to month 12 with no further treatments beyond the 1 administration (APOLLO) or 3 administrations (ARTEMIS 1 and 2) required by the protocol. This extended duration of effect may be related to prostaglandins' effect on a group of proteins called matrix metalloproteinases **(see Sidebar: Matrix Metalloproteinases and Intraocular Pressure, p 9).**

Significant differences in the rate of visual field loss were also seen in the 2 treatment groups in ARTEMIS 1 and 2.[59] Review of the visual field mean deviation in the bimatoprost SR group showed stable sensitivity. The control group, timolol, slowly lost some of the visual field.

Common safety issues in the patients receiving bimatoprost SR 10 µg (n = 372) or timolol (n = 370) in ARTEMIS 1 and 2 included conjunctival hyperemia (27.2% vs 16.8%, respectively), foreign body sensation (10.2% vs 3.5%, respectively), eye pain (9.7% vs 4.3%, respectively), photophobia (8.6% vs 1.1%, respectively), and conjunctival hemorrhage (7.5% vs 5.9%, respectively).[59] To distinguish between injection- and drug-related adverse events, a separate analysis of adverse events occurring more than 2 days after implant/sham administration was conducted. The analysis revealed substantially lower rates of the aforementioned adverse events, which were similar between the groups, suggesting they are primarily attributable to the injection procedure. As in APOLLO, endothelial cell density changes in the pooled ARTEMIS

studies were minimal (5.4% over 20 months with bimatoprost SR 10 µg vs 3.0% with timolol; difference not significant),[56,59] and no changes in central corneal thickness were observed over 20 months.[59] As reported in the ARTEMIS 1 study, however, a series of 3 device implantations given once every 16 weeks was associated with changes in endothelial cell density, with 10.2% of eyes in the 10-µg group and 21.8% in the 15-µg group manifesting ≥ 20% loss of endothelial cell density.[60] Furthermore, the occurrence of corneal events in some patients appeared to be related to accumulation of implant material in the iridocorneal angle; these corneal events may have been abated with less frequent administration.

Travoprost Implant

The travoprost titanium implant measures 1.8 × 0.5 mm and is designed for continuous drug delivery directly into the anterior chamber **(Figure 6)**. It features a scleral anchor on one end and a drug repository on the other end. It is loaded with a proprietary formulation of high-potency travoprost, and drug elution is membrane controlled, with zero-order kinetics. The device is preloaded onto an inserter, and is intended for ab interno implantation through the trabecular meshwork, with the anchor engaging sclera to ensure stability of the device.

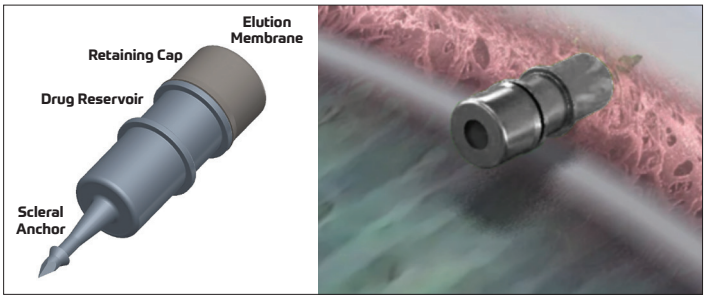

Figure 6. Travoprost sustained drug delivery system

Images courtesy of Ike K. Ahmed, MD, FRCSC

In a phase 2 trial in the United States, the travoprost implant was compared with twice-daily topical timolol, 0.5%.[61] Two versions of the device were tested: a fast-eluting design and a slow-eluting design. Through 1 year of follow-up, mean IOP reduction with the travoprost implants was approximately 30% vs baseline. Of note, the timolol group required 31% more supplemental medications than the implant groups at month 12 (average of 0.55 medications/eye in the implant groups and 0.72 medications/eye in the timolol group). Interestingly, no cases of hyperemia were reported in either of the implant groups.[61] Phase 3 trials are under way.[62,63]

Subconjunctival Micropump

In contrast to the sustained delivery platforms described previously, which use passive drug delivery, the subconjunctival micropump is designed to actively deliver drug into the eye. The device consists of a drug reservoir that can be refilled transconjunctivally, a battery, the necessary electronics components, and an electrolysis chamber, in which formed gases generate pressure in the reservoir and impel the drug through a transscleral cannula into the eye **(Figure 7)**.[64] The

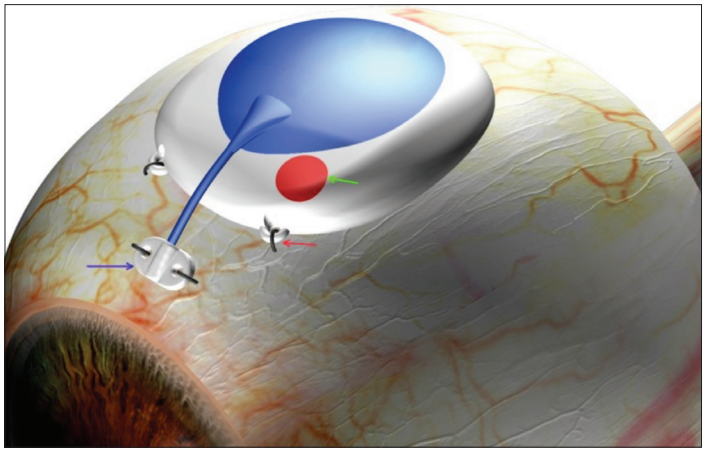

Figure 7. Schematic illustrating the components of the subconjunctival micropump[64]

Republished with permission of The Association for Research in Vision & Ophthalmology, from One-year feasibility study of Replenish MicroPump for intravitreal drug delivery: a pilot study, Gutiérrez-Hernández JC, Caffey S, Abdallah W, et al, 3, 2014; permission conveyed through Copyright Clearance Center, Inc.

gases then recombine to form water when the pump is turned off. A first-in-humans proof-of-concept study in 11 eyes with diabetic macular edema reported no complications.[65] Seven of the 11 devices delivered the intended dose of ranibizumab, whereas 4 devices delivered smaller-than-intended doses. A 1-year study in dogs demonstrated biocompatibility of the titanium, silicone, and parylene components of the device, with no inflammation or tissue ingrowth through the sclerotomy site.[64]

Effect of Sustained Drug Delivery on Patient Care

The successful development and commercialization of ≥ 1 sustained drug delivery platforms for glaucoma will have immediate implications for patients. These delivery systems offer many advantages over topical therapy. They have the potential to improve drug safety by reducing adverse effects, a consequence of targeted drug delivery to the tissue of action while minimizing off-target tissue exposure.[33] Evidence for this has already been reported, with greatly reduced conjunctival hyperemia rates with intraocular prostaglandin delivery compared with topical dosing.[61] Reducing the drug burden will also reduce exposure to excipient ingredients, such as preservatives, potentially reducing the rate of OSD in patients with glaucoma.

In addition, there is the potential for greater efficacy with a sustained drug delivery system. Topically applied medications must penetrate the eye to reach their target tissues in the intraocular space. Ocular penetration is a well-known limiting factor in the dose-response relationship,[66] and some drugs require corneal enzymes to convert prodrugs to their active forms. Bypassing the ocular surface and the eye wall, delivering medication directly into the anterior chamber, may facilitate greater efficacy with lower doses of medication.

Perhaps most importantly, removing patient responsibility for daily self-dosing of topical therapy eliminates the nonadherence issue that limits the effectiveness of glaucoma therapy. Consistent long-term drug delivery will produce more consistently controlled IOP,

which can reduce the risk of glaucoma progression. Taken together, drop independence, freedom from drug adverse effects, and better disease control would be expected to improve quality of life, the ultimate goal of glaucoma therapy.[31,32]

A transition from topical to sustained drug delivery glaucoma therapy will also have a significant effect on the nature of glaucoma care in the office. The burden of medical therapy will be shifted from the patient to the physician. Similar to the retina specialists who now spend substantial portions of office time delivering intravitreal injections of vision-saving medications for retinal vascular conditions, glaucoma specialists will have to evaluate and revise staffing and workflow processes to account for the time needed for education and delivery of drug systems that can be deployed in the office, and will have to adjust surgical time to adapt to the increase in operative procedures for implantable devices.

Patient Selection for Sustained Drug Delivery of Therapy

Physicians will also need to adopt strategies to identify the ideal patients to receive sustained delivery of therapy. These sustained-release drugs are not likely to be considered first-line options for most patients. When are they best deployed? Which patients are most likely to benefit? Obvious choices are patients who are intolerant to topical medical therapy and those with physical or cognitive infirmities that preclude consistent self-dosing with topical therapy. A trial of therapeutic responsivity to the drug of interest through a topical trial may be useful before applying a long-term delivery system, as was practiced in the ARTEMIS 1 and 2 trials.[59,60] In combination with minimally invasive glaucoma surgeries, the sustained drug delivery systems may further reduce the need for topical medical therapy. In patients with otherwise recalcitrant glaucoma, these systems may prevent or delay the need for incisional surgery.

Take-Home Points

- Topical medical therapy is effective and safe but has limitations, including nonadherence, tolerability, and cost
- Both glaucoma and its treatment have negative effects on patient quality of life
- Multiple diverse sustained drug delivery platforms are in clinical development to reduce the burden of daily topical self-dosing of glaucoma medications
- Various systems offer the possibility of better IOP control, lower progression rates, and improved quality of life for patients with glaucoma
- Sustained delivery platforms can improve safety by minimizing exposure of nontarget tissues to active and inactive ingredients
- Sustained drug delivery systems can deliver drug for weeks to months at a time, obviating the need for daily dosing by patients
- Transferring responsibility for administration of medical therapy to the provider will necessitate alterations in office staffing and workflow

Matrix Metalloproteinases and Intraocular Pressure

In eyes with primary open-angle glaucoma, intraocular pressure (IOP) becomes elevated owing to changes in the trabecular meshwork (TM) that reduce aqueous outflow through the trabecular pathway.[1] Extracellular matrix (ECM) proteins—such as collagen, elastin, laminin, and fibronectin—play a role in regulating outflow resistance and, in turn, the homeostatic turnover of ECM in both the TM and the uveoscleral outflow pathways.

The ECM is continuously remodeled by proteolytic enzymes called matrix metalloproteinases (MMPs) produced by both TM and ciliary muscle cells.[1] To keep the process homeostatically regulated, these cells also produce tissue inhibitors of metalloproteinases (TIMPs), which inhibit MMP activity. It is the balance of MMPs and TIMPs that provides steady-state outflow in healthy eyes.

When IOP becomes elevated, trabecular cells sense increased mechanical stretching forces.[1] They respond by upregulating production and secretion of MMP-2, -3, and -14 while simultaneously downregulating production of TIMP-2; together, this increases ECM turnover.[1]

Prostaglandins increase the production of several MMPs in ciliary smooth muscle cells[2,3] as well as in TM cells,[4] which may explain the IOP-lowering effects of prostaglandins on the uveoscleral and, to a lesser extent, trabecular outflow pathways. Morphologic evaluation of anterior segment tissue changes in monkey eyes treated with bimatoprost and other prostaglandin agonists revealed enlarged spaces for aqueous humor outflow between muscle bundles in the anterior ciliary muscle that were not present in control eyes.[5] Because MMP expression is dose related to exposure to bimatoprost and other prostaglandin agonists,[6] these prostaglandin-induced outflow-enhancing spaces likely persist well after the cessation of exposure to prostaglandins. This may explain why IOP remained decreased well after bimatoprost was depleted from the sustained-release implant in the ARTEMIS 1 and 2 studies.

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1. What percentage of patients with glaucoma continue to consistently refill their glaucoma medication prescriptions after 3 years of therapy?
   a. 12%
   b. 37%
   c. 54%
   d. 85%

2. What percentage of patients fail to get glaucoma drops into their eye when self-dosing?
   a. 10%
   b. 33%
   c. 50%
   d. 75%

3. What percentage of patients using topical glaucoma medications have symptoms of OSD?
   a. 15% to 25%
   b. 30% to 40%
   c. 50% to 60%
   d. 75% to 85%

4. For how long can the bimatoprost ring be expected to lower IOP?
   a. 1 month
   b. 3 months
   c. 6 months
   d. 12 months

5. Which of the following is a sustained drug delivery platform that delivers medication to the ocular surface?
   a. Bimatoprost SR implant
   b. Subconjunctival pump
   c. Travoprost implant
   d. Bimatoprost conjunctival ring

6. Compared with topical medical therapy, which is NOT typically considered a benefit of sustained drug delivery platforms?
   a. Improved tolerability profiles
   b. Minimal impact on glaucoma care center workflow
   c. Less responsibility for daily self-dosing
   d. More consistent IOP reduction over time

7. In phase 2 testing of the travoprost implant (fast- and slow-eluting devices), what percentage of patients had hyperemia?
   a. 0%
   b. 5%
   c. 10%
   d. Could not be determined

8. A series of 3 bimatoprost SR implants delivered at 16-week intervals provided IOP control through month 12 with no further treatments in ___ of patients in the pooled ARTEMIS data analysis.
   a. 14%
   b. 36%
   c. 54%
   d. 80%

9. In the pooled ARTEMIS data analysis, IOP reductions in the bimatoprost 10-µg SR group were _____ to those in the timolol group.
   a. Superior
   b. Inferior
   c. Noninferior

10. For which patient would a sustained drug delivery system for glaucoma provide the least benefit?
    a. A patient with early dementia and forgetfulness who still lives alone
    b. A patient with severe rheumatoid arthritis in his hands
    c. A patient who is allergic to BAK
    d. A patient with stable glaucoma using a topical prostaglandin analogue with mild OSD symptoms