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## USHERING IN A NEW TREATMENT PARADIGM FOR GLAUCOMA: UPDATES ON NOVEL THERAPEUTICS AND DISEASE-MODIFYING TREATMENTS

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# Ushering in a New Treatment Paradigm for Glaucoma: Updates on Novel Therapeutics and Disease-Modifying Treatments

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Medical/topical therapy is the first-line choice for most physicians treating patients with primary open-angle glaucoma (POAG), yet some patients will have visual field loss despite adequate IOP control. This supplement focuses on the investigative agents that will help deliver treatment in a more consistent and patient-friendly manner.

## TARGET AUDIENCE

This certified CME/CE activity is designed for specialists and other allied eye care practitioners involved in the management of glaucoma and associated disorders.

## LEARNING OBJECTIVES

Upon completion of this activity, the participant should be able to:

- **Identify** all available treatment regimens for mild-to-moderate POAG.
- **Evaluate** novel drug devices for the treatment of POAG as part of individualized therapy.

- **Recognize** issues with compliance and adherence.
- **Compare** the efficacy of novel therapeutics with traditional prostaglandins.
- **Explain** the likelihood of achieving better IOP management with monotherapy compared with combination regimens.

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1. Please rate your confidence in your ability to use novel drug devices for the treatment of primary open-angle glaucoma (POAG) as part of individualized therapy (based on a scale of 1 to 5, with 1 being not at all confident and 5 being extremely confident).

1. Not at all Confident
- 2.
3. Neutral
- 4.
5. Extremely Confident

2. Please rate your confidence in your ability to explain to patients the likelihood of achieving better intraocular pressure (IOP) management with monotherapy compared with combination regimens (based on a scale of 1 to 5, with 1 being not at all confident and 5 being extremely confident).

1. Not at all Confident
- 2.
3. Neutral
- 4.
5. Extremely Confident

3. A 65-year-old woman with moderate POAG uses topical bimatoprost and tolerates it well but forgets to take his drops several times each week. Her visual field tests are stable, and in the office her IOPs are 12 mm Hg. Which of the following rationales might support the use of intracameral prostaglandin analogue sustained-release therapy?

- a. Topical therapy intolerance
- b. Disease progression
- c. Noncompliance
- d. Nonresponder to topical therapy

4. In the phase 3 clinical trials, bimatoprost SR was compared to what therapy in the fellow eye?

- a. Latanoprost
- b. Timolol maleate
- c. Placebo
- d. The bimatoprost ring

5. Selective laser trabeculoplasty (SLT) works by:

- a. Changing the trabecular endothelial cell population
- b. Macrophage migration into the region
- c. Changes to the extracellular matrix through metalloproteinases
- d. All the above

6. Trabecular bypass in the United States is:

- a. Good first-line therapy
- b. Has about 85% success in IOP control at 2 years
- c. Done only in conjunction with cataract surgery
- d. Limits future options for canal-based surgery

7. Which of the following is NOT a typical characteristic of microinvasive glaucoma surgery procedures?

- a. Rapid visual recovery
- b. Performed via a microincisional approach
- c. Consistently greater efficacy compared with that of trabeculectomy
- d. Favorable safety profile compared with that of trabeculectomy

8. Topical medications for glaucoma are a known cause of ocular surface disease in patients with glaucoma.

- a. True.
- b. False.

9. In the LiGHT trial, what percentage of eyes of patients in the SLT group were within target IOP at more visits compared to than eyes in the medication group?

- a. 93%
- b. 91%
- c. 74%
- d. 36%

10. In certain patients, IOPs measuring below 10 mm Hg may cause hypotony maculopathy in all BUT which one?

- a. Patients with high myopia
- b. Older patients with thick sclera
- c. Patients with greater retinal nerve fiber layer thickness
- d. Very young patients with thin, deformable sclera

11. Most clinicians do not use SLT as a first-line therapy in glaucoma. However, the LiGHT study showed \_\_\_\_\_.

- a. Patients believe drops are safer than laser therapy
- b. SLT is not as efficacious as topical drops after 36 months
- c. SLT has equal efficacy to topical medications, but is cost prohibitive
- d. SLT had a higher percentage of patients within target IOP at 36 months with none requiring glaucoma surgery

12. In the phase 3 ARTEMIS 1 and 2 studies, how many patients who received a bimatoprost SR implant dosed every 4 months had probability of sustained IOP lowering with no additional treatment needed for at least a year?

- a. <10%
- b. 20%
- c. 28%
- d. >80%

13. Meibomian gland dysfunction is present in up to \_\_\_\_\_ of patients using prostaglandin analogues.

- a. 25%
- b. 58%
- c. 74%
- d. 92%

14. The travoprost sustained-release device currently in clinical trials is designed to deliver the medication to the ocular surface for up to how many days?

- a. 30
- b. 60
- c. 90
- d. 120

# Ushering in a New Treatment Paradigm for Glaucoma: Updates on Novel Therapeutics and Disease-Modifying Treatments

All of us who take care of patients who have glaucoma are familiar with the statistics. Glaucoma is a leading cause of preventable blindness in the United States.<sup>1</sup> More than 3 million Americans have glaucoma, and the National Eye Institute projects this number will reach 4.2 million by 2030.<sup>1,2</sup>

During the past several years, we have seen remarkable innovations in therapies for glaucoma, from pharmaceuticals, surgery, and laser procedures, to implantable devices and new instruments and techniques to deliver them. Yet challenges remain.

While most clinicians still rely on topical medications as first-line therapy for primary open-angle glaucoma,<sup>3</sup> issues with compliance and adherence often limit their effectiveness.<sup>4-7</sup> In fact, studies have shown that up to 60% of patients with glaucoma are noncompliant or nonadherent with their treatment regimens,<sup>8-12</sup> and adherence continues to drop as the number of medications increases.<sup>5,13,14</sup> Among the challenges are side effects that patients can't tolerate, forgetfulness, dexterity problems that hamper instillation, access to medications, and high costs.<sup>15</sup>

For patients on maximum medical therapy whose IOPs are still inadequately controlled, implantation of various types of devices via microinvasive glaucoma surgery (MIGS) is a newer option to consider, while laser trabeculoplasty and incisional surgery are mainstays.<sup>16</sup> Some promising technologies are on the horizon to deliver therapy in a more consistent and patient-friendly manner.

This continuing medical education activity is designed to help clinicians identify and evaluate all available treatments for mild-to-moderate primary open-angle glaucoma, with a goal of individualizing treatment with monotherapy or combination regimens for more effective pressure management.

—Nathan M. Radcliffe, MD, Program Moderator

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## UPDATES ON SELECTIVE LASER TRABECULOPLASTY AND LESS-INVASIVE SURGERY

### Alternatives to topical medications as first-line therapy.

EARL RANDY CRAVEN, MD

Researchers have been studying laser trabeculoplasty, its mechanisms of action, and its impact on the anatomy of the eye, and by extension, glaucoma, for some 40 years, starting with work by Wise and Witter.<sup>1</sup> Further studies by Acott, Samples, and colleagues supported the hypothesis that laser trabeculoplasty causes early cell division by a population of cells in the anterior meshwork, and these new cells then migrate and repopulate the burn sites over a period of weeks.<sup>2</sup> As research continued, clinicians sought to under-

stand where laser trabeculoplasty would fit in clinical practice.

The Glaucoma Laser Trial assessed the efficacy and safety of argon laser trabeculoplasty (ALT) as an alternative to topical medication (timolol) for controlling IOP in patients with primary open-angle glaucoma (POAG).<sup>3</sup> After 2 years of follow-up, 44% of the laser-first eyes had controlled IOPs versus 30% of the eyes treated with timolol. These results were somewhat disappointing, as the investigators saw some synechiae in the ALT eyes, and the pressure-lowering in these eyes was

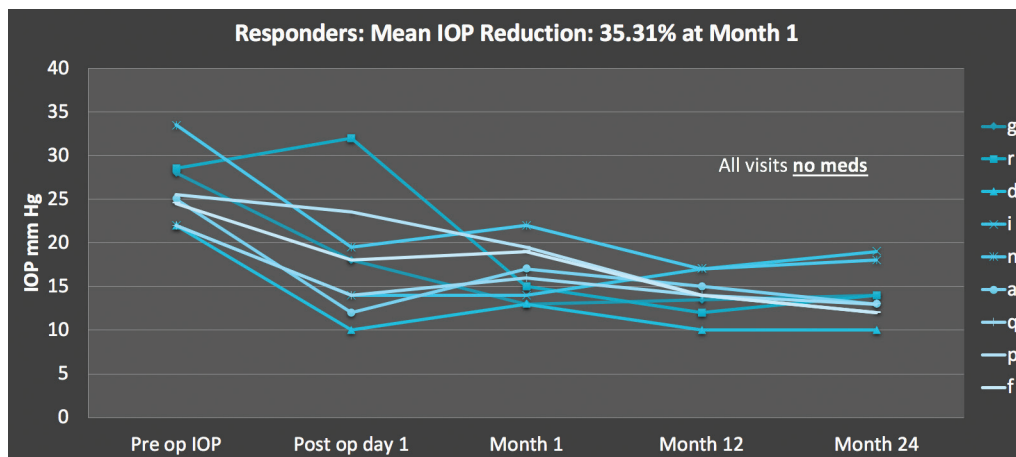


Figure 1. Patients who responded to treatment with the Glaukos stent had a 35% drop in IOP immediately after surgery.

not statistically significant. The common thinking was that ALT is more of a second-line therapy for eyes that haven't responded well to drops.

Selective laser trabeculoplasty (SLT) was invented by Latina in the 1990s, and subsequent studies examined its effect inside the eye.<sup>4-6</sup> There seemed to be less evidence of destruction compared with ALT, suggesting that SLT was altering the trabecular meshwork (TM) in a different way. Using eye bank tissue in a test model, SooHoo and colleagues found less thermal concavity damage with SLT than with ALT.<sup>7</sup> These findings seemed to support what we'd suspected all along, that SLT is less destructive to the meshwork than ALT.

The mechanism of action of laser trabeculoplasty has been a subject of much debate, with two primary schools of thought. One is that a mechanical change creates a disruption in the TM, allowing increased aqueous outflow. Another theory suggests a biologic effect from matrix metalloproteinase induction. In other words, once cells are treated with SLT, they alter how they allow aqueous to pass

through. Work by Alvarado suggested macrophage migration might have a role in helping to decrease IOP.<sup>8</sup>

An overwhelming body of evidence seems to suggest that SLT may be an effective initial therapy. But can we predict which eyes will have the best outcomes?

Pillunat and colleagues looked at preoperative IOP as a predictor of SLT efficacy.<sup>9</sup> They found that the higher the initial pressures were, the better the response; however, there seems to be a "floor" with SLT. If pressures are 14 mm Hg or less, SLT doesn't seem to have much effect on the IOP.

Hutnik and colleagues compared SLT with ALT in patients treated previously with 360° SLT.<sup>10</sup> They found that the pressure dropped 0.33 mm Hg more, on average, in the SLT group. While that wasn't statistically significant, they noted a strong trend, in that ALT failed more quickly than SLT.

While SLT gained ground as the preferred laser therapy to treat glaucoma, clinicians continued to weigh its value as initial treatment.

### SLT VERSUS MEDICATIONS AS FIRST-LINE THERAPY

Katz and colleagues published results of a study in 2012 in which they randomly assigned 69 patients (127 eyes) to receive SLT or medical therapy with a prostaglandin analogue as initial treatment.<sup>11</sup> They found that IOP reduction was similar in both arms after 9 to 12 months of follow-up and concluded that these results support the option of SLT as a safe and effective initial therapy in POAG or ocular hypertension (OHT).

Probably the most important update on SLT to date is the Laser

in Glaucoma and Ocular Hypertension (LiGHT) trial.<sup>12</sup> Investigators in the UK enrolled 718 treatment-naïve patients with POAG or OHT and randomly assigned them to initial therapy with topical antiglaucoma medications or SLT. Objective target IOPs were set according to glaucoma severity using a specific algorithm, as defined by the Canadian work group.<sup>13</sup>

Looking at pressure control at 36 months, the investigators found 74% of patients in the SLT group required no drops to maintain IOP at target. Eyes of patients in the SLT group were within target IOP at more visits (93%) than eyes in the medication group (91%), and no patients in the SLT group required glaucoma surgery to lower IOP versus 11 patients in the medication group.

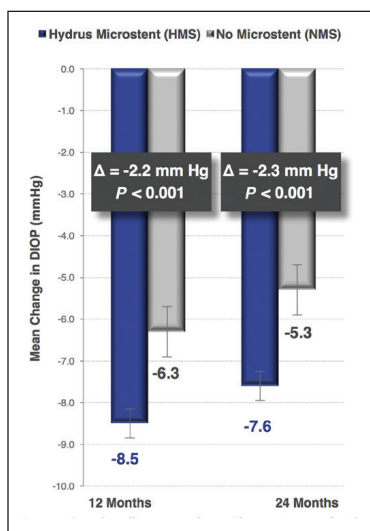


Figure 2. At 12 months, modified diurnal IOP was reduced by 8.5 mm Hg in the Ivantis microstent eyes, and at 24 months, the reduction was 7.8 mm Hg.

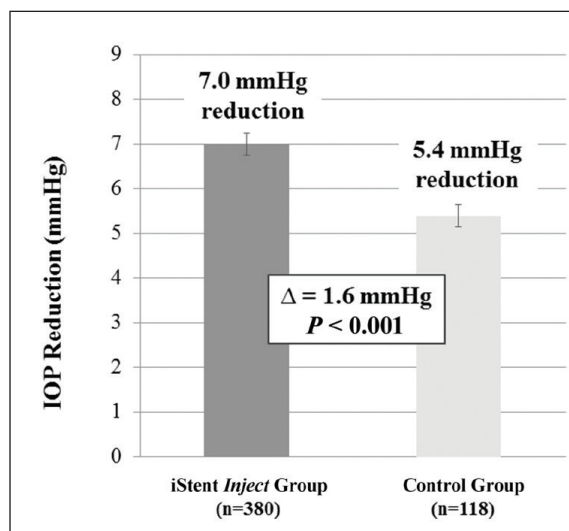


Figure 3. In a pivotal trial, clinically and statistically greater reductions in IOP without medication were achieved after implantation of the Glaukos multidirectional stents with cataract surgery versus cataract surgery alone.

These results suggest that SLT may be disease-modifying and should be considered for initial treatment.

## SURGICAL OPTIONS

When treating glaucoma in the United States, a key factor to consider is whether a patient is ready to have cataract surgery. We might lean toward cataract surgery alone if a patient has a healthy optic nerve head, only slightly elevated IOP (<25 mm Hg), and is using one or no medications. If a patient has mild disease, is using two medications, and you want to give him or her a chance to use fewer medications in the future, or if you want to get more of an IOP reduction than from cataract surgery alone, then you might consider a microinvasive glaucoma surgery (MIGS) at the same time as the cataract surgery.

For patients with significant disease, we have several options, including filtration surgery with antimetabolites, tube shunts, deep sclerectomy often with nd:YAG laser goniopuncture and antimetabolites, MIGS, maximum medications, or multiple combinations. However, safety must be a primary consideration. For example, any of the MIGS procedures can cause pressure spikes. We have to be careful when considering a MIGS option for a patient who has advanced field loss that's encroaching on fixation.

We also must consider how low a pressure a patient can tolerate and how it will affect the visual outcome. For instance, pressures below 10 mm Hg may cause hypotony maculopathy in patients with high myopia, in very young patients with thin, deformable sclera, and in patients with greater retinal nerve fiber layer thickness. Prior cyclophotocoagulation can cause low aqueous production. We must strike a balance between lowering the IOP and the risks involved in doing so.

## TRABECULAR BYPASS PROCEDURES

There are two stents available in the United States designed to bypass the TM and increase the flow of aqueous into the canal of

Schlemm. In the United States, these devices are approved for use only in conjunction with cataract surgery. Standalone procedures are approved in Europe and the Middle East.

Johnstone described the TM as functioning like a trampoline.<sup>14</sup> During a blink or when the eye moves, the meshwork moves and facilitates the outflow of aqueous into the canal of Schlemm and out through the collector channels. There is some physiologic purpose for having the TM intact, but in some individuals—for instance, those with hereditary glaucoma, people using steroids, and those who have had uveitis—the TM becomes less functioning and perhaps less compliant. In these cases, it is probably better that it be removed rather than bypassed. These are some of the factors to consider when choosing a surgical treatment.

The Glaukos stent was the first trabecular bypass device approved by the FDA. While it was shown to be somewhat more effective in lowering IOP than cataract surgery alone,<sup>15</sup> it wasn't a game-changer for most clinicians.

As I was part of the Glaukos study group, I went back through my patients' charts and analyzed what made the difference for them.<sup>16</sup> I found that visualization and placement of the micro-bypass stent seemed to matter. Patients with correctly placed stents who responded to treatment had a 35% drop in IOP immediately after surgery, and they seemed to sustain pressure reduction (Figure 1).

This led me to try various methods of verifying the placement of the stent to facilitate trabecular outflow. My conclusion was that a broader stent that spans multiple clock hours or multiple stents that can be visualized throughout surgery might result in further pressure reduction.

Visualization of the Hydrus microstent is similar to what we see with the Glaukos device. It is inserted through a clear corneal incision and guided through the TM into Schlemm canal.

The HORIZON investigators randomly assigned patients to receive a single Hydrus device or no stent after uncomplicated cataract surgery.<sup>17</sup> Medication washout and modified diurnal IOP measure-

ments were repeated at 12 and 24 months. At 12 months, modified diurnal IOP was reduced by 8.5 mm Hg in the Hydrus eyes, and at 24 months, the reduction was 7.8 mm Hg, which is significantly higher than with cataract surgery alone (Figure 2).

The newer Glaukos multidirectional device, which consists of two stents, is designed to improve placement of the stent into the canal. In a prospective, randomized, controlled pivotal trial, clinically and statistically greater reductions in IOP without medication were achieved after device implantation with cataract surgery versus cataract surgery alone (Figure 3).<sup>18</sup>

Another approach currently being investigated outside the United States is what I call "MIGS 'n' Meds." In a study performed in Armenia, two classic Glaukos stents were implanted in each of 39 eyes in standalone procedures.<sup>19</sup> The patients were then prescribed a prostaglandin analogue. Mean

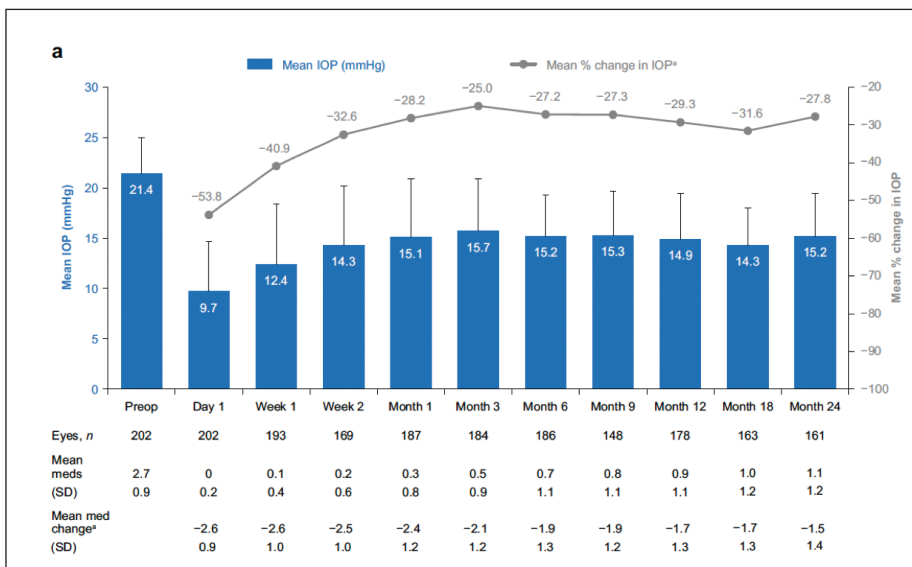


Figure 4. The Allergan stent effectively reduced IOP and medication needs over 2 years in POAG that was uncontrolled medically.

IOPs at baseline were 22.2 mm Hg. After 18 months, mean IOPs were 11.8 mm Hg. For patients who want to avoid a trabeculectomy, there's something to be said for looking at a standalone MIGS plus one medication.

With continued improvements in trabecular bypass devices and the potential for FDA approval of standalone procedures, I believe trabecular bypass "MIGS n' Meds" will be our future.

Also in the realm of trabecular bypass procedures are extirpation, which is removal of the TM through goniotomy or trabeculectomy, and canaloplasty, which dilates the canal. In my opinion, trabecular extirpation is indicated for patients who have a less functioning meshwork. Some surgeons use this approach for exfoliative eyes, pigmentary dispersion syndrome, and the like.

### MIGS IMPLANTS: CREATING A BLEB

The Allergan stent is a subconjunctival implant indicated for patients with refractory glaucoma that failed previous surgical treatment and for patients with POAG, pseudoexfoliative or pigmentary glaucoma with open angles who are not responsive to maximum medical therapy.

Reitsamer and colleagues found the gel stent effectively reduced IOP and medication needs over 2 years in POAG that was uncontrolled medically, with an acceptable safety profile (Figure 4).<sup>20</sup>

### COMING SOON

A device that likely will be approved in 2020 is a microshunt (Santen) originally developed by InnFocus. It was developed by engineer Leonard Pinchuk, using a new biomaterial called poly(styrene-block-isobutylene-block-styrene) or SIBS, which induces virtually no foreign body reaction in the body and has a low likelihood of fibrosis.<sup>21</sup> The theory is, if you can place a minishunt into the angle through an external approach, the result will be a better bleb with fewer problems. The FDA trial is awaiting publication. Battle and colleagues found very good pressure control in a small subset of eyes.<sup>22</sup>

Our continued search for the perfect treatment for glaucoma continues. Fortunately, we do have some good options and better understanding about what and when we use something. The next-generation treatments look promising, as well.

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## IMPACT OF GLAUCOMA THERAPY ON THE OCULAR SURFACE

### Emphasizing the need for novel therapeutics.

PREEYA K. GUPTA, MD

The Tear Film & Ocular Surface Society Dry Eye Workshop II (TFOS DEWS II) definition of dry eye highlights some of the key areas associated with this disease: loss of homeostasis of the tear film accompanied by hyperosmolarity and inflammation, which lead to damage on the ocular surface.<sup>1</sup>

Topping the list of risk factors for dry eye disease are female sex, older age, and meibomian gland dysfunction (MGD).<sup>1</sup> Among the iatrogenic causes of ocular surface disease (OSD), topical medications, particularly those that contain the preservative benzalkonium chloride (BAK), are probably the greatest offenders. Laser vision cor-

rection and cataract surgery cause a transient and sometimes long-lasting neurotrophic effect, leading to breakdown of the ocular surface. Systemic medications, such as nonsteroidal anti-inflammatory drugs, antihistamines, antihypertensives, and hormone replacement therapies, also increase the risk of dry eyes.

What does dry eye have to do with glaucoma? The prevalence of both increases with age. The therapies we prescribe to treat glaucoma induce dry eye disease; and chronic inflammation leads to alteration of the ocular surface anatomy.

I'd like to dive a little deeper into OSD and glaucoma, because the

literature offers a lot of insight, and I think sometimes, because we're treating glaucoma, and glaucoma is a blinding disease, we forget about the potential impact of our treatments on the ocular surface.

### GLAUCOMA DROPS AND THE OCULAR SURFACE

Zhang and colleagues reported that as many as 60% of patients using antiglaucoma eye drops have OSD.<sup>2</sup> They theorized that some

OSD might have been preexisting, but in all cases, the medication exacerbated the disease. According to Leung and colleagues, the prevalence and severity of OSD symptoms correlates with the frequency of drop use and BAK exposure.<sup>3</sup> They found a two-fold increase in the likelihood of developing OSD with each additional prescribed BAK-containing eye drop.

In the early stages of glaucoma, we typically prescribe a topical

**Table. Glaucoma Medications and Their Impact on the Ocular Surface**

Reference	Type of Study	Patient Population	Medications being compared	Time frame of medication	Results
Baudoin, 1998	Crossover, randomized double-blind	30 healthy volunteers	Topical 2% carteolol with and without preservative	3 days	TBUT was significantly reduced at 3 hours and after 3 days in the PF carteolol No difference in Schirmer test, corneal aesthesiometry, IOP-lowering effect, subjective tolerance
Henry, 2008	Prospective, multicenter, historical control	691 patients with ocular hypertension or POAG	Switching from latanoprost or bimatoprost to travoprost BAK-free	3 months	Mean OSDI scores were significantly improved, mean IOP was significantly decreased, conjunctival hyperemia significantly decreased in PF travoprost
Jaenen, 2007	Multicenter, cross-sectional, epidemiologic survey in four European countries	9,658 patients with open-angle glaucoma	Preservative vs PF beta-blocking drops	Varies	Pain or discomfort during instillation, foreign body sensation, stinging or burning, dry eye sensation significantly less frequent in PF group
Januleviciene, 2012	Prospective, observer-masked	60 eyes of 30 open-angle glaucoma patients	Switching from BAK-preserved latanoprost to PF tafluprost	3 months	Tear film osmolarity decreased significantly; mean TBUT increased significantly; abnormal fluorescein staining decreased significantly; subjective complaints decreased significantly in the PF group No statistically significant difference in IOP
Kanamoto, 2015	Prospective, randomized, observer unmasked, multicenter crossover	174 glaucoma patients	Tafluprost with 0.001% BAK vs travoprost with SofZia	3 months	Total superficial punctate keratopathy scores, conjunctival hyperemia scores decreased in patients using SofZia-preserved travoprost No statistically significant difference in TBUT, IOP-lowering effect, superficial punctate keratopathy scores of the superior/central/inferior areas
Martone, 2009	Retrospective, single-masked clinical	84 patients with POAG or ocular hypertension and 20 health age-matched volunteers	Untreated vs timolol with 0.01% BAK vs PF timolol vs latanoprost with 0.02% BAK vs timolol/latanoprost combination drop with 0.02% BAK vs timolol with 0.01% BAK and latanoprost with 0.02% BAK separately	23 to 28.7 months	Patients on glaucoma drops statistically more significant OSD than untreated eyes. Corneal sensitivity, Schirmer I test, TBUT, superficial epithelial cell density significantly lower in the preservative medication groups compared to PF group Stromal keratocyte activation higher in preservative medication groups
Wong, 2018	Cross-sectional, investigator-masked, paired-eye comparison	33 patients with open-angle glaucoma or ocular hypertension receiving medication in only one eye	88% of study participants used prostaglandin analogues; 100% used drops with BAK	at least 6 months	Treated eyes had statistically significant poorer tear film osmolarity, decreased TBUT, decreased tear meniscus height, and increased eyelid margin abnormality scores. No statistically significant difference in meibomian dropout, expressed meibum content, ocular surface staining
Yamazaki, 2010	Prospective multicenter, open-label uncontrolled	45 patients with POAG or ocular hypertension	Switching from BAK-preserved latanoprost to SofZia-preserved travoprost	3 months	Mean superficial punctate keratopathy score decreased significantly in the whole cornea after switching for SofZia-preserved travoprost

Adapted from Zhang X, Vadoothker S, Wuqaas M, et al. Ocular surface disease and glaucoma medications: a clinical approach. *Eye Contact Lens*. 2019; 45(1):11-18.



Figure 1. Some glaucoma medications may permanently damage the meibomian glands. of the ocular surface.<sup>2</sup>

Not all topical glaucoma medications affect the ocular surface in the same way. Prostaglandin analogues (PGAs) tend to cause more MGD, while alpha-adrenergic agonists have a high ocular allergy rate. Carbonic anhydrase inhibitors can alter the corneal endothelial pump function and lead to corneal thickening. Beta blockers act on the beta receptor of the lacrimal gland and reduce the basal tear turnover rate. They also can alter mucus formation in the tear film, causing increased staining of the cornea and conjunctiva.

When we talk about glaucoma, a blinding disease that causes irreversible damage, it's important to also discuss how some of the medications we use to treat glaucoma can induce irreversible damage to the ocular surface. That's where meibomian gland-related atrophy and dysfunction come into play.

Mocan and colleagues found that 92% of patients using a PGA, compared with 58% of patients using a non-PGA medication, had MGD.<sup>4</sup> Arita and colleagues reported a higher prevalence of meibomian gland atrophy in patients using glaucoma medications (Figure 1).<sup>5</sup> While not all patients with meibomian gland atrophy will have issues related to the ocular surface, it's an important consideration, because once atrophy sets in, it's irreversible. With decades of therapy, increasing age, and other comorbid risk factors, many of our glaucoma patients are having vision issues as much from their ocular surface disease as from their glaucoma.

Histologically, patients who have OSD and are using topical antiglaucoma medications experience increased conjunctival inflammation. The corneal epithelial cells become devitalized and have difficulty recovering. Over time, BAK can lead to neurotrophic corneas. As a result, we often

drop and observe its effect on pressure control. If one drop doesn't produce the desired response, we often add a second and sometimes even a third agent. This has real consequences for patients who are using these medications. The Table shows a plethora of studies that highlight the various medications we use to treat glaucoma and their negative impact on

see patients in our clinics who have been using topical medications for many years and are now reporting blurry vision but no pain.

When we look at the tear film, reduced tear breakup time is common, in part because of MGD and hyperosmolarity, which is a key mechanism that drives OSD and dry eye in particular. That leads to a signaling cascade to create chronic inflammation on the surface.

### BARRIERS TO COMPLIANCE: SIDE EFFECTS

While our current glaucoma medications cause dry eye and MGD, we're also challenged to manage patients who cannot or will not adhere to the regimen we prescribe.<sup>6,7</sup> Some of our elderly patients are hampered by poor dexterity,<sup>8</sup> and frequently when the drops are working, they're causing side effects that patients can't tolerate.<sup>9</sup>

I often ask colleagues, "If you had to take a multivitamin every night, how many of you would take it?" Typically, only about 25% would comply. Now, think about prescribing eye drops for patients who can't relate the medication to their glaucoma, because it starts in the periphery of their vision, and you're telling them to use an eye drop that will irritate their ocular surface over time. We're creating a situation where compliance is not rewarded. We need to be cognizant of that fact. The literature certainly confirms that noncompliance exists,<sup>10-12</sup> and I think all of us in clinical practice concur.

If we ask ourselves, "Do patients have to be 100% compliant?" The answer is yes. Patients who are not compliant have visual field progression (Figure 2).<sup>10</sup> Therefore, we need therapies that take concerns about compliance out of the picture.

### BARRIERS TO COMPLIANCE: COST AND ACCESS

When prescribing or recommending a medication to our patients, many extraneous factors are involved, such as insurance coverage and what's happening at the pharmacy (pharmacists are often incentivized to make certain substitutions). And the question remains: Is the patient actually getting the medication that you prescribed? Patients may have a high copay and may not be able to afford the drug. If they do get the medication, they may stop using it because of the side effects.

There's also a cost to the practice when we prescribe eye drops. We must take the time to explain how to use them and the importance of compliance. Clinicians and staff will need to field phone calls from patients related to side effects, and, of course, we're all familiar with the phone calls and staff time required to obtain prior authorizations.

We have had some advances in our traditional glaucoma therapies.

Preservative-free formulations of topical medications are available, and many more patients today are undergoing selective laser trabeculoplasty. We also have an entirely new category, microinvasive glaucoma surgery, which is an option in the United States for patients who are having cataract surgery. We're trying to rely less

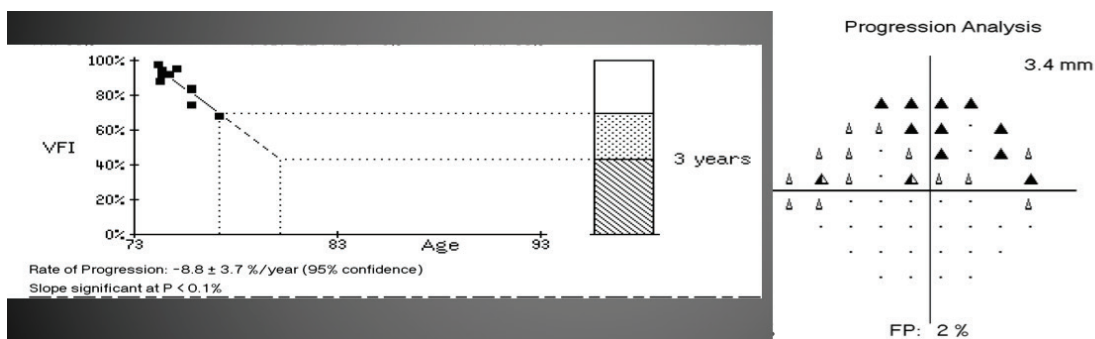


Figure 2. Patients who are not compliant have visual field progression.<sup>10</sup>

Adapted from Stewart WC et al. *Am J Ophthalmol.* 1993;116:176-181.

on topical drops, or if we're using drops, we're trying to use those that are friendlier to the ocular surface.

Despite these advances, we need more options. We need therapies that work at the target site of activity and deliver medication without topical toxicity, which I truly believe is a huge issue as it relates to compliance. Our next-level treatment needs to take that into consideration. We need novel drug delivery platforms to improve patient care and reduce the blindness burden from glaucoma.

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## FOCUSING ON SUSTAINED-RELEASE DRUG DELIVERY

Researchers aim to address long-standing glaucoma treatment challenges with new devices.

ROBERT N. WEINREB, MD

The development of sustained-release drug delivery devices is a rapidly emerging area in the field of glaucoma. Current development programs, almost all of which are utilizing the proven efficacy of the prostaglandin analogues, aim to demonstrate long-lasting efficacy, reduce side effects, and improve patients' adherence to treatment.

Investigators are looking at two major approaches to overcome this challenge. One involves applying devices to the ocular surface through, for example, a contact lens-like ring or intracanalicular implant. The second requires intracameral injection. Most of these studies are currently in phase 2, and keep in mind, none of the devices I discuss here have FDA approval.

### DELIVERY TO THE OCULAR SURFACE

The travoprost sustained-release device (Ocular Therapeutix) is administered as an intracanalicular depot through the punctum and is designed to deliver the medication to the ocular surface for up to 90 days. One of the benefits with this device is that the depot can be visualized with a blue light (Figure 1). This is important, because one of the issues with any of the intracanalicular devices is that, like a punctal plug, they can fall out. If a patient is being treated for dry eye, and a punctal plug falls out without the patient's knowledge, that's not so critical. If a patient with glaucoma is depending on an intracanalicular device

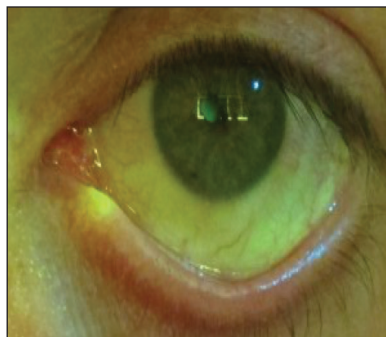


Figure 1. The travoprost sustained-release depot can be visualized using a blue light source with a yellow filter.

for IOP control and it falls out, undetected, that can have significant consequences.

In a phase 2 study, comparing the travoprost depot to timolol and a placebo plug, the average pressure reduction over 3 months with the travoprost depot was similar to what was observed with topical travoprost (Figure 2).<sup>1</sup> A phase 3 clinical trial, which enrolled more than 554 patients with ocular hypertension or primary open-angle glaucoma, failed to meet the primary endpoint of significant superiority in the reduction of IOP.<sup>2</sup> An argument might be made that the use of this device could improve adherence.

Another product, an L-shaped punctal plug with a latanoprost core (Mati Therapeutics), is designed to create unidirectional flow into the tear film and, therefore, reduce systemic absorption. Phase 2 studies showed a 20% reduction in IOP at 3 months with 92% retention.<sup>3</sup> The device is implanted in the canaliculus, and although it is cosmetically invisible, it is detectable clinically (Figure 3).

The bimatoprost sustained-release ring was developed by ForSight Vision and acquired by Allergan. The periocular ring is

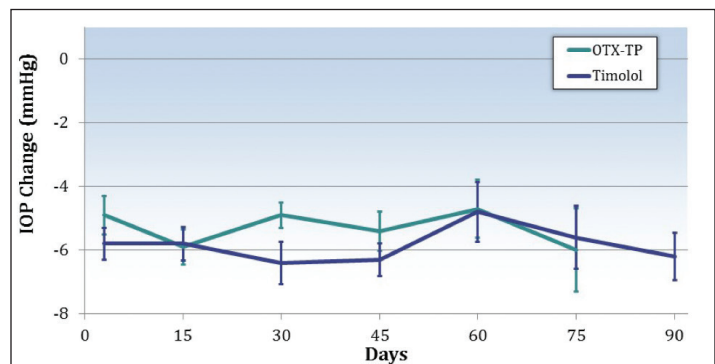


Figure 2. Average IOP reduction over 3 months with the travoprost depot was consistent with the reduction observed with topical travoprost.



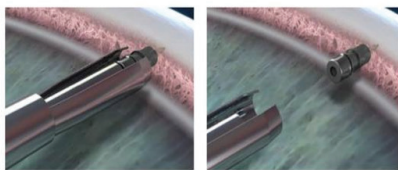
Figure 3. A punctal plug delivery system by Mati Therapeutics is inserted in the canaliculus.



Figure 4. This sustained-release ring is formulated with bimatoprost and rests under the eyelids.

**Intraoperative Adverse Events**

None reported (n=105)



**Blood Plasma Levels**

All implant samples below level of quantitation (BLQ) for travoprost

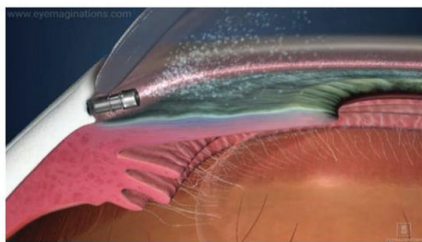


Figure 5. Investigators reported preliminary safety data for the travoprost intracameral implant.

**Bimatoprost**

**+**

**Biodegradable Polymers**

Similar to those used in biodegradable sutures

Supplied preloaded in a single-use applicator with a 28-gauge needle

Figure 6. This first-in-class implant is designed to lower IOP for at least 4 months.

inserted into the conjunctival cul-de-sac and rests under the eyelid (Figure 4). The ring must be replaced by a clinician once the drug is depleted every 3 to 6 months.

In a phase 2 study, 130 patients were randomly assigned to treatment with timolol or the bimatoprost ring.<sup>4</sup> Patients in the bimatoprost ring group experienced a mean reduction from baseline IOP of 3.2 to 6.4 mm Hg compared with 4.2 to 6.4 mm Hg for the timolol group over 6 months. The bimatoprost ring is not inferior to timolol.

One potential advantage is that the prostaglandin analogues have sustained pressure-lowering over 24 hours in comparison to timolol, which lowers pressures during the day but not during the night. What's more, adherence to a drop regimen is poor, particularly when compared with a medication that is in the eye for 3 months or longer.

**INTRACAMERAL DRUG DELIVERY**

A number of intracameral devices are currently in development. The travoprost extended-release biodegradable implant (Envisia Therapeutics) and a latanoprost free-acid implant (PolyActiva) are in phase 1/2 trials.

There are preliminary safety data from a phase 2 trial of the travoprost intracameral implant (Glaukos; Figure 5)<sup>5</sup> and a phase 3 trial is underway. Ocular Therapeutix has a travoprost implant in phase 1 trials.

Allergan has a first-in-class bimatoprost sustained-release biodegradable implant designed to lower IOP for at least 4 months (Figure 6). The implant is supplied in a preloaded single-use applicator and is deposited within the anterior chamber using a 28-gauge needle.

In the 2-year phase 1/2 APOLLO trial, 75 patients with open-angle glaucoma received various doses of the bimatoprost sustained-release implant (6 µg, 10 µg, 15 µg, or 20 µg) in the study eye and topical bimatoprost 0.3% once daily in the fellow eye.<sup>6</sup> Over 16 weeks, mean IOP reduction from baseline in the bimatoprost sustained-release implant group ranged from 7.2 mm Hg to 9.5 mm Hg, depending on dose, compared with 8.4 mm Hg in topically treated eyes. At 24 months, 28% of patients had not required any additional treatment after a single implant administration. Sustained effects through 24 months were reported for all dose cohorts and were not dose dependent.

In two 20-month phase 3 studies (ARTEMIS 1 and 2), patients were randomized to receive a bimatoprost sustained-release implant dosed every 4 months for a total of three administrations or twice daily timolol 0.5% eye drops. One study has recently completed, and the other is ongoing, but the primary database lock phase 3 results showed that bimatoprost sustained-release implant met the primary endpoint of noninferiority to topical timolol in the primary efficacy period through week 12. In addition, after receiving three implants over 8 months, more than 80% of patients had probability of sustained IOP lowering with no additional treatment needed for at least a year.<sup>7</sup> The results, in my opinion, were nothing short of stunning and transformative.

More than 20 years ago, my laboratory at the University of California San Diego, in collaboration with Paul Kaufman, MD, at the University of Wisconsin, investigated the extracellular matrix of the ciliary muscle, which is integral with the uveoscleral outflow pathway.<sup>8</sup> In particular, the effect of prostaglandins in altering the extracellular matrix was studied. One aspect of our studies

evaluated the release of a group of substances within the outflow pathway called metalloproteinases. We observed that prostaglandins alter these substances, and we concluded that these observations supported the hypothesis that increased metalloproteinase production by ciliary muscle cells has a role in increasing uveoscleral outflow facility after administration of topical prostaglandins.

Would this explain how this implant has such a great effect? One possibility is extracellular material is being washed out. The muscle is being altered, which is creating a sustained effect on uveoscleral outflow. This remains to be determined.

## SUMMARY

We currently have two major forms of sustained delivery. One is largely products that deliver medication to the external surface of the eye, whether it's a ring, an intracanalicular implant, or a punctal plug. The other is the intracameral approach, which, to me, is most impactful. Besides lowering IOP, these devices have the potential to reduce ocular surface disease. Both types of drug delivery will improve adherence.

Sustained drug delivery is arriving, and new classes, molecules, and mechanisms will be arriving in the coming months to years. Many new avenues and interactions with existing therapies have yet to be explored. There's no question that they will be disease-modifying or paradigm-changing.

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# MAKING A CASE FOR A SUSTAINED-DELIVERY DRUG IN GLAUCOMA THERAPY

## A case-based roundtable discussion.

**T**his 55-year-old patient with untreated open-angle glaucoma had initial pressures of 26 mm Hg. The visual field glaucoma hemifield test (Figure 1) appears to be within normal limits in the left eye.

The right eye has a small borderline inferior defect and some corresponding thinning of the retinal nerve fiber layer superiorly.

The patient had been using latanoprost for 2 years, and as shown in Figure 2, some punctate epitheliopathy of the cornea is present. As a glaucoma specialist, I see corneas like this one every day, but Dr. Gupta, maybe you would tell me something else is happening.

**DR. GUPTA:** Chronic use of topical medications, specifically those containing benzalkonium chloride (BAK), can absolutely lead to punctate staining and other forms of ocular surface disease. Certainly, in this patient, I'd want to look at the meibomian glands and the other ocular surface structures.

**DR. RADCLIFFE:** In terms of management, what happens when a patient with good pressure control on monotherapy develops dry eye? How do you proceed?

**DR. CRAVEN:** When a patient is having problems with topical medications, I would discuss selective laser trabeculoplasty (SLT). Evidence shows that it's effective at reducing pressures when they are in the mid-20s without treatment.<sup>1</sup>

**DR. GUPTA:** I appreciate that Dr. Craven suggested a nonpharmacologic therapy. I often see patients who are using several medications, perhaps for many years, and who have meibomian gland disease and are frustrated by poor vision. Sometimes our knee-jerk reaction is to add cyclosporine or lifitegrast, or to advise them to use tears six times a day or add other therapies. In these cases, we need to pause and determine what's driving the ocular surface disease. I often send my patients back to the glaucoma doctor and recommend SLT or something else to avoid adding another medicine.

**DR. WEINREB:** How do you all feel about nonpreserved products and products with alternative preservatives?

**DR. CRAVEN:** I think it's reasonable to try those products, because some patients do better with them. It's not an absolute guarantee, though. Some of my patients who are using preservative-free products still have meibomian gland dysfunction that doesn't seem to resolve.

**DR. WEINREB:** Dr. Radcliffe, do you ever use nonpreserved products?

**DR. RADCLIFFE:** I have mixed feelings about them. I would say this case is atypical, because a once-a-day prostaglandin analogue usually carries a modest preservative load. I've been impressed with the meibomian gland dysfunction, which is present in up to 92% of patients

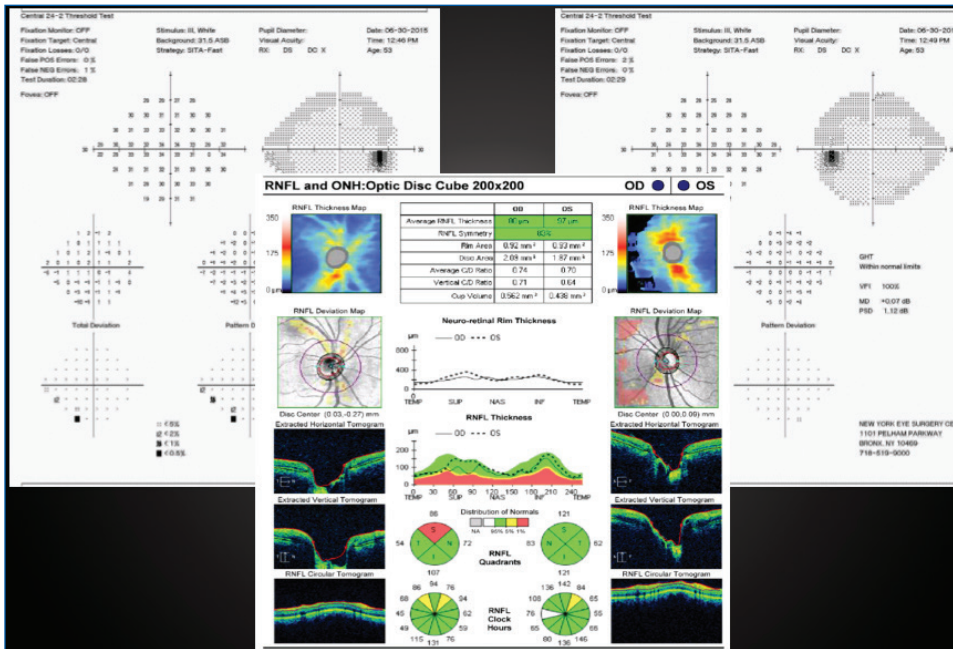


Figure 1. OCT and visual fields suggest glaucoma.

using prostaglandin analogues.<sup>2</sup> I think getting these great drugs inside of the eye instead of on top of or around the eye might be the key to avoiding some of these topical side effects. What's your experience with preservative-free drops?

**DR. WEINREB:** Some patients still are averse to SLT, and a preservative-free product provides an alternative. But I agree that patients who have epitheliopathy often continue to have epitheliopathy, even

when they're using a preservative-free medication or one with an alternative preservative to BAK.

**DR. GUPTA:** One of the issues with preservative-free products is that they can be cost-prohibitive. I may want to prescribe this alternative therapy that will be less toxic to the ocular surface, but sometimes it becomes financially unfeasible for patients to pay so much for a medication annually.

**DR. WEINREB:** It's also inconvenient, because preservative-free drops come in small, one-time-use vials that need to be refrigerated, which is difficult if someone is traveling for example.

**DR. CRAVEN:** When I was in the Middle East, I had the opportunity to use the Ivantis microstent and the Glaukos multidirectional stent as a primary treatment, which is off-label in the United States. I think that would be a good option for a patient like this. Patients tolerate it well, and I was surprised at how well it works as a primary treatment in eyes that are similar to this patient's.

**DR. RADCLIFFE:** We don't always use our therapies in the right order here in the United States. We started with laser as a last resort, but it probably does very well, early on. Perhaps that's the same with how we're using microinvasive glaucoma surgery (MIGS).

In this case, the patient is getting older, has dry eyes, and improved after SLT. His pressure is good for a few years, and then it pops back up, as can happen occasionally after SLT. As I explain to patients, sometimes SLT lasts for 10 years, sometimes it doesn't work

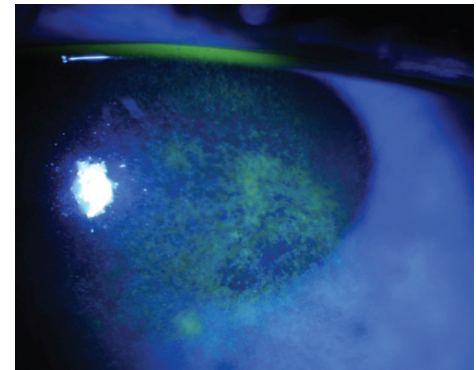


Figure 2. The patient developed dry eye and blurred vision after 2 years of prostaglandin analogue therapy.

Figure 3. The patient underwent SLT, but the effect did not persist. It lasted 2 years.

at all. In this case, it wore off after a few years, and we see some progression (Figure 3).

While the visual fields appear reasonably full, the retinal nerve fiber layer has changed from normal thickness to borderline. The IOP has increased to 23 mm Hg and the OCT is showing progression. Where would you take this patient next?

**DR. GUPTA:** To me, a sustained-delivery medication would be ideal in this case; however, we don't have the option of an FDA-approved sustained-release implant at this time. When a medication can be delivered over several months, the risk for topical toxicity is eliminated, as is the risk for nonadherence to a regimen that may require patients to instill drops frequently throughout the day.

**DR. CRAVEN:** I agree that this patient is a perfect candidate for a sustained-release medication. If that's available, I would consider it.

**DR. RADCLIFFE:** Let's think about the different options for sustained delivery. We have rings and plugs that sit on the surface of the eye, and we have intracameral options. How would your conversation go with that patient? What might you recommend?

**DR. CRAVEN:** The data show stronger efficacy with the intracameral device,<sup>3</sup> and this patient needs pressure reduction. I'd probably discuss that option with the patient first. If the patient isn't interested in that, then I might discuss the external methods, if they're available. If standalone MIGS were available, that would be a good discussion at this point, and I might even discuss a trabeculectomy. So much of what I would discuss would depend on the individual patient's circumstances—what my greatest concern is, the status of the other eye, family history, and various other associated factors.

**DR. RADCLIFFE:** Dr. Weinreb, how would you proceed?

**DR. WEINREB:** This patient has early glaucoma. There was loss

in an area of retinal nerve fiber layer that corresponded to a small change in the visual field. There's been a small amount of progression. The rate isn't rapid, so there's no urgency in dropping the pressure significantly.

SLT is an option. In the LiGHT trial,<sup>1</sup> treatment-naïve patients did quite well with SLT compared with drop treatment. I suspect a quarter of the patients had SLT repeated over the 3 years, and it seemed to be effective.

Restarting topical therapy, using a preservative-free medication or a different type of preserved medication, is a reasonable choice. Many of the new medications that we're using today, although effective, just beat up the ocular surface. I'm always looking at my patients and thinking, what can I do for their ocular surface. It's a big problem.

I agree that sustained-delivery of antiglaucoma medications will be transformative for us and for our patients. I would keep standalone MIGS in the background for this patient. It's still a surgical procedure, and being a surgical procedure, there is the potential, albeit very small, for complications.

**DR. RADCLIFFE:** I tell my patients that I don't repeat SLT frequently. I think they need to hear that to understand that they're not being sentenced to a lifetime of biennial SLT treatments, but I agree, this patient is a great candidate for repeat SLT. I also agree that we have many great potent therapies, but this patient needs a great, extremely well-tolerated, potent therapy. I'm not sure we have a perfect medication for him, but an intracameral implant will be ideal, once available.

That said, I believe this patient would be a wonderful candidate for an the Glaukos micro-bypass stent if he is ready for cataract surgery. Otherwise, I would repeat the SLT. ■

1. Gazzard G, Konstantakopoulou E, Garway-Heath D, et al. Selective laser trabeculectomy versus eye drops for first-line treatment of ocular hypertension and glaucoma (LiGHT): a multicentre randomised controlled trial. *Lancet*. 2019;393(10180):1505-1516.

2. Mocan MC, Uzunosmanoglu E, Kocabeyoglu S, et al. The association of chronic topical prostaglandin analog use with meibomian gland dysfunction. *J Glaucoma*. 2016;25(9):770-774.

3. Lewis RA, Christie WC, Day DG, et al.; Bimatoprost SR Study Group. Bimatoprost sustained-release implants for glaucoma therapy: 6-month results from a phase I/II clinical trial. *Am J Ophthalmol*. 2017;175:137-147.

## INSTRUCTIONS FOR CREDIT

To receive credit, you must complete the attached Posttest/Activity Evaluation/Satisfaction Measures Form and mail or fax to Evolve Medical Education LLC; 353 West Lancaster Avenue, Second Floor, Wayne, PA 19087; Fax: (215) 933-3950. To answer these questions online and receive real-time results, please click <https://evolvemed.com/online-courses/1931-supplement>. If you are experiencing problems with the online test, please email us at [info@evolvemed.com](mailto:info@evolvemed.com). Certificates are issued electronically; please be certain to provide your email address below.

Please type or print clearly, or we will be unable to issue your certificate.

Name \_\_\_\_\_  MD/DO participant  OD  non-OD participant

Phone (required) \_\_\_\_\_  Email (required) \_\_\_\_\_

Address \_\_\_\_\_

City \_\_\_\_\_ State \_\_\_\_\_ Zip \_\_\_\_\_

License Number \_\_\_\_\_

OE Tracker Number \_\_\_\_\_

## DEMOGRAPHIC INFORMATION

Profession	Years in Practice	Patients Seen Per Week (with the disease targeted in this educational activity)	Region	Setting	Models of Care
<input type="checkbox"/> MD/DO	<input type="checkbox"/> > 20	<input type="checkbox"/> 0	<input type="checkbox"/> Northeast	<input type="checkbox"/> Solo Practice	<input type="checkbox"/> Fee for Service
<input type="checkbox"/> OD	<input type="checkbox"/> 11-20	<input type="checkbox"/> 1-15	<input type="checkbox"/> Northwest	<input type="checkbox"/> Community Hospital	<input type="checkbox"/> ACO
<input type="checkbox"/> NP	<input type="checkbox"/> 6-10	<input type="checkbox"/> 16-30	<input type="checkbox"/> Midwest	<input type="checkbox"/> Government or VA	<input type="checkbox"/> Patient-Centered Medical Home
<input type="checkbox"/> Nurse/APN	<input type="checkbox"/> 1-5	<input type="checkbox"/> 31-50	<input type="checkbox"/> Southeast	<input type="checkbox"/> Group Practice	<input type="checkbox"/> Capitation
<input type="checkbox"/> PA	<input type="checkbox"/> <1	<input type="checkbox"/> 51+	<input type="checkbox"/> Southwest	<input type="checkbox"/> Other	<input type="checkbox"/> Bundled Payments
<input type="checkbox"/> Other				<input type="checkbox"/> I do not actively practice	<input type="checkbox"/> Other

## LEARNING OBJECTIVES

### DID THE PROGRAM MEET THE FOLLOWING EDUCATIONAL OBJECTIVES?

	AGREE	NEUTRAL	DISAGREE
• <b>Identify</b> all available treatment regimens for mild-to-moderate primary open-angle glaucoma.	_____	_____	_____
• <b>Evaluate</b> novel drug devices for the treatment of primary open-angle glaucoma as part of individualized therapy.	_____	_____	_____
• <b>Recognize</b> issues with compliance and adherence.	_____	_____	_____
• <b>Compare</b> the efficacy of novel therapeutics with traditional prostaglandins.	_____	_____	_____
• <b>Explain</b> the likelihood of achieving better IOP management with monotherapy compared with combination regimens.	_____	_____	_____

## POSTTEST QUESTIONS

1. Based on this activity, please rate your confidence in your ability to use novel drug devices for the treatment of primary open-angle glaucoma (POAG) as part of individualized therapy (based on a scale of 1 to 5, with 1 being not at all confident and 5 being extremely confident).

1. Not at all Confident
- 2.
3. Neutral
- 4.
5. Extremely Confident

2. Based on this activity, please rate your confidence in your ability to explain to patients the likelihood of achieving better IOP management with monotherapy compared with combination regimens (based on a scale of 1 to 5, with 1 being not at all confident and 5 being extremely confident).

1. Not at all Confident
- 2.
3. Neutral
- 4.
5. Extremely Confident

3. A 65-year-old woman with moderate POAG uses topical bimatoprost and tolerates it well but forgets to take his drops several times each week. Her visual field tests are stable, and in the office his IOPs are 12 mm Hg. Which of the following rationales might support the use of intracameral prostaglandin analogue sustained-release therapy?

- a. Topical therapy intolerance
- b. Disease progression
- c. Noncompliance
- d. Nonresponder to topical therapy

4. In the phase 3 clinical trials, bimatoprost SR was compared to what therapy in the fellow eye?

- a. Latanoprost
- b. Timolol maleate
- c. Placebo
- d. The bimatoprost ring

5. Selective laser trabeculoplasty (SLT) works by:

- a. Changing the trabecular endothelial cell population
- b. Macrophage migration into the region
- c. Changes to the extracellular matrix through metalloproteinases
- d. All the above

6. Trabecular bypass in the United States is:

- a. Good first-line therapy
- b. Has about 85% success in IOP control at 2 years
- c. Done only in conjunction with cataract surgery
- d. Limits future options for canal-based surgery

7. Which of the following is NOT a typical characteristic of microinvasive glaucoma surgery procedures?

- a. Rapid visual recovery
- b. Performed via a microincisional approach
- c. Consistently greater efficacy compared with that of trabeculectomy
- d. Favorable safety profile compared with that of trabeculectomy

8. Topical medications for glaucoma are a known cause of ocular surface disease in patients with glaucoma.

- a. True.
- b. False.

9. In the LiGHT trial, what percentage of eyes of patients in the SLT group were within target IOP at more visits compared to than eyes in the medication group?

- a. 93%
- b. 91%
- c. 74%
- d. 36%

10. In certain patients, IOPs measuring below 10 mm Hg may cause hypotony maculopathy in all BUT which one?

- a. Patients with high myopia
- b. Older patients with thick sclera
- c. Patients with greater retinal nerve fiber layer thickness
- d. Very young patients with thin, deformable sclera

11. Most clinicians do not use SLT as a first-line therapy in glaucoma. However, the LiGHT study showed \_\_\_\_\_.

- a. Patients believe drops are safer than laser therapy
- b. SLT is not as efficacious as topical drops after 36 months
- c. SLT has equal efficacy to topical medications, but is cost prohibitive
- d. SLT had a higher percentage of patients within target IOP at 36 months with none requiring glaucoma surgery

12. In the phase 3 ARTEMIS 1 and 2 studies, how many patients who received a bimatoprost SR implant dosed every 4 months had probability of sustained IOP lowering with no additional treatment needed for at least a year?

- a. <10%
- b. 20%
- c. 28%
- d. >80%

13. Meibomian gland dysfunction is present in up to \_\_\_\_\_ of patients using prostaglandin analogues.

- a. 25%
- b. 58%
- c. 74%
- d. 92%

14. The travoprost sustained-release device currently in clinical trials is designed to deliver the medication to the ocular surface for up to how many days?

- a. 30
- b. 60
- c. 90
- d. 120

## ACTIVITY EVALUATION

Your responses to the questions below will help us evaluate this CME/CE activity. They will provide us with evidence that improvements were made in patient care as a result of this activity.

Rate your knowledge/skill level prior to participating in this course: 5 = High, 1 = Low \_\_\_\_\_

Rate your knowledge/skill level after participating in this course: 5 = High, 1 = Low \_\_\_\_\_

This activity improved my competence in managing patients with this disease/condition/symptom. \_\_\_\_ Yes \_\_\_\_ No

I plan to make changes to my practice based on this activity. \_\_\_\_ Yes \_\_\_\_ No

Please identify any barriers to change (check all that apply):

- |   |   |                              |
|---|---|------------------------------|
| <input type="checkbox"/> Cost   | <input type="checkbox"/> Lack of opportunity (patients) | Other. Please specify: _____ |
| <input type="checkbox"/> Lack of consensus or professional guidelines | <input type="checkbox"/> Reimbursement/insurance issues | _____                        |
| <input type="checkbox"/> Lack of administrative support               | <input type="checkbox"/> Lack of resources (equipment)  | _____                        |
| <input type="checkbox"/> Lack of experience                           | <input type="checkbox"/> Patient compliance issues      |                              |
| <input type="checkbox"/> Lack of time to assess/counsel patients      | <input type="checkbox"/> No barriers                    |                              |

The design of the program was effective for the content conveyed. \_\_\_\_ Yes \_\_\_\_ No

The content was relative to your practice. \_\_\_\_ Yes \_\_\_\_ No

The content supported the identified learning objectives. \_\_\_\_ Yes \_\_\_\_ No

The faculty was effective. \_\_\_\_ Yes \_\_\_\_ No

The content was free of commercial bias. \_\_\_\_ Yes \_\_\_\_ No

You were satisfied overall with the activity. \_\_\_\_ Yes \_\_\_\_ No

Would you recommend this program to your colleagues? \_\_\_\_ Yes \_\_\_\_ No

Please check the Core Competencies (as defined by the Accreditation Council for Graduate Medical Education) that were enhanced through your participation in this activity:

- |  |   |
|--|---|
| <input type="checkbox"/> Patient Care                            | <input type="checkbox"/> Medical Knowledge                      |
| <input type="checkbox"/> Practice-Based Learning and Improvement | <input type="checkbox"/> Interpersonal and Communication Skills |
| <input type="checkbox"/> Professionalism                         | <input type="checkbox"/> System-Based Practice                  |

Additional comments:

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I certify that I have participated in this entire activity.

This information will help evaluate this CME/CE activity; may we contact you by email in 3 months to see if you have made this change? If so, please provide your email address below.

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