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SUSTAINED-RELEASE DEVICES FOR THE TREATMENT OF CHRONIC EYE DISEASES

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Sustained-Release Devices for the Treatment of Chronic Eye Diseases

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CONTENT SOURCE

This continuing medical education (CME) activity captures content from a roundtable discussion that occurred on April 15, 2019.

ACTIVITY DESCRIPTION

Traditional topical drug delivery for the treatment of ocular diseases has a number of challenges including compliance; tearing and blinking, which results in medication spillage and drug dilution; tear film turnover; and inadequate absorption. In addition, medication noncompliance and loss to follow-up are additional common problems, especially for patients with with chronic diseases like age-related macular degeneration, diabetic macular edema and glaucoma.

To combat these challenges to treatement, researchers are evaluating new sustained-release devices and methods to extend drug delivery and enhance the options currently available. Ongoing education about novel delivery devices and technologies is warranted to ensure eye care providers can deliver the best patient care possible.

TARGET AUDIENCE

This certified CME activity is designed for eye care professionals and specialists involved in the management of patients with chronic eye diseases.

LEARNING OBJECTIVES

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

- **Assess** data from the latest clinical studies on sustained-release devices and methods.
- **Describe** the benefits and challenges of sustained-release devices and methods versus conventional treatments.
- **Identify** the various sustained-release devices on the market and in the pipeline.
- **Evaluate** how to incorporate sustained-release devices into treatment regimens.

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1. PLEASE RATE YOUR CONFIDENCE ON YOUR ABILITY TO APPLY UPDATES IN SUSTAINED-RELEASE DEVICES IN THE CLINIC (BASED ON A SCALE OF 1 TO 5, WITH 1 BEING NOT AT ALL CONFIDENT AND 5 BEING EXTREMELY CONFIDENT).

a. 1
b. 2
c. 3
d. 4
e. 5

2. PLEASE RATE HOW OFTEN YOU CURRENTLY USE SUSTAINED-RELEASE DEVICES FOR THE MANAGEMENT OF PATIENTS WITH CHRONIC EYE DISEASES (BASED ON A SCALE OF 1 TO 4, WITH 1 BEING NEVER AND 5 BEING ALWAYS).

a. 1
b. 2
c. 3
d. 4
e. 5

3. THE ADVANCED GLAUCOMA INTERVENTION STUDY SHOWED THAT FLUCTUATION IN INTRAOCULAR PRESSURE (IOP) LED TO AN INCREASED RATE OF VISUAL FIELD PROGRESSION BY WHAT PERCENTAGE?

a. 10%
b. 20%
c. 30%
d. 40%

4. WHICH ONE OF THESE IS NOT CONSIDERED A BARRIER TO GLAUCOMA DROP COMPLIANCE?

a. First-time prescriptions do not get filled
b. Adding a second drop to improve compliance rates
c. Elderly patients need multiple attempts to get drops into the eye properly
d. Medication costs

5. MOST CLINICIANS DO NOT USE SELECTIVE LASER TRABECULOPLASTY (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

6. ALL OF THE FOLLOWING SUSTAINED-RELEASE DRUG DELIVERY SYSTEMS ARE DESIGNED TO RELEASE DRUG FOR 36 MONTHS *EXCEPT*?

a. 0.7-mg dexamethasone intravitreal implant
b. 0.19-mg fluocinolone acetonide implant
c. 0.18-mg fluocinolone acetonide implant
d. 0.59-mg fluocinolone acetonide implant

7. WHAT IS THE RECOMMENDED FIRST-LINE TREATMENT FOR A PATIENT WITH DIABETIC MACULAR EDEMA?

a. Dexamethasone injection followed by a 3-year fluocinolone implant
b. Anti-VEGF monotherapy
c. Combination dexamethasone and anti-VEGF therapy
d. Three-year fluocinolone acetonide implant

8. WHICH ANTI-VEGF AGENT WAS FOUND IN CLINICAL STUDIES TO MAINTAIN STABLE VISION IN 91% OF PATIENTS WITH NEOVASCULAR AGE-RELATED MACULAR DEGENERATION (AMD) ON A FIXED 12-WEEK REGIMEN?

a. Ranibizumab
b. Aflibercept
c. Brolucizumab
d. Abicipar pegol

9. WHICH OF THESE TREATMENTS IS COMMONLY USED AS THE FIRST-LINE TREATMENT FOR A PATIENT WITH NEOVASCULAR AMD?

a. Intravitreal anti-VEGF therapy
b. Photodynamic therapy
c. Steroids
d. Laser photocoagulation

10. A PORT DELIVERY SYSTEM FOR RANIBIZUMAB FOR NEOVASCULAR AMD IS CURRENTLY IN CLINICAL TRIALS. THE LADDER TRIAL DEMONSTRATED THAT THE MEDIAN TIME TO REFILL FOR THE HIGHEST DOSE WAS _____.

a. 5 months
b. 10 months
c. 15 months
d. 20 months

Sustained-Release Devices for the Treatment of Chronic Eye Diseases

Traditional topical drug delivery for the treatment of chronic ocular diseases such as glaucoma, age-related macular degeneration (AMD), and diabetic macular edema (DME) come with many challenges that significantly impact their efficacy, such as poor adherence, medication spillage, and inadequate absorption.[1-6] Medication noncompliance and loss to follow-up are common problems in the management of these diseases, and studies have shown that up to 60% of patients with glaucoma are noncompliant with their treatment regimens.[7-9] In an effort to overcome these barriers, many sustained-release devices are currently marketed and in development to continuously deliver localized therapy within the eye itself.[10-13] These novel drug delivery devices and technology open up new possibilities for patients and clinicians.

— Inder Paul Singh, MD, Moderator

ADDRESSING PATIENT COMPLIANCE IN GLAUCOMA AND RETINA

Glaucoma

Q | INDER PAUL SINGH, MD: Many of the advancements in glaucoma and retina in recent years are related to maintaining patient satisfaction and improving patient quality of life while treating the disease states. In glaucoma specifically, we've seen incredible advancements in minimally invasive glaucoma surgery (MIGS) with the development of the iStent (Glaukos), Hydrus (Ivantis), Ab Interno Canaloplasty (Ellex, Sight Sciences), and goniotomy/trabeculotomy (Trabectome, NeoMedix), Kahook Dual Blade (New World Medical), and Omni (Sight Sciences).[14-18] How important is the development of sustained-release devices in glaucoma? Does it help with compliance issues?

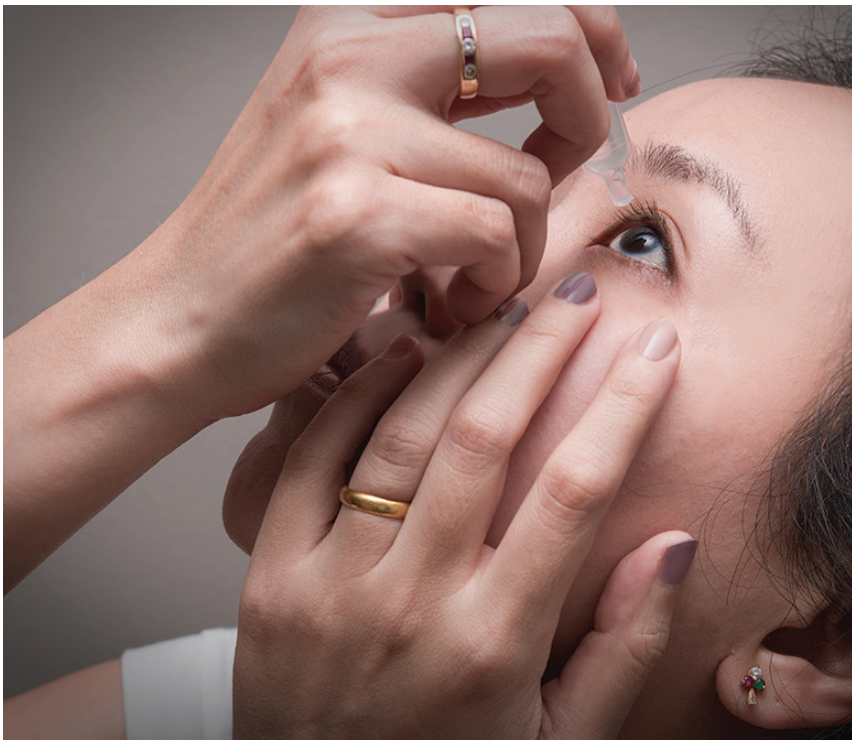
JONATHAN S. MYERS, MD: Patients don't take their glaucoma medications as they should.[7-9] Up to half of patients take less than three out of four doses of their medication, and about a quarter of patients may not even take half.[7-9]

DR. SINGH: Medical management of glaucoma compliance is probably the biggest issue I face in managing patients. And it's so hard to keep patients coming back to your office, paying their copays, filling their prescriptions, and making sure they can instill the drop correctly.[19] Forgetfulness, medication cost, and side effects are significant barriers to compliance.

Data from the Advanced Glaucoma Intervention Study showed that fluctuation in intraocular pressure (IOP) led to a higher risk of visual field progression.[20-22] Even in patients with relatively low pressure—in the 10.8 mm Hg range—had an increased rate of progression of 30% if their IOP fluctuated by more than 3 mm Hg. IOP fluctuation is a huge risk factor for progression, especially in patients with advanced disease.[23,24] Short-term fluctuations were first evaluated in the 1990s using self-performed home tonometry five times a day for 5 days.[24] In this study, the relative risk of disease progression at 5 years was roughly six times greater for eyes with an IOP fluctuation of 5.5 mm Hg compared to those with an IOP fluctuation of 3 mm Hg. There is no doubt poor compliance leading to fluctuating IOP is a risk factor for glaucoma progression in certain patients.

What barriers do glaucoma specialists face with getting a drop in the eye and to the target tissue?

DR. MYERS: The first barrier is the substantial percentage of prescriptions we give for first-time therapy that never get filled.[25] Assuming the patient did fill the prescription, studies show that it can take elderly patients seven attempts to get one drop in the eye.[26] That's before you take into account the loss of use with time, side effects, and cost; the drops don't last as long as they are intended to



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because it takes multiple doses to get one dose in.[19,27] Studies show that if you add a second drop to their treatment regimen the refill rate drops further.[28] There are a lot of barriers, even beyond cost and access to medications.

DR. SINGH: What are the physical barriers?

DR. MYERS: Most of our eye drops are between 20 µl and 50 µl of fluid, and we think the conjunctival fornix can hold maybe 10 µl or 15 µl of fluid. The rest of the medication immediately goes onto the face or down through the punctum into the nasolacrimal duct to deliver drug side effects to the rest of the body. Most of the drop is wasted. That's why the intraocular administration of drugs is so appealing; we reduce the troublesome side effects such as dry eye, allergic reaction, toxicities, and perhaps avoid reduced surgical results after long-term reduced topical administration of glaucoma medications.[29-32]

Retina

Q | DR. SINGH: In the retina space, recent advances in drug delivery include intravitreal injections and sustained delivery of medication. How do frequent injections impact compliance and satisfaction in patients with retinal disease?

SUMIT SHARMA, MD: Clinical trials for intravitreal injections show that monthly injections are better for the patients' disease.[33-41] However, this isn't reflective of real-world practice. Data from the American Society of Retina Specialists and the physician Preferences and Trends surveys[42-45] show that the majority of US retina specialists use the treat-and-extend (T&E) treatment regimen.

When we look at the investigator-initiated T&E studies, we see that the patients who received monthly injections tend to do better, but that's a high burden in the number of visits and compliance.[33-35] T&E is the compromise. Five-year CATT study data shows that patients don't do as well once they switch from monthly to as-needed or T&E injections.[41] Sustained release is something that is needed in the retina space, especially for the treatment of AMD.

Q | DR. SINGH: Are you having difficulty maintaining the high volume of patients you now need to see? How difficult is it to keep patients coming monthly?

DAVID CALLANAN, MD: In retina, one of the biggest issues for compliance is getting elderly patients to the clinic. Oftentimes, a family member or caregiver has to take off work to bring them, which is a significant burden. Further, elderly patients commonly develop a concurrent illness and end up in the hospital. By the time they come into my office, it's been 2 months and suddenly they have a subretinal bleed because they weren't receiving their regular medicine. If you give patients a choice of monthly injections or T&E, they will always choose T&E, even though that may not be the best treatment course for them.

DR. SINGH: Retina specialists pioneered the intravitreal injection because topical drops did not access the area of pathology to sufficiently control disease. In retina, is there even more of a need to address site of pathology? In glaucoma treatment, we are treating a risk factor (intraocular pressure; IOP) rather than the actual optic nerve hypoplasia and retinal nerve fiber layer. How do you see targeting the medication to the site of pathology advancing further?

DR. SHARMA: I think targeting the site of pathology will progress in retina because if you think about it from a disease burden standpoint, it doesn't make sense that we give this bolus of an injection. You can get a very high dose for a short period of time, and then it goes away and we have the patient come back 2 or 3 months later and repeat it. It would make more sense if we had a sustained-release therapy that we could deliver to the right location, and then continue to treat them over an extended period. Also, we have multiple trials ongoing with more targeted therapy such as suprachoroidal delivery or subretinal delivery, some of these will become standard practice in the future.

DR. SINGH: Do you think there's more disease-modifying potential if we have consistent administration or release of medication in the area of pathology?

DR. SHARMA: Yes, there may be, but we don't know for sure yet. For example, optical coherence tomography angiography data shows us the neovascular complexes change over time with each injection, and you end up with mature vessels. If we can continuously give an anti-vascular endothelial growth factor (anti-VEGF) agent, maybe that wouldn't be the case. That's pure speculation on my part, but it will be very interesting to see what happens with time.

SUSTAINED DRUG DELIVERY IN GLAUCOMA

Q | DR. SINGH: What's in the pipeline for sustained delivery of medications in glaucoma?

DR. MYERS: The major initiative is bimatoprost SR, which is currently in phase 3 trials. Bimatoprost SR is a sustained-release delivery system using a small pellet of drug placed in the anterior chamber. In phase 1/2 trials, the implant showed a mean IOP reduction from baseline of 7.2 to 9.5 mm Hg in 75 eyes 4 months after the injection in clinical trials. The implant lowered IOP in 92% of patients at 4 months and 71% at 6 months. No serious adverse events were reported.[46, 47] Top-line results from the phase 3 trial comparing bimatoprost SR and timolol were just released.[48] The study included 594 patients with open-angle glaucoma (OAG) or ocular hypertension. Bimatoprost SR reduced IOP by 30% over the 12-week period. It also showed the potential for patients to remain treatment free for 1 year after the last implant was inserted.[48]

There are studies of bimatoprost versus other treatment modalities ongoing; we hope the treatment will be available within the next year as a commercial product.

"If you look at the phase 1/2 studies of bimatoprost SR, after 2 years, 30% of patients were rescue-free and still experiencing significant efficacy."

—Inder Paul Singh, MD

DR. SINGH: If you look at the phase 1/2 studies of bimatoprost SR, after 2 years, 30% of patients were rescue-free and still experiencing significant efficacy.[46,47] The initial thought was that the effect of bimatoprost SR would last 4 to 6 months, but a significant portion of patients actually had a longer duration of effect. Why are certain patients seeing such long duration with sustained-release delivery versus topical medication? Is the amount of drug that's concentrated in the pellet more potent? Are we increasing the metalloproteinase relationship versus the tissue inhibitor of metalloproteinase? We don't know the cause, but there's definitely something else going on, and it may be disease modification. The study showed no signs of periorbital pigmentation, hyperemia, or iris pigmentation changes. Many of the issues we face with the topical prostaglandin analogs (PGAs) were not see with bimatoprost SR.

DR. MYERS: Other novel drug-delivery approaches in the pipeline include the bimatoprost ring.[49] Results of a recent trial compared the bimatoprost ring to topical timolol and showed the ring achieved good pressure reduction out to 6 months and was well tolerated by the majority of patients.[49] The ring-shaped implants sat in the cul-de-sac and under the upper lid, and did not come out at a significant rate. When it did come out, patients were able to tell the ring needed to be replaced.

There's also the OTX-TIC (Ocular Therapeutix), a sustained-release, injectable intracameral travoprost implant that is under development in phase 2 studies. OTX-TIC is injected into the anterior chamber of the eye, with a target duration of drug delivery of 3 to 4 months[50] Early results from a study of 10 patents in two dosing cohorts were reported during the 2019 American Society of Cataract and Refractive Surgery Annual Meeting.[51] The first cohort, which included five patients, had an average IOP reduction greater than what was achieved with once-a-day topical travoprost. Three of the five patients had adverse events, however, which included iritis or peripheral anterior synechiae, and one patient needed topical rescue therapy. The company's recent press release regarding phase 3 data reported superior IOP reduction versus placebo at 8 of 9 time points, but the trial failed to meet its primary endpoint of achieving a statistically superior mean reduction of IOP from baseline for patients treated with OTX-TP compared with a placebo insert at nine different time points, three diurnal time points, and at 2, 6, and 12 weeks following insertion.[51]

Glaukos developed the iDose, a small titanium canister that has a drug-eluting membrane, which allows a concentrated solution of travoprost to be dosed into the anterior chamber over the course of a year. The device is injected and anchored in the anterior chamber through the trabecular meshwork (TM). It has an anchoring peg, and it's about a millimeter and a half canister filled with concentrated travoprost. The iDose was tested in a phase 2 trial of 154 patients. The trial evaluated two models of the iDose with two different travoprost elution rates, compared with topical timolol. The primary efficacy endpoint was noninferiority to topical timolol.[52] The iDose travoprost cohort had a 30% reduction in mean IOP compared with baseline IOP during the first 12 months. There were no adverse events of hyperemia reported to date in either group. The iDose is currently in phase 3 trials.

DR. SINGH: Let's assume bimatoprost SR is approved for use in the United States. What would that do to your practice in terms of flow and efficiency?

DR. MYERS: It would require a real transition. First, we have to determine which patients will be most interested in sustained release. We can break those patients into two groups. The first group will be interested in it for convenience. These patients are young, active, have demanding jobs, travel, and want to be free of drops. The second population of patients are ones the physician flags due to compliance or mobility issues.

Q | **DR. SINGH:** Do you think a sustained-release platform will be a first-line option in the future or will glaucoma specialists always try drops first?

DR. MYERS: I think we probably first should start a topical prostaglandin to show it's efficacious. After a month of established efficacy, I'd reassess and potentially switch over. We don't need to

demonstrate noncompliance first because we already know that most people are noncompliant. Safety has to come first, and we need a good, sterile technique. I also see this moving to a slit-lamp environment with care and precautions for safety.

DR. SINGH: Describe the injection process for bimatoprost SR.

DR. MYERS: First, we numb the eye and then do a sterile betadine preparation. It's very similar to doing a paracentesis. You enter the anterior chamber using a small-gauge needle. You need to advance the needle into the anterior chamber to make sure the implant doesn't track back to your paracentesis. I've personally never had a problem with this, but I do recommend a slow withdrawal. It's very easy. My experience has been positive overall.

DR. SINGH: I agree, it is very efficient and intuitive. Many of us have performed a paracentesis at the slit lamp before. The injector itself is similar to the intravitreal 0.7-mg dexamethasone implant injector that our retina colleagues use. Once you're in the anterior chamber, over the iris, and pointed toward the inferior angle, you press a button and the device releases the bimatoprost pellet. It then settles into the inferior angle. What are your experiences with this postoperatively?

DR. MYERS: The postoperative experience varies, but the device slowly melts away over 4 to 6 months. You may see past 8 months a husk of the tiny little residual implant. It tends to sit in the inferior angle for the vast majority of patients. One reason why inserting it at the slit-lamp may be easier is because as you inject it, the device may drop right down at the angle very quickly and easily. Most patients are unaware it's in their eye, although it can move in some patients as their eye moves.

Q | **DR. SINGH:** The LiGHT study showed that selective laser trabeculoplasty (SLT) was a potentially better option as a first-line therapy than drops.[53] In that UK-based study, 74.2% of patients in the SLT group needed no drops to maintain target IOP, and more patients (93%) were within target IOP at 36 months than patients in the eye-drop group (91.3%). Glaucoma surgery was necessary in none of the SLT patients but was necessary in 11 patients in the eye-drop group. That led the authors to suggest SLT should be offered as a first-line treatment in clinical settings. This study, I think, will help to change the mind set of eye care providers to think of a procedure rather than topical drops earlier in the disease.

Do you think that topical mediations will be used less frequently in glaucoma or abandoned totally with the advent of newer treatment modalities?

DR. MYERS: I certainly hope so, but that shift will take time. We'll also need buy in from patients because most patients choose drops before SLT, even if it's not in their best interest.

DR. SINGH: What are the barriers to SLT adoption?

DR. MYERS: Patients view drops as harmless, and they believe they will be the person who doesn't miss a dose. As physicians, we know that is not usually the case, but that's not the patient's intuitive judgement.

DR. SINGH: Good points. It's important to educate patients that drops are not necessarily harmless. For instance, we do see increased risk of ocular surface disease over time with the increased number of glaucoma medications. We also see orbital fat pad loss and changes to the lid margin in some patient using topical PGAs. I do think providers need to start feeling more comfortable offering SLT as a first-line therapy. Many doctors I speak with would actually prefer SLT as a first-line therapy if they had glaucoma but at the same time, do not often offer it as a first-line to their patients. I do think these developments will improve the treatment paradigm and allow us to do more types of interventions earlier rather than simply relying on drops.

Another benefit of SLT is the ability to address the site of pathology causing IOP rise. The earlier you treat with SLT in the disease state, the greater the chance it will be efficacious and for longer. I think some of the negative perceptions of SLT were due to clinicians waiting to perform SLT until the patient developed more advanced disease, which in turn, makes it more likely there is disease beyond the TM, in the Schlemm canal and distal channels. By then, the disease is too far along for SLT to work well. In my opinion, SLT helps naturally rejuvenate the outflow system. The earlier you increase flow through the TM, the theoretical less chance for further collapse of the outflow system going forward. We may be delaying the further collapse of the TM and canal by increasing outflow earlier in the disease.

SUSTAINED DRUG DELIVERY IN RETINA

Q | **DR. SINGH:** What is in development in the anti-VEGF world for patients with AMD?

DR. SHARMA: There have been a few advancements in sustained-release delivery for retina during the past decade, including a 0.59-mg fluocinolone acetonide intravitreal implant (Bausch + Lomb) designed to release the drug locally to the posterior segment to deliver corticosteroid therapy for more than 3 years.[54,55] The device must be sutured into place, making it a surgical procedure. It's implanted into the posterior segment of the affected eye through a pars plana incision to provide long-term inflammation control in patients with chronic noninfectious posterior uveitis. The implant consists of a tablet encased in a silicone elastomer cup containing a release orifice and a polyvinyl alcohol membrane positioned between the tablet and the orifice. In clinical trials, the implant stabilized or improved visual acuity (VA) in 80% of patients with posterior noninfectious uveitis and reduced the percentage of patients requiring systemic corticosteroid therapy from 47% to 63% to 5% to 10% after 34 weeks.[55,56]

A new technology, developed by EyePoint Pharmaceuticals, uses a miniaturized, injectable, sustained-release drug-delivery system for small molecules that can last for up to 3 years, administered in an office setting through a 25-gauge needle. Two products using this technology and fluocinolone acetonide have been approved by the

FDA to date: a 0.19-mg fluocinolone acetonide intravitreal implant for the treatment of DME[57-59] (Alimera Sciences) and a 0.18-mg fluocinolone acetonide intravitreal implant (EyePoint Pharmaceuticals) for the treatment of chronic, noninfectious posterior segment uveitis.[60]

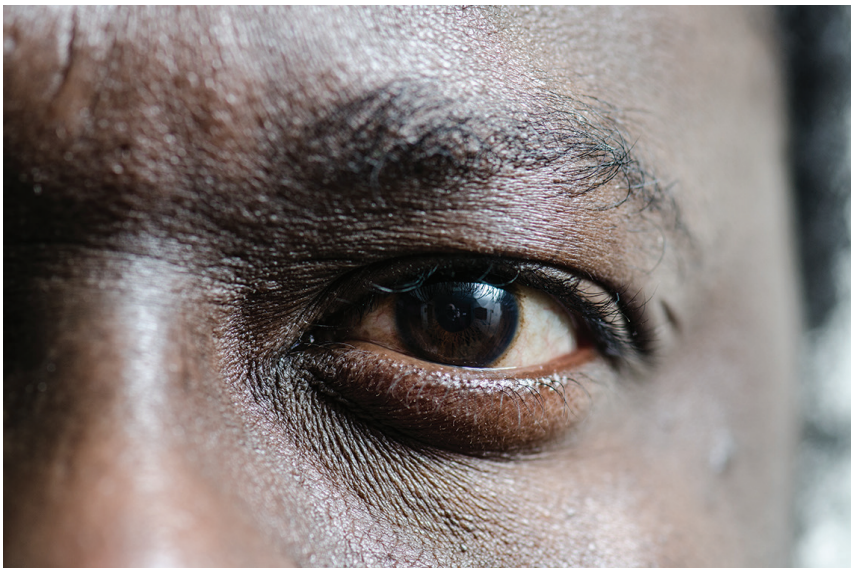
A single 0.19-mg fluocinolone acetonide implant delivers treatment for up to 36 months, and during a 3-year clinical trial, 75% of patients treated with Iluvien only needed one implant.[61] The pivotal trials for the 0.19-mg implant were the FAME studies, which evaluated 953 eyes in patients with persistent DME after one or more laser therapy treatments, randomized 1:2:2 for sham injection (n = 185), low-dose fluocinolone acetonide implant (0.2 µg/d, n = 375), or high-dose fluocinolone acetonide implant (0.5 µg/d FAc, n = 393). At 36 months, 27.8% (high dose) and 28.7% (low dose) of all implant-treated eyes compared with 18.9% of sham eyes demonstrated an improvement of 15 or more letters (P = .018). In addition, preplanned subgroup analysis showed a significant and increased benefit, especially in patients with chronic DME.[58,62] One of the big benefits of the 0.19-mg implant is that it's an office-based procedure.

The FDA approved in late 2018 the fluocinolone acetonide intravitreal 0.18-mg implant, which is injected through a 25-gauge needle and releases about one-third of the dose of fluocinolone as the surgically implanted insert designed to last 3 years. EyePoint reported positive 36-month follow-up phase 3 data during the 2019 Association for Research in Vision and Ophthalmology Annual Meeting.[63] The trial enrolled 129 patients across 33 centers. Eighty-seven eyes were treated with the fluocinolone acetonide intravitreal 0.18-mg implant; 42 eyes received sham injections. At 36 months, the recurrence rate with the fluocinolone acetonide intravitreal 0.18-mg implant was significantly lower than in sham-treated eyes (56.3% vs 92.9%, respectively; P < .001). VA gains of 3 lines were more common with the fluocinolone acetonide intravitreal 0.18-mg implant (33% vs 15%) and losses were more common with sham (9% vs 1%). I've only just started using it. It's exciting because it allows us to deliver sustained-release steroids for uveitis in the office without a surgical procedure. The implant is very similar to the one we use for DME, which also lasts for 3 years. I don't think the 0.18-mg implant will completely replace the 0.59-mg implant, however, as some patients have a greater need for steroids than the 0.18-mg implant will provide, but I do think it will help a large portion of our patients.

The intravitreal 0.7-mg dexamethasone implant (Allergan), which is delivered through a 22-gauge injection in the clinic, is another sustained-release device that is commercially available.[64-69] This implant uses a solid polymer drug-delivery system and was approved in June 2009 for treatment of macular edema following branch or central retinal vein occlusion. It has subsequently been approved for treatment of DME and noninfectious posterior segment uveitis. Although it was designed to last 6 months, I find I get 3 to 4 months out of it before the uveitis recurs.

Q | DR. SINGH: How do you select which implant is appropriate for which patient?

DR. CALLANAN: It's much more difficult to get the approval for a fluocinolone injectable, but insurance companies will pay for the dexamethasone implant without issue because of the cost of treatment. However, if you treat a patient with uveitis with just the dexamethasone implant, they require an intravitreal injection every 3 months. If they have bilateral uveitis, they now need injections in both eyes every 3 months for a condition that will last for years. That's not a very satisfactory treatment. We also know that patients with uveitis who only receive intermittent treatment have flares and will eventually lose vision.



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DR. SINGH: When you see a DME patient, would you go straight for the steroid or do you always start with an anti-VEGF?

DR. SHARMA: I tend to start with anti-VEGF for all DME patients, if they have a suboptimal response or want something with longer duration of action, then I consider steroids. The approval for the 0.19-mg fluocinolone acetonide implant requires that the patient has not had a steroid-related IOP response before. Not every patient with DME responds well to steroids, so I will often do the dexamethasone injection first to make sure it works and then supplement with a 3-year fluocinolone implant. The fluocinolone implant tends to do a better job of keeping edema at bay rather than resolving it. I resolve the edema first with dexamethasone and then give them fluocinolone a few months later. That combination tends to work well in my hands.

DR. SINGH: Would you ever combine dexamethasone and anti-VEGF therapy for DME?

DR. SHARMA: Yes, I have used them in combination. When you look at the DME cytokine profile, there is an elevation in VEGF levels. However, there are multiple other cytokines that are elevated, and we don't address any of those with just anti-VEGF. By adding the steroid, you can address some of the other cytokines that are elevated. Patients who have an incomplete response to anti-VEGF

or poor response to anti-VEGF often do very well with the combination approach of supplementing with one of the available steroid injectables.

DR. CALLANAN: Most clinicians start with anti-VEGF therapy because, if you can get a reasonable response with it, you don't have to worry about the side effects related to the intravitreal steroids. Data from the Diabetic Retinopathy Clinical Research Network studies show that if you continue to deliver anti-VEGF therapy in diabetic patients, there is a slight regression in the diabetic retinopathy scores, similar to what we see with steroids.[70-72] If we can get close to the same effect with just an anti-VEGF, physicians tend to use that.

One thing that's in the pipeline for DME is a port delivery system of ranibizumab, which is currently in clinical trials for AMD.[73] The phase 2 LADDER trial included 220 patients, with 58, 62, 59, and 41 patients randomized to a port delivery system containing 10 mg/mL, 40 mg/mL, and 100 mg/mL of ranibizumab and the monthly intravitreal ranibizumab 0.5-mg arm, respectively. The port delivery system was well tolerated and demonstrated a dose response across multiple endpoints in patients with AMD. The 100 mg/mL arm had visual and anatomic outcomes comparable with monthly intravitreal ranibizumab 0.5-mg injections, but with a reduced total number of ranibizumab treatments.[73] At 6 months, using its highest dose, 80% of the patients did not need a refill in the trial. A phase 3 study is currently in recruitment. I think that device is going to give us a way to deliver a continuous dose of anti-VEGF for up to 6 months at a time.

If the system proves successful in AMD, you could potentially have an implant for DME that releases a low level of anti-VEGF over a 6-month period, which would be the better way to go.

DR. SHARMA: The most interesting thing from LADDER was that the median time to refill for that highest dose, which is the dose they're proceeding with, was 15 months.[73] The phase 3 trial is designed for refill every 6 months, but it may last much longer than that. That said, even if you can get to 6 months, that would be a huge improvement for patients. The down side is that it is a surgically implanted procedure during which the conjunctiva has to be taken down and you make an incision down to the choroid. You then laser the choroid and insert the small implant into the eye. It can be refilled in the office transconjunctively. The biggest issue in the phase 1 and phase 2 studies in terms of side effects were vitreous hemorrhage. However, the implantation procedure was changed for the phase 2 trial, which decreased the vitreous hemorrhage rate to about 5%.[73]

There were additional side effects as well, such as irritation, conjunctival hyperemia, and conjunctival erosion. We're hopeful that with a better surgical technique, including closing both tenons and conjunctiva, you won't have those issues.

A clear biopolymer (KSI-301) with anti-VEGF embedded in it is about to enter phase 2 studies. The company completed a 12-week phase 1a of KSI-301 in nine patients with severe DME in 2018.[74] Eight of the nine patients responded, with improvement in baseline vision, anatomy, or both as quickly as 1 week after the injection. The treatment effect increased through 4 weeks and resulted in a median improvement in best corrected visual acuity (BCVA) of 12.5 letters and median improvement in central retinal thickness on OCT of 120 µm. At 12 weeks, patients had a median BCVA improvement of 9 letters and median OCT improvement of 121 µm.[74]

"Abicipar pegol, which is designed for dosing every 8 to 12 weeks, is also being studied, and top-line results from two positive phase 3 trials in 2018 were recently released."

—SUMIT SHARMA, MD

Phase 3 studies for extended dosing of brolucizumab, up to 12 weeks were just completed.[75] The HAWK and HARRIER trials showed that brolucizumab was noninferior to aflibercept in visual function at week 48, and more than 50% of patients treated with brolucizumab 6 mg were maintained on a 12-week dosing interval through week 48. Anatomical outcomes favored brolucizumab over aflibercept, but overall safety was similar between both agents. The ability to reliably assess the likelihood of patients remaining on quarterly dosing could help physicians and patients better manage, personalize and optimize treatment plans.[75]

Abicipar pegol, which is designed for dosing every 8 to 12 weeks, is also being studied, and top-line results from two positive phase 3 trials in 2018 were recently released. Abicipar is currently the only anti-VEGF agent to maintain stable vision in 91% of patients on a fixed 12-week regimen. The clinical trials achieved their primary endpoint of noninferiority to monthly ranibizumab at week 52 and demonstrated the efficacy of 12-week abicipar dosing with 50% fewer injections versus ranibizumab.[76] The hope is these products will be available in late 2019.

Q | DR. SINGH: Are there any barriers to the adoption of a new agent like abicipar?

DR. SHARMA: For abicipar, the big concern is the increased rate of intraocular inflammation. The MAPLE study showed a reduction compared to the original phase 3 study, but it may be still higher than the other anti-VEGF agents.[77] If that's the case, that's a concern. I'll be interested to see the full data once it's released. I think cost will play a role as well, as will physician comfort. Although we're very excited to try the new medicines, if you have a patient who has been

stable for years on one treatment, there may be some resistance from both the physician and the patient to switch.

DR. SINGH: Is bevacizumab your first-line treatment, or do you start with some of the newer agents like ranibizumab or aflibercept?

DR. SHARMA: I start everyone on bevacizumab, but my hospital self-compounds the agent. That's a big concern for a lot of clinicians; do you have access to well-compounded bevacizumab that you can trust? That's not the case everywhere.

DR. CALLANAN: One of the biggest issues for us in retina is step therapy. The government, Medicare, and Centers for Medicare & Medicaid Services are evaluating the possible mandate that we use a drug that has never been approved for use in the eye as our first-line therapy for patients with AMD. We're going to be forced to use compounded bevacizumab in Medicare patients, even though commercially available versions are safer. In addition, the newer agents will allow for fewer injections compared with bevacizumab.

DR. SHARMA: The compounding pharmacy challenge is a major issue. Studies have shown there are lower rates of endophthalmitis with a prefilled syringe versus syringes you fill yourself immediately before the injection.[78] It can be very difficult to know if the compounded bevacizumab that you're getting is safe. In addition to endophthalmitis, there's a concern for silicone oil droplets, which can be visually significant and cause glaucoma. It's going to be interesting to see how the landscape changes in the next few years.

DR. SINGH: Is there a situation in retina where the sustained delivery is too long?

DR. CALLANAN: When it comes to AMD, there are the one-hit-wonder patients. They get one injection and stay dry for a long period of time. Those patients don't need a sustained delivery. Longer acting or sustained-release devices are better for the patients who seem to constantly need anti-VEGF therapy. I don't see too much of a downside to sustained delivery in diabetic patients as long as there's not an increase in the side effects.

SUSTAINED-RELEASE DEVICES FOR CATARACT SURGERY

Q | **DR. SINGH:** There have been exciting changes and new advances in the cataract world in relation to drug delivery. We're going to have multiple drug-delivery platforms that help decrease the drop burden in cataract patients, which is huge. Noncompliance can be an issue in the cataract surgery world as well. In my practice, complaints of postoperative drops are the most common cause of dissatisfaction following cataract surgery.

Recently, the FDA approved dexamethasone intraocular suspension 9% for postoperative inflammation (EyePoint Pharmaceuticals).[79,80] The proprietary sustained-release drug delivery technology delivers a biodegradable extended-release formulation of dexamethasone is delivered into the eye with a single injection at the end of surgery. The steroid is released with the highest concentrations in the first 2 weeks, then with a naturally decreasing concentration over the next 2 weeks. This is similar to what clinicians do with topical steroids. Eliminating issues with patient compliance and adherence with the steroid is important because many tapering of steroids can be confusing and frustrating for many patients. Do you think sustained drug delivery will be used more in the cataract space?

DR. MYERS: I think patients would embrace true dropless surgery if it's affordable and equally safe. Many alternatives we've had for so-called dropless cataract surgery are not entirely dropless and some of the methods by which they have to be applied aren't convenient or don't give surgeons confidence. However, there are newer alternatives that may augment drops and improve convenience for some patients and outcomes for other less adherent patients. Some of these newer options will be very exciting and may also have a potential role after glaucoma surgery.

DR. SINGH: Just recently I performed my first few dozen intracameral injections of dexamethasone intraocular suspension 9% in standard cataract cases and in a couple of patients with combined cataract and MIGS. In the phase 3 trials, they found no significant difference in IOP spikes between intracameral dexamethasone and topical formulations of prednisolone.[79,80] There was also significant reduction of anterior chamber inflammation at day 8 compared to placebo, and 60% of patients had zero cell and flare. That was encouraging to see. So far in our practice, the results look good. I was also surprised the placement of the drug was fairly straight forward and was comforting not to have to place it in the vitreous but rather behind the iris in the anterior chamber.

Recently, a dexamethasone intracanalicular implant was approved by the FDA for postoperative pain. The corticosteroid insert is placed in the punctum and is designed to deliver dexamethasone to the ocular surface for up to 30 days without topical drops or preservatives. Following treatment, the plug resorbs and exits the nasolacrimal system without the need for removal.[81,82] One big advantage of the intracanalicular implant is the ability to place the implant in the office either pre- or postoperatively and remove it if needed.

Thank you all for your comments and insights into the current landscape of sustained-release devices for the management of chronic eye diseases. ■

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SUSTAINED-RELEASE DEVICES FOR THE TREATMENT OF CHRONIC EYE DISEASES

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DEMOGRAPHIC INFORMATION

Profession
___ MD/DO
___ OD
___ NP
___ Nurse/APN
___ PA
___ Other

Years in Practice
___ > 20
___ 11-20
___ 6-10
___ 1-5
___ <1

Patients Seen Per Week (with the disease targeted in this educational activity)
___ 0
___ 1-15
___ 16-30
___ 31-50
___ 50+

Region
___ Northeast
___ Northwest
___ Midwest
___ Southeast
___ Southwest

Setting
___ Solo Practice
___ Community Hospital
___ Government or VA
___ Group Practice
___ Other
___ I do not actively practice

Models of Care
___ Fee for Service
___ ACO
___ Patient-Centered Medical Home
___ Capitation
___ Bundled Payments
___ Other

LEARNING OBJECTIVES

DID THE PROGRAM MEET THE FOLLOWING EDUCATIONAL OBJECTIVES?	AGREE	NEUTRAL	DISAGREE
Assess data from the latest clinical studies on sustained-release devices and methods.	_____	_____	_____
Describe the benefits and challenges of sustained-release devices and methods versus conventional treatments.	_____	_____	_____
Identify the various sustained-release devices on the market and in the pipeline.	_____	_____	_____
Evaluate how to incorporate sustained-release devices into treatment regimens.	_____	_____	_____

POSTTEST QUESTIONS

1. **PLEASE RATE YOUR CONFIDENCE ON YOUR ABILITY TO APPLY UPDATES IN SUSTAINED-RELEASE DEVICES IN THE CLINIC BASED ON THIS ACTIVITY (BASED ON A SCALE OF 1 TO 5, WITH 1 BEING NOT AT ALL CONFIDENT AND 5 BEING EXTREMELY CONFIDENT).**
   a. 1
   b. 2
   c. 3
   d. 4
   e. 5

2. **AFTER COMPLETING THIS ACTIVITY, HOW OFTEN DO YOU INTEND TO USE SUSTAINED-RELEASE DEVICES FOR THE MANAGEMENT OF PATIENTS WITH CHRONIC EYE DISEASES (BASED ON A SCALE OF 1 TO 4, WITH 1 BEING NEVER AND 5 BEING ALWAYS).**
   a. 1
   b. 2
   c. 3
   d. 4
   e. 5

3. **THE ADVANCED GLAUCOMA INTERVENTION STUDY SHOWED THAT FLUCTUATION IN INTRAOCULAR PRESSURE (IOP) LED TO AN INCREASED RATE OF VISUAL FIELD PROGRESSION BY WHAT PERCENTAGE?**
   a. 10%
   b. 20%
   c. 30%
   d. 40%

4. **WHICH ONE OF THESE IS NOT CONSIDERED A BARRIER TO GLAUCOMA DROP COMPLIANCE?**
   a. First-time prescriptions do not get filled
   b. Adding a second drop to improve compliance rates
   c. Elderly patients need multiple attempts to get drops into the eye properly
   d. Medication costs

5. **MOST CLINICIANS DO NOT USE SELECTIVE LASER TRABECULOPLASTY (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

6. **ALL OF THE FOLLOWING SUSTAINED-RELEASE DRUG DELIVERY SYSTEM ARE DESIGNED TO RELEASE DRUG FOR 36 MONTHS *EXCEPT*?**
   a. 0.7-mg dexamethasone Intravitreal implant
   b. 0.19-mg fluocinolone acetonide implant
   c. 0.18-mg fluocinolone acetonide implant
   d. 0.59-mg fluocinolone acetonide implant

7. **WHAT IS THE RECOMMENDED FIRST-LINE TREATMENT FOR A PATIENT WITH DIABETIC MACULAR EDEMA?**
   a. Dexamethasone injection followed by a 3-year fluocinolone implant
   b. Anti-VEGF monotherapy
   c. Combination dexamethasone and anti-VEFG therapy
   d. 3-year fluocinolone implant

8. **WHICH ANTI-VEGF AGENT WAS FOUND IN CLINICAL STUDIES TO MAINTAIN STABLE VISION IN 91% OF PATIENTS WITH NEOVASCULAR AGE-RELATED MACULAR DEGENERATION (AMD) ON A FIXED 12-WEEK REGIMEN?**
   a. Ranibizumab
   b. Aflibercept
   c. Brolucizumab
   d. Abicipar pegol

9. **WHICH OF THESE TREATMENTS IS COMMONLY USED AS THE FIRST-LINE TREATMENT FOR A PATIENT WITH NEOVASCULAR AMD?**
   a. Intravitreal anti-VEGF therapy
   b. Photodynamic therapy
   c. Steroids
   d. Laser photocoagulation

10. **A PORT DELIVERY SYSTEM FOR RANIBIZUMAB FOR AMD IS CURRENTLY IN CLINICAL TRIALS. THE LADDER TRIAL DEMONSTRATED THAT THE MEDIAN TIME TO REFILL FOR THE HIGHEST DOSE WAS _____.**
    a. 5 months
    b. 10 months
    c. 15 months
    d. 20 months

ACTIVITY EVALUATION/SATISFACTION MEASURES

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):

_____ Cost

_____ Lack of administrative support

_____ Lack of time to assess/counsel patients

_____ Reimbursement/insurance issues

_____ Patient compliance issues

_____ Lack of consensus or professional guidelines

_____ Lack of experience

_____ Lack of opportunity (patients)

_____ Lack of resources (equipment)

_____ No barriers

_____ Other. Please specify: _____

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

The content supported the identified learning objectives. ___ Yes ___ No

The content was free of commercial bias. ___ Yes ___ No

The content was relative to your practice. ___ Yes ___ No

The faculty was effective. ___ 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:

_____ Patient Care

_____ Practice-Based Learning and Improvement

_____ Professionalism

_____ Medical Knowledge

_____ Interpersonal and Communication Skills

_____ System-Based Practice

Additional comments:

_____

_____ 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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