THE EMERGENCE OF BREAKTHROUGH PROCEDURAL PHARMACEUTICAL THERAPIES



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ABSTRACT:

Although topical medications are the most common treatment for many ocular conditions, their utility can be limited by local and systemic side effects, ocular surface disease, difficulty with self-administration, diminished quality of life, high rates of nonadherence, and negative impact on future surgical outcomes. In the context of these limitations, procedural pharmaceuticals have emerged which alleviate the burden of self-administration from the patient. Procedural pharmaceuticals have existed in some ophthalmic subspecialties, such as retina, for several years; while in others, such as glaucoma, their use is relatively novel. This article summarizes the impact that procedural pharmaceuticals have had across glaucoma, retina, uveitis, and genetic ophthalmic diseases, as well as practical implications such as coding and administration that their implementation entails.

INTRODUCTION:

Across all ophthalmic subspecialties, the overarching goal is to preserve or improve vision. Depending on the disease state, treatments have typically involved topical medications, laser procedures, and/or incisional surgery(ies). More recently, this treatment armamentarium has been augmented by the emergence of an increasing number of procedural pharmaceutical therapies. Procedural pharmaceuticals are therapies that combine an active drug agent with an implant or administration modality in order to deliver treatment to targeted tissues or anatomical structures. A key benefit of procedural pharmaceuticals is that they are designed to allow active pharmaceutical agents to be delivered continuously in a 24/7 manner to targeted tissues at indicated doses, some with a sustained duration. They also are not affected by the adherence issues that limit the efficacy of many other ocular treatments. Using this augmented armamentarium, it is increasingly possible to deliver optimized care that reduces the topical medication burden and improves quality of life. This article will discuss the impact that procedural pharmaceutical therapies have on clinical practice and patient care and how they are changing standard of care across ophthalmic specialties, including glaucoma, retina, uveitis, and genetic diseases.

PROCEDURAL PHARMACEUTICALS IN GLAUCOMA:

As agents with different mechanisms of action and novel drug delivery devices become approved and available, the feasibility of providing safe and individualized management at earlier stages in the disease process is able to be realized. Using glaucoma treatment as an example, topical therapy traditionally has maintained a stronghold as first-line treatment for more than a century, despite barriers like suboptimal adherence and associated side effects. Patients may be non-adherent to treatment due to a lack of knowledge, forgetfulness, difficulties with drop instillation, apathy, and intolerance to side effects.[1,2] Such non-adherence to topical glaucoma treatment has been associated with worsening visual field outcomes and disease progression.[3]

In light of these limitations, in recent years, the treatment paradigm has been shifting toward a more proactive "interventional glaucoma" approach.[4-8] Such an approach includes the adoption of novel drug delivery devices and minimally invasive surgical and laser techniques in order to lessen the burden of multiple times-per-day topical drug use. Procedural interventions no longer need to be reserved for eyes that have progressed due to a suboptimal response to drops. Clinicians now have the opportunity to take action earlier, limiting disease progression. As long-term data emerge and clinical experience grows, topical therapies are being questioned as the default first-line choice, allowing the responsibility of adherence to be lifted from patients.

The most recent addition to the procedural pharmaceutical armamentarium in glaucoma management is the IDOSE TR® intracameral implant, from Glaukos Corporation (Aliso Viejo, California), consisting of a titanium reservoir, an anchor, and an eluting membrane that delivers a proprietary formulation of the prostaglandin analog, travoprost, in a controlled and sustained manner directly to the target tissues. IDOSE TR is typically administered in an ambulatory surgery center under local anesthetic. In clinical studies, >80% of patients receiving IDOSE TR were free of IOP-lowering topical medications at 12 months;[9,10] and at 36 months, 69% of IDOSE TR eyes were well controlled on the same or fewer topical IOP-lowering medications vs preoperative, compared to 45% that received topical timolol, twice daily.[11] The intracameral implant is designed to provide continuous delivery of steadily-maintained therapeutic levels of travoprost, removing the occurrence of the peaks and troughs of topical therapy and their associated fluctuations in IOP.

There is also a free-floating biodegradable bimatoprost implant, DURYSTA® (Allergan and AbbVie, North Chicago, Illinois), which provides sustained delivery of bimatoprost. DURYSTA is inserted under aseptic conditions into the anterior chamber via a 28-gauge needle injector, typically in an office or small procedure room. In clinical studies, one implant demonstrated IOP reduction for 15 weeks.[12]

PROCEDURAL PHARMACEUTICALS IN RETINAL DISEASES:

Intravitreal injections of anti-vascular endothelial growth factor (VEGF) and other targeted agents have become the most common ocular procedure

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performed worldwide.[13] They have revolutionized the management of a spectrum of retinal diseases, demonstrating stabilized or improved vision, dramatically improving prognoses for millions. Additionally, treatment can be individualized, guided by the patient's clinical response in order to optimize outcomes. Key limitations to anti-VEGF medications include the need for repeat injections, often at short time intervals (e.g. 1-3 months for many), with associated risks such as endophthalmitis, vitreous hemorrhage, and elevated IOP. Some of the newer agents may allow for longer intervals between doses.

Intravitreal anti-VEGF agents are most often used to treat common retinal vascular disorders, including diabetic retinopathy (DR), neovascular age-related macular degeneration (nAMD), diabetic macular edema (DME) and retinal vein occlusion (RVO). The first on-label entry into the anti-VEGF landscape was LUCENTIS® (ranibizumab; Genentech, South San Francisco, California), approved to treat nAMD in 2006 based on data from the landmark MARINA and ANCHOR trials, followed by EYLEA® (aflibercept; Regeneron, Tarrytown, New York) in 2011, following data from the VIEW studies.[14-16] Both ranibizumab and aflibercept would later be approved for the treatment of DME and RVO. The next agent to enter the space was in 2019, with the approval of BEOVU® (brolucizumab; Novartis, Basel, Switzerland) and most recently, VABYSMO® (faricimab; Genentech), a bispecific antibody that targets both VEGF-A and angiopoietin-2 (Ang-2). VABYSMO was evaluated in the TENYA and LUCERNE studies for nAMD and YOSEMITE and RHINE for DME, receiving FDA approval in 2022.[17,18]

In addition to these more common indications, a recent approval offers a new treatment for our smallest and youngest patients. EYLEA (aflibercept) recently became the first intravitreal injection to receive approval for treatment of infants with retinopathy of prematurity. Although anti-VEGF injections of different agents at various volumes and doses have been used off label for many years, this procedural pharmaceutical now offers an effective on-label alternative to laser photocoagulation and its associated drawbacks in these premature infants.

Under two years ago, there were no approved options to treat the millions of eyes losing vision as a consequence of non-neovascular ("dry") AMD. Now, however, there are two procedural pharmacotherapies available. Recent approvals of intravitreal SYFOVRE® (pegcetacoplan; Apellis Pharmaceuticals, Inc., Waltham, Massachusetts), a C3 inhibitor, and IZERVAY® (avacincaptad pegol; Astellas Pharma US, Inc., Northbrook, Illinois), a C5 inhibitor, have allowed clinicians to offer treatment to patients with geographic atrophy secondary to AMD. These medications have demonstrated significant reduction in the growth of geographic atrophy lesions by up to 20% in the OAKS, DERBY and GATHER trials, by inhibiting the complement system, which has been implicated in the pathogenesis and progression of geographic atrophy.[19,20] However, the benefit on long-term vision retention remains unclear.[21]

Despite effectiveness of intravitreal injection therapy, frequent readministration can be a burden to patients and practices, and there are recognized challenges with patient compliance with treatment schedules.[22] We also now appreciate the benefits of maintaining a steady level of therapy, and the long-term consequences to structure and outcomes when fluctuations continue to occur. Short-duration intravitreal treatments can allow edema to recur, resulting in fluctuations in retinal thickness and subsequent retinal damage over time.[23,24] For these reasons, drug delivery systems such as SUSVIMO® (Genentech) Port Delivery System with ranibizumab (PDS) were designed for the continuous delivery of ranibizumab into the vitreous for 6 months and beyond. This implant is indicated for nAMD, and was shown in the ARCHWAY clinical study to achieve equivalent vision gains to patients receiving monthly ranibizumab injections, and more than 98% went six months before their first refill.[25]

Two other sustained-release procedural pharmaceuticals are the fluocinolone acetonide intravitreal implant (ILUVIEN®; Alimera Sciences, Inc., Alpharetta, Georgia) and dexamethasone intravitreal implant (OZURDEX®; Allergan and Abbvie), which can be administered in an in-office procedure and deliver continuous microdosing therapy with a corticosteroid for up to 3 years to treat eyes with DME.

PROCEDURAL PHARMACEUTICALS IN UVEITIS:

Intravitreal implants that harness targeted drug delivery at high concentrations for a prolonged period can be highly advantageous to manage posterior segment inflammation. OZURDEX (mentioned above) is approved for treatment of non-infectious uveitis; RETISERT® (fluocinolone acetonide intravitreal implant; Bausch + Lomb, Rochester, NY) is approved for treatment of chronic non-infectious uveitis affecting the posterior segment and is anchored surgically to the sclera; while YUTIQ® (fluocinolone acetonide; Alimera Sciences, Inc.) has the same indication, but does not require surgical delivery as it can be administered intravitreally in the clinic setting via a 25 gauge injector. RETISERT approval was based on two clinical trials of patients with chronic non-infectious uveitis, demonstrating reductions in recurrence rates from 40-54% prior to study entry, to 7-14% within the 34 week post-implantation period.[26] The 36-month, phase 3 clinical trial for YUTIQ demonstrated significantly lower uveitis recurrence rates at 6 months (28% vs 91%), 12 months (38% vs 98), and 36 months (66% vs 98%) compared to the control group.[27]

PROCEDURAL PHARMACEUTICALS IN GENETIC DISEASES:

An emerging treatment in ophthalmology is gene therapy, targeting a 'one and done' strategy for many common conditions, including AMD, DME and DR, with many products working their way through the pipeline. Examples include Ixoberogene soroparvovec (formerly ADVM-022) from Adverum Biotechnologies (Redwood City, CA), currently in phase II trials being developed for the treatment of nAMD; this utilizes vector capsid, AAV.7m8, carrying an aflibercept coding sequence. ATMOSPHERE and ASCENT are two currently enrolling pivotal trials of subretinally delivered ABBV-RGX-314 (Regenex Bio, Rockville, MD) in patients with nAMD; and AAVIATE and ALTITUDE are phase II trials evaluating suprachoroidal delivery of ABBV-RGX-314 for nAMD and DR. Currently, LUXTURNA® (Voretigene neparvovec; Spark Therapeutics, Inc., Philadelphia, Pennsylvania) is the only U.S. FDA-approved gene therapy for ocular disease. It is indicated for inherited retinal dystrophy caused by an RPE65 gene mutation. It is delivered in the operating room, via subretinal injection, while the patient is under anesthesia.

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TABLE 1.

Procedural Pharmacotherapy	Indication	J-code
GLAUCOMA		
IDOSE TR® (travoprost intracameral implant)	reduction of IOP in open-angle glaucoma or ocular hypertension	J7355
DURYSTA® (bimatoprost implant)	reduction of IOP in open-angle glaucoma or ocular hypertension	J7351
RETINA		
LUCENTIS® (ranibizumab) Intravitreal injection	neovascular AMD, macular edema following RVO, DME, diabetic retinopathy, and myopic choroidal neovascularization	J2778
EYLEA® (aflibercept) Intravitreal injection	neovascular AMD, macular edema following RVO, DME, diabetic retinopathy, and retinopathy of prematurity	J0178
VABYSMO® (faricimab) Intravitreal injection	neovascular AMD, DME, and macular edema following RVO	J3590
BEOVU® (brolucizumab) Intravitreal injection	neovascular AMD and DME	J0179
SYFOVRE® (pegcetacoplan) Intravitreal injection	geographic atrophy secondary to AMD	J2781
IZERVAY® (avacincaptad pegol) Intravitreal injection	geographic atrophy secondary to AMD	J2782
ILUVIEN® (fluocinolone acetonide) implant	DME	J7313
OZURDEX® (dexamethasone intravitreal implant)	macular edema, non-infectious uveitis, and DME	J7312
UVEITIS		
RETISERT® (fluocinolone acetonide implant)	chronic non-infectious uveitis affecting the posterior segment of the eye	J7311
YUTIQ® (fluocinolone acetonide implant)	chronic non-infectious uveitis affecting the posterior segment of the eye	J7314
GENETIC		
LUXTURNA® (voretigene neparvovec)	vision loss due to confirmed biallelic RPE65-mediated inherited retinal disease	J3398

AMD, age-related macular degeneration; DME, diabetic macular edema; IOP, intraocular pressure; RVO, retinal vein occlusion.

ADMINISTRATION/CODING:

Safe and effective treatments that are minimally invasive and fit easily into a clinic workflow are very attractive additions to any practice. An important consideration as we move toward the utilization of more procedural pharmaceutical therapies is the implementation of associated J-Codes in order to ensure the drug component of administering these therapies is covered appropriately. First and foremost, it is important to note that the process of coding and billing for procedural pharmaceuticals is fundamentally different from that of device-based surgery. J-codes are permanent reimbursement codes used by government payers and commercial insurers to facilitate billing of Medicare Part B treatments. They are specific to each individual medication or drug – each of which has an assigned price that has been reached through a comprehensive and educated appraisal of the drug's potential impact and utility. J-codes simplify the billing, coverage and reimbursement processes, allowing for efficient claims processing. Streamlining the billing processes of procedural pharmaceuticals enables broader access and more reliable coverage for the patients who would benefit from these treatments. A table listing the procedural pharmaceuticals discussed in this article, along with their indications and J-codes, is provided above (Table 1).

CONCLUSION

Minimally invasive interventions such as procedural pharmaceuticals are providing the opportunity for the ophthalmic community to take action and intervene at earlier stages in progressive and degenerative diseases, including in glaucoma, retinal, uveitic, and genetic disorders. Earlier intervention allows for greater potential to preserve and even improve visual function in these conditions. In addition to earlier intervention, these treatments are addressing many of the challenges that have burdened patients and clinicians for years. In some cases, procedural pharmaceuticals have provided therapy where none existed previously. The demonstrated durability of some procedural pharmacotherapies in glaucoma and retinal disease means that effective drug concentrations can be delivered continuously and directly to target tissues,

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thereby alleviating adherence issues. Less frequent follow-up also reduces the manpower demands on practices, and J-codes streamline the coding and billing process.

With the growing array of minimally invasive interventions such as procedural pharmaceuticals, clinicians are shifting toward taking earlier action and applying longer-term solutions. Across ophthalmology, this is steadily shifting how our ophthalmic patients are managed. This emergence and acceptance of procedural pharmaceutical therapies into clinical practice ultimately has the potential to improve how optimized care is delivered to benefit patients. ■

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IMPORTANT SAFETY INFORMATION:

Indications And Usage

iDose TR (travoprost intracameral implant) is indicated for the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma (OAG) or ocular hypertension (OHT).

Dosage And Administration

For ophthalmic intracameral administration. The intracameral administration should be carried out under standard aseptic conditions.

Contraindications

iDose TR is contraindicated in patients with active or suspected ocular or periocular infections, patients with corneal endothelial cell dystrophy (e.g., Fuch's Dystrophy, corneal guttatae), patients with prior corneal transplantation, or endothelial cell transplants (e.g., Descemet's Stripping Automated Endothelial Keratoplasty [DSAEK]), patients with hypersensitivity to travoprost or to any other components of the product.

Warnings And Precautions

iDose TR should be used with caution in patients with narrow angles or other angle abnormalities. Monitor patients routinely to confirm the location of the iDose TR at the site of administration. Increased pigmentation of the iris can occur. Iris pigmentation is likely to be permanent.

Adverse Reactions

In controlled studies, the most common ocular adverse reactions reported in 2% to 6% of patients were increases in intraocular pressure, iritis, dry eye, visual field defects, eye pain, ocular hyperaemia, and reduced visual acuity.

Please see full Prescribing Information.

You are encouraged to report all side effects to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

You may also call Glaukos at 1-888-404-1644.

PRESCRIBING INFORMATION:

https://www.idosetrhcp.com/wp-content/uploads/2024/01/iDose-TR-Prescribing-Information.pdf

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