Are Eye Drops Dead?

New Medical Delivery Systems for Glaucoma

James D. Brandt, M.D.
Professor of Ophthalmology & Vision Science
Vice-Chair for International Programs and New Technology
Director, Glaucoma Service
Tschannen Eye Institute
University of California, Davis

Financial Disclosures

- Allergan
  - Consulting
    - Proposed PI of planned Phase 3 clinical trial of the bimatoprost sustained-release ring insert
    - Forsight Vision5 Laboratories (acquired by Allergan in 2016)
      - Research Support
        - PI of Phase 2 clinical trial of the bimatoprost sustained-release ring insert
      - Travel support
- Aerie Pharmaceuticals
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- Carl Zeiss Meditec
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- Graybug Vision
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- National Eye Institute
  - PI of UC Davis Clinical Center for the Ocular Hypertension Treatment Study (OHTS) 20 year follow-up study
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The Treatment Paradox

Highly effective treatments for glaucoma and ocular hypertension exist…

- Prostaglandin Analogues (PGAs) Reduce the Likelihood of Progression by 34 - 42% / year\(^1\)
  - Approved by FDA in 1990s; Excellent Safety Profile
- PGAs are widely used as 1\(^{st}\) line treatment\(^2\)

2. Calculated as follows: IMS data shows 14.25MM Rx’s in 2012 for PGAs in USA. Mean medication possession ratio = 0.64 (Friedman et al., Invest Ophthalmol Vis Sci 2007;48:5552–5557). ((14.25MM)/12 months)/0.64 Rx/Pt/Month = 1.9MM patients
Non-Adherence in Glaucoma

…but our patients don’t take their drops

– Non-adherent glaucoma patients represent a large unmet need: >50%* of patients
– Physicians are notoriously poor at identifying poorly-adherent patients†

* Newman-Casey et al. Patterns of glaucoma medication adherence over four years of follow-up Ophthalmology 2015;122:2010-2021


Non-Adherence in Glaucoma

Sustained release (SR) delivery of glaucoma medications may help address this challenge
SR has the potential to provide long-term IOP lowering *without the need for daily dosing*.

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**Why Sustained Release?**

- May reduce several barriers to treatment adherence
  - Struggling to get drops into the eye
Drops aren’t easy

Video clips courtesy of Alan Robin, M.D. – Baltimore MD

Drops aren’t easy

Video clips courtesy of Alan Robin, M.D. – Baltimore MD
Why Sustained Release?

- May reduce several barriers to treatment adherence
  - Struggling to get drops into the eye
  - Remembering multiple daily doses
  - Adverse effects caused by preservative exposure to ocular surface or surrounding tissues

The SR Balancing Act

- **Efficacy & Duration**
- **Ease of Use**
- **Tolerability (patient acceptance)**
- **Consistency of Effect**
- **Reversibility**
- **Safety**
- **Persistence (patient replaceable)**
• Glaucoma is a slowly-progressive disease
  – For *early* disease (and ocular hypertension), *safety must be the highest priority*
    • In the OHTS the NNT (number needed to treat) was 20

• What is an acceptable NNH (number needed to harm)?
The SR Balancing Act

- Glaucoma is a slowly-progressive disease
  - For *early* disease (and ocular hypertension), *safety must be the highest priority*
    - In the OHTS the NNT (number needed to treat) was 20
  - What is an acceptable NNH (number needed to harm)?
    - For *advanced* disease, a modest safety penalty may be acceptable to achieve higher efficacy & duration of action

The SR Glaucoma Pipeline*

<table>
<thead>
<tr>
<th>Implantable</th>
<th>External</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subconjunctival</td>
<td>Cornea</td>
</tr>
<tr>
<td>- Erodible drug pellets</td>
<td>- Contact lens</td>
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<tr>
<td>- Drug-containing microspheres</td>
<td>- Drug-eluting punctal plug</td>
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* Based on publicly-available information as of mid-2019
The SR Glaucoma Pipeline*

**Implantable**
- Subconjunctival
  - Erodible drug pellets
  - Drug-containing microspheres
  - Mechanical reservoir (device)
- Intraocular
  - Intravitreal
  - Suprachoroidal
  - Intracameral (erodible & device)

**External**
- Cornea
  - Contact lens
- Punctal
  - Drug-eluting punctal plug
- Conjunctival (cul-de-sac)
  - Drug-eluting ring
  - Microsphere-containing polymer gel

* Based on publicly-available information as of mid-2019

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**The Sustained Release Pipeline**

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**FIGURE 3.** Gonioscopic photographs of bimatoprost sustained-release implant 10 μg in the anterior chamber of an eye of a representative patient diagnosed with open-angle glaucoma at (Left) 2 weeks, (Center) 9 months, and (Right) 12 months after injection.
**Bimatoprost SR**

**Study week**

![Graph showing Mean change from baseline IOP (mm Hg) with different study weeks.](image)

- **Bimatoprost SR 6 µg (N = 18)**
- **Bimatoprost SR 10 µg (N = 21)**
- **Bimatoprost SR 15 µg (N = 21)**
- **Bimatoprost SR 20 µg (N = 16)**
- **Topical bim 0.03% all fellow eyes (N = 75)**

*P ≤ .001 vs baseline for all postbaseline values*


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**Bimatoprost SR**

**Mean IOP in Patients Receiving the Bim SR 10- or 15-µg Dose Strengths Without Rescue or Retreatment**

![Graph showing Mean IOP in patients receiving Bimatoprost SR 10- or 15-µg dose strengths.](image)

- **Bim SR 10 µg (n=21)**
- **Bim SR 15 µg (n=21)**
- **Bim 0.03% (10-µg group; n=21)**
- **Bim 0.03% (15-µg group; n=21)**

*Analysis based on observed values with data censored at rescue or retreatment*

Bimatoprost SR – Phase 3 Studies

• Bimatoprost SR q16 weeks versus daily timolol drops
• Primary endpoint: IOP change from baseline at Week 12
• Two matching studies
• Enrollment ongoing

ClinicalTrials.gov Identifier: NCT02247804, NCT02250651

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Bimatoprost SR – Phase 3 Studies

• Bimatoprost SR q16 weeks versus selective laser trabeculoplasty (SLT)
• Primary endpoint: IOP change from baseline during 24 weeks
• Two matching studies
• Enrollment ongoing

ClinicalTrials.gov Identifier: NCT02636946, NCT02507687
NDA for Bimatoprost SR

- New Drug Application (NDA) filed 7/17/2019
- Detailed Phase 3 data not yet public, press statement* only:

In the two Phase 3 ARTEMIS studies, Bimatoprost SR reduced intraocular pressure (IOP) by 30 percent over the 12-week primary efficacy period, meeting the predefined criteria for non-inferiority to the study comparator. The ARTEMIS studies evaluated 1,122 subjects on the efficacy and safety of Bimatoprost SR versus timolol, a FDA standard comparator for registrational clinical trials, in patients with open-angle glaucoma or ocular hypertension. After 3 treatments with Bimatoprost SR, greater than 80 percent of patients remained treatment free and did not need additional treatment to maintain IOP control for at least 12 months. Bimatoprost SR was well tolerated in the majority of patients.


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**Glaukos Travoprost SR device**

- Titanium implant containing 6+ month supply of travoprost
- Placed and re-placed surgically, anchors in the trabecular meshwork

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**Average IOP Reductions from Baseline through Month 12**

Timolol group required 31% more medications on average, compared to Dose cohorts.

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Travoprost XR (ENV515)

- Intracameral erodible platform delivering travoprost
- PRINT® technology permits production of <100 nm particles to >1 mm implants
- Early Phase 2 data (ARVO 2017*) demonstrated sustained IOP lowering out to 11 months (5 patients)
- Aerie Pharmaceuticals purchased the rights to PRINT® Technology for glaucoma and retinal applications (October 2017)

*S navratil t, conley j, verhoeven rs et al. Extended PGA Delivery Results in Significant Drug Sparing Compared to Topical PGAs and Achieves Sustained IOP Lowering for 11 Months without Any Loss of Efficacy. ARVO 2017

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### Punctal Plug drug delivery

![Punctal Plug Implant](image)

Source: Ocular Therapeutix
http://www.ocutx.com/pipeline/travoprost-punctum-plug

![Punctal Plug Implant](image)

Source: http://www.matitherapeutics.com/pipeline

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Bimatoprost Ocular Insert

- Simple, non-invasive ocular insert – rests under eyelids
- Easily applied by the eye care provider
- Impregnated with bimatoprost; preservative-free
- Not bioabsorbable – replaced by physician q6 months
- Can be designed to carry more than 1 drug (bimatoprost + timolol ring recently completed Phase 1)

Brandt JD, Sall K, Dubiner H et al.
Six-Month IOP Reduction with a Topical Bimatoprost Ocular Insert: Results of a Phase II Randomized Controlled Study
Ophthalmology 2016;123(8):1685-1694

Brandt JD, Sall K, Dubiner H et al.
Long-term Safety and Efficacy of a Sustained-Release Bimatoprost Ocular Ring
Ophthalmology 2017;124(10):1565-1566

Placement Procedure

Filmed at the Sall Research Medical Center
Results (Diurnal IOP):
Observed Efficacy through 13 months

Rescue therapy IOPs censored

Not Rescued, %: 100% 100% 100% 100% 100% 91% 88% 83%

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Reality Check
SR Platforms *are* coming in 2020

Questions to Ask about **ALL** the SR Platforms
Considerations for all SR Platforms

**How predictable is the duration of action?**

- If a sustained release drug is labeled for 6 months, when do you need to bring patients back for monitoring or re-dosing?

---

**Duration of action**

- **Baseline (injection)**
- 1 week
- 1 month
- 2 months
- 4 months
- 6 months
- 9 months

Target IOP
Duration of action

Target IOP

Baseline (injection) 1 week 1 month 2 months 4 months 6 months 9 months

Follow-up for Repeat dosing
Duration of action

Target IOP

Duration of action

Target IOP

Follow-up for Repeat dosing
**Duration of action**

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**Target IOP**

**Follow-up for Repeat dosing**

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**Considerations for all SR Platforms**

**Glaucoma ≠ AMD or DME**

- “Treat & Extend” paradigm won’t work in glaucoma
  - Patients **do** fall through the cracks & fail to return on time
  - Even poorly-compliant AMD or DME patients will usually initiate a return visit when their vision starts to drop
- Our patients don’t know when their IOP is rising
  - Home tonometry may help with this part of the challenge
Considerations for all SR Platforms

What if the patient has a drug side-effect?
  – All SR platforms in the pipeline use one of the three major PGAs
  – Eyes at risk of CME are excluded from pivotal trials
  – Will you go to the OR to remove a pellet or implant from a patient developing CME?

Considerations for all SR Platforms

What if the patient needs more than one drug?
OHTS

- Despite its modest (20%) IOP target, ~ 50% of OHTS subjects required 2 or more medications to reach target
- This was true even for those originally in the observation group, who were started on PGAs half way through the study

Considerations for Injectables

**Workflow concerns**
- Glaucoma is usually bilateral
  - Each patient will typically need 2 injections
  - Will you inject both eyes on the same day?
- What about patients requiring multiple drugs?

**Safety Concerns**
- How many injections can a cornea take?
  - Platform(s) may remain months after drug is gone
- Effect on endothelial counts?
- Cumulative risk of endophthalmitis
Conclusions

Are Eyedrops Dead?
Are Eyedrops Dead?

• Serious hurdles to adoption will have to be sorted out, e.g.
  – safety frequency & timing of office visits
  – clinic flow & logistics
  – reimbursement models

Are Eyedrops Dead?

Eyedrops aren’t going away soon…
Are Eyedrops Dead?

Eyedrops aren’t going away soon…

… but today’s pace of innovation suggests that by 2030, eyedrops will not be the primary method of glaucoma treatment, supplanted by:

- SR platforms
- Primary SLT*
- Better stand-alone MIGS