New Options Shaking Up The Glaucoma Treatment Paradigm

The Grand Canyon Regional Ophthalmology Meeting

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Disclosures

• New World Medical, C
• Aerie Pharmaceuticals, S
Glaucoma Treatment

- IOP-lowering is the only proven method to prevent development and/or progression of glaucoma

- Neurovascular protection, gene therapy on the horizon
What’s the Evidence?

- EMGT\(^1\)
  - 1 mm Hg IOP-lowering → 10% reduced risk of visual field progression

- Significant increase in glaucoma risk with every 3 mm Hg increase in IOP\(^2\)


Setting a Treatment Target

- Range of IOPs at which further glaucomatous damage unlikely

- Based on stage of disease as well as IOP level at which damage has occurred

- Remains an *estimate* for low risk of disease progression
# Target Based on Disease Stage

<table>
<thead>
<tr>
<th>Glaucoma Stage</th>
<th>Initial Target Reduction</th>
<th>Relevant Clinical Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ocular Hypertension</td>
<td>20%</td>
<td>OHTS</td>
</tr>
<tr>
<td>Early/Mild Glaucoma</td>
<td>&gt;30%</td>
<td>EMGT, CIGTS</td>
</tr>
<tr>
<td>Moderate/Severe Glaucoma</td>
<td>40-50%</td>
<td>AGIS</td>
</tr>
<tr>
<td>Normal Tension Glaucoma</td>
<td>30%</td>
<td>CNTGS</td>
</tr>
</tbody>
</table>
Choosing an Initial Agent

- Considerations:
  - Efficacy
  - Side Effects
  - Cost
  - Dosing Schedule
  - Preservative Load
First-Line Therapy

- Prostaglandin Analogues
  - Good efficacy (25-30%) with single agent
  - Minimal risk of systemic side effects
  - Once daily dosing regimen
• 410 randomized patients
• Primary outcome = mean IOP change at week 12
• Similar IOP reduction in all 3 groups (P<0.001)
What Next?

Adjunctive Therapy Market:
- Non-PGA Products
  - CAI: 8%
  - AA: 10%
  - Non-PGA Fixed Combo: 15%
  - BB: 14%

Initial Therapy Market:
- PGA Products
  - Latanoprost: 33%
  - Travoprost: 9%
  - Bimatoprost: 10%

PGA: Prostaglandin analogue; BB: Beta Blocker; AA: Alpha Agonist; CAI: Carbonic Anhydrase Inhibitor
Source: IMS MIDAS. IMS NPA
New Options!

• Netarsudil 0.02%

• Netarsudil 0.02%/Latanoprost 0.005%

• Latanoprostene Bunod 0.024%
Netarsudil 0.02%
Rho-Kinase

Disruption of Actin Stress Fibers

1) Decrease outflow resistance
2) Decrease aqueous production
3) Decrease episcleral venous pressure
Clinical Efficacy

• ROCKET-1 & ROCKET-2 Studies
  
  • Double-masked, randomized, multicenter, phase 3 trials
  
  • Netarsudil 0.02% qdaily vs. timolol 0.5% bid in patients with IOP > 20 mm Hg and < 25 mm Hg (post-hoc endpoint for ROCKET-1)
  
  • Primary efficacy at 8AM, 10AM, 4PM time points at week 2, week 6, month 3

Netarsudil Efficacy Summary
Netarsudil Efficacy Summary

• ROCKET-1
  • Netarsudil: 20.6-22.4mmHg → 16.2-18.2mmHg (15-22% reduction)
  • Timolol: 20.5-22.5mmHg → 17.0-17.9mmHg (17-22% reduction)

• ROCKET-2
  • Netarsudil: 20.4-22.5mmHg → 16.7-18.2mmHg (16-21% reduction)
  • Timolol: 20.7-22.5mmHg → 15.7-17.6mmHg (18-23% reduction)
Prior PGA Use $\rightarrow$ Greater Response
Adverse Effects

• Conjunctival hyperemia (50-53%)
• Conjunctival hemorrhage (13.3-15%)
• Cornea verticillata (5.4-9%)
Case

• 67 yo WF self-referred to transition glaucoma care

• Hx POAG OU tx’d with PGA and dorzolamide

• Timolol intolerance (hair loss)

• Tmax = mid-20s OU

• Mild Glare OU at night
Case

- **VA**
  - OD: 20/20: -0.74+0.25x075
  - OS: 20/25: plano

- **IOPs**
  - OD: 19 mm Hg
  - OS: 17 mm Hg

- **CCTs**
  - 543 um OD, 559 um OS

- **SLE**: 1-2+ NS cats OU

- **Gonio**: Schaeffer II-III x 360
Optic Discs
OCT RNFL
Visual Fields
Case

• Assessment
  • POAG – moderate stage OD, mild stage OS
  • 24% reduction from baseline OD, 32% reduction from baseline OS

• PLAN
  • Suggest phaco/MIGS \(\rightarrow\) patient defers
  • Start Netarsudil OU QHS with goal additional 10-15% lowering
Case – Follow-up

- Follow-up IOPs
  - OD: 14, 12 mm Hg (48% reduction)
  - OS: 14, 14 mm Hg (44% reduction)
Netarsudil/Latanoprost
Efficacy
Adverse Effects

• Conjunctival hyperemia (587%)

• Cornea verticillata (15.4%)

• Conjunctival hemorrhage (10.8%)
Mechanism of Action

• Prodrug metabolized by corneal esterase into
  1) latanoprost acid
  2) butaendiol mononitrate → Nitric Oxide

• Nitric Oxide relaxes trabecular meshwork cells to decrease outflow resistance

• Enhanced uveoscleral outflow via latanoprost
In Vitro Effects

Pooled Results vs. Timolol

Latanoprostene: 26.7mmHg → 17.8mmHg at 3 mos
Timolol: 26.5mmHg → 19.1mmHg at 3 mos
P<0.001

Latanoprostene vs. Latanoprost

![Graph showing the reduction in mean diurnal IOP (mm Hg) for different treatment groups. The graph indicates that Latanoprostene has a lower reduction in IOP compared to Latanoprost at the 0.005% concentration.](image)

- LBN 0.006%: -7.81 mm Hg
- LBN 0.012%: -8.26 mm Hg
- LBN 0.024%: -9.00 mm Hg
- LBN 0.040%: -8.93 mm Hg
- Latanoprost 0.005%: -7.77 mm Hg

Statistical significance:

* $P=0.005$ vs. Latanoprost

† $P=0.009$ vs. Latanoprost
Adverse Effects

• Conjunctival hyperemia
  ➢ Increase from 32.6% at baseline to 45.5% at 3 mos

➢ No significant increase in timolol comparator group
AGS 2019 – Real World Data

• Retrospective data from 5 tertiary care centers

• Netarsudil or Latanoprostene added as adjunctive therapy to 1-4 meds in 140 patients

• Unpaired t-test and ANOVA statistical analysis to compare outcomes
# AGS 2019 – Real World Data

<table>
<thead>
<tr>
<th></th>
<th>Netarsudil</th>
<th>Latanoprostene</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of eyes (patients)</strong></td>
<td>134 (98)</td>
<td>62 (42)</td>
</tr>
<tr>
<td><strong>Age in year (mean ± STDEV)</strong></td>
<td>63 ± 9 years</td>
<td>67 ± 12 years</td>
</tr>
</tbody>
</table>

## Change in IOP

<table>
<thead>
<tr>
<th></th>
<th>Netarsudil</th>
<th>Latanoprostene</th>
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</thead>
<tbody>
<tr>
<td><strong>Change in IOP</strong></td>
<td>3.53 (p &lt;0.0001)</td>
<td>3.27 (p&lt;0.001)</td>
</tr>
</tbody>
</table>

## % Reduction in IOP

<table>
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<tr>
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<tbody>
<tr>
<td><strong>% Reduction in IOP</strong></td>
<td>15.69</td>
<td>15.06</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>3% Upper</th>
<th>3% Upper</th>
</tr>
</thead>
<tbody>
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<td>Change in IOP</td>
<td>3.53 (p &lt;0.0001)</td>
<td>3.27 (p&lt;0.001)</td>
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<tr>
<td>% Reduction in IOP</td>
<td>15.69</td>
<td>15.06</td>
</tr>
<tr>
<td>Change log MAR BCVA</td>
<td>0.04 (p &lt;0.59)</td>
<td>0.014 (p&lt;0.92)</td>
</tr>
<tr>
<td># Patients stopped</td>
<td>Dec-98</td>
<td>Jul-42</td>
</tr>
<tr>
<td>Follow up duration in days (range)</td>
<td>54.3 (7-120)</td>
<td>82.9 (7-210)</td>
</tr>
</tbody>
</table>
AGS 2019 – Real World Data

Netarsudil

<table>
<thead>
<tr>
<th>Duration of therapy (days)</th>
<th>0 days</th>
<th>7 days</th>
<th>21 days</th>
<th>30 days</th>
<th>45 days</th>
<th>60 days</th>
<th>90 days</th>
<th>120 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracocular Pressure Lowering (mmHg)</td>
<td>NS</td>
<td>***</td>
<td>****</td>
<td>****</td>
<td>***</td>
<td>***</td>
<td>***</td>
<td>***</td>
</tr>
</tbody>
</table>

Latanoprostene Bunod

<table>
<thead>
<tr>
<th>Duration of therapy (days)</th>
<th>0</th>
<th>21</th>
<th>30</th>
<th>45</th>
<th>60</th>
<th>90</th>
<th>120</th>
<th>150</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracocular Pressure Lowering (mmHg)</td>
<td>*</td>
<td>***</td>
<td>*</td>
<td>***</td>
<td>**</td>
<td>****</td>
<td>*</td>
<td>**</td>
</tr>
</tbody>
</table>
24-hour IOP Lowering

• Peak IOP at night in most individuals

• Agents shown to lower IOP at night:
  ➢ Latanoprost
  ➢ Brinzolamide
  ➢ Fixed combination brinzolamide/brimonidine
  ➢ Netarsudil (pilot study, n=12)
Comparing Diurnal and Nocturnal Effects of Brinzolamide and Timolol on Intraocular Pressure in Patients Receiving Latanoprost Monotherapy

John H. K. Liu, PhD, Felipe A. Medeiros, MD, PhD, J. Rigby Slight, MD, Robert N. Weinreb, MD
Don’t Forget the Ocular Surface

- Preservative-free therapies
- Combination agents
- Oral agents
- Non-medical therapy
Sustained Drug Delivery
Bimatoprost Ring
Bimatoprost Ring Efficacy

• Mean IOP Lowering
  - Bimatoprost Ring: 3.2 to 6.4mmHg (≥ 20% reduction)
  - Timolol BID: 4.2 to 6.4mmHg

Bimatoprost Ring Adverse Effects

• Mucus Discharge (21.3% at 12 mos)

• Device Dislodgment (20.8% men, 5.2% women)

• Otherwise similar to PGAs
Sustained Release Punctum Plugs
Punctum Plugs

• Travoprost Punctum Plug (OTX-TP, Ocular Therapeutix, Bedford, MA)
  • Encapsulated travoprost within resorbable hydrogel rod
  • Hydrolysis over 90-day period
  • Fluorescein incorporated within rod for visualization
  • Phase 2b: 4.5-5.7 mm Hg reduction at 90 days
    • 88% retention at 75 days

• Latanoprost Punctal Plug Delivery System (Evolute, Mati Therapeutics, Austin, TX)
  • Latanoprost matrix surrounded by silicone
  • 20% IOP reduction and 92-96% retention at 90 days
Bimatoprost Intraocular Implant
Bimatoprost Intraocular Implant

- Bimatoprost SR: 7.2-9.5 mm Hg lowering at week 16
- Topical Bimatoprost 0.03%: 8.4 mm Hg lowering at 16 weeks

iDose Implant

- Titanium implant
- Filled with travoprost formulation
- Designed to elute drug over 1 year
- Replaceable drug reservoir
iDose Implant – Phase 2 Results

Mean IOP

<table>
<thead>
<tr>
<th>Implant</th>
<th>Week 12 Mean IOP</th>
<th>IOP Reduction At Week 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fast-Elution (n=51)</td>
<td>17.4 mm Hg</td>
<td>31%</td>
</tr>
<tr>
<td>Slow-Elution (n=54)</td>
<td>17.3 mm Hg</td>
<td>30%</td>
</tr>
</tbody>
</table>
• Questionnaire administered to 178 glaucoma patients

• Questions regarding barriers to medical care, receptivity to placement of sustained release device

• Collection of ocular history and demographics
Would you be receptive to placement of a sustained release device by a physician if this allowed for partial replacement of your eye drops?

Would you be receptive to placement of a sustained release device by a physician if this allowed for complete replacement of all your eye drops?
# Patient Perspectives, AGS 2019

<table>
<thead>
<tr>
<th>Barriers to Adherence</th>
<th>Complete Replacement of Eye Drops</th>
<th>Partial Replacement of Eye Drops</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost of Medication</td>
<td>1.20 (.15)</td>
<td>1.08 (.12)</td>
</tr>
<tr>
<td>Physical Instillation</td>
<td>1.24 (.23)</td>
<td>1.17 (.18)</td>
</tr>
<tr>
<td>Insufficient Medication</td>
<td>1.13 (.14)</td>
<td>1.02 (.11)</td>
</tr>
<tr>
<td>Remembering to Place Drops</td>
<td>1.22 (.22)</td>
<td>1.13 (.18)</td>
</tr>
<tr>
<td>Side Effects</td>
<td>.91 (.14)</td>
<td>.84 (.13)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Complete Replacement of Eye Drops</th>
<th>Partial Replacement of Eye Drops</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>.67 (.11)</td>
<td>.98 (.01)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>X2(3)=.805</td>
<td>X2(3)=.792</td>
</tr>
<tr>
<td>Number of Glaucoma Eye Drops</td>
<td>1.44 (.258)</td>
<td>1.60 (.28)</td>
</tr>
<tr>
<td>Severity of Disease</td>
<td>1.05 (.24)</td>
<td>1.18 (.26)</td>
</tr>
</tbody>
</table>

**Receptivity Table**

- **X2 or Odds Ratio**: The statistical measure used to assess the significance of the relationship between the variable and adherence.
- **p-value**: The probability of observing the difference by chance, with lower values indicating stronger evidence against the null hypothesis.
Glaucoma Treatment Paradigm

Disease Stage

MIGS

Therapy
Glaucoma Treatment Paradigm

Disease Stage

Therapy

MIGS

SR Tx
Thank you
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