Changing Paradigms in the Management of Glaucoma

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Disclosures

- Aeon
- Alcon
- Allergan
- AqueSys
- Calhoun Vision
- Carl Zeiss Meditec
- ForSight Labs
- Glaukos
- InnFocus
- IRIDEX
- Ivantis
- NeoMedix
- Ocular Therapeutix
- Ocunetics
- SOLX
- Transcend Medical
- TrueVision Systems
- WaveTec Vision
Case 1. Clinical History

• 72 y.o. man presents for regular yearly examination complaining of ocular redness, ocular FB sensation and difficulty reading fine print
• Past Ocular History: POAG OU
• Past Medical History: Coronary artery disease
• Family History: Multiple family members with POAG
• Medications: Timolol 0.5% OU QAM; Latanoprost OU QHS
Clinical Examination

- Best-corrected Visual Acuity: 20/30 OU, but does glare to 20/50 OU
- Manifest Refraction: -1.50 sphere OU
- Visual fields: Early arcuate defects OU
- Corneal Pachymetry: 540 um OD; 546 um OS
- Goldmann Tonometry: 23 mm Hg OU
- OHS: 0.7 OU with disc heme inferiorly OD
How do you recommend that we manage this patient?

1) Alter glaucoma medication regimen
2) Laser trabeculoplasty
3) Filtration surgery alone
4) Combined cataract and filtration surgery
5) Combined cataract and iStent surgery
Case 2. Clinical History

• 64 y.o. woman presents for regular yearly examination complaining of glare difficulty while driving at night
• Past Ocular History: unremarkable
• Past Medical History: systemic hypertension
• Family History: Maternal grandmother with chronic angle closure glaucoma
Clinical Examination

• Best-corrected Visual Acuity: 20/25 OU, but does glare to 20/50 OU
• Manifest Refraction: +2.50 sphere OU
• Visual fields: full OU
• Corneal Pachymetry: 520 um OD; 525 um OS
• Goldmann Tonometry: 22 mm Hg OU
Slit Lamp Examination

- 1-2 Nuclear Sclerosis OU
- Healthy ONHs OU (0.2 CDR OU)
Indentation Gonioscopy
How do you recommend that we manage this patient?

1) Close observation
2) Laser peripheral iridotomy
3) Laser peripheral iridoplasty
4) Cataract surgery alone
5) Cataract surgery combined with iStent
What Has Changed?

Improved Glaucoma Diagnostic Technology
Advances in Medical Therapy
Advances in Laser Technology
Advances in Incisional Surgery
Advances in OCT

- Advanced RPE Analysis
- Ganglion Cell Analysis
- GPA™ with Optic Nerve Head

Existing Cirrus Cube data
Ganglion Cell Analysis

- Measures thickness for the sum of the ganglion cell layer and inner plexiform layer (GCL + IPL layers) using data from the Macular 200 x 200
- or 512 x 128 cube scan patterns.

RNFL distribution in the macula depends on individual anatomy, while the GCL+IPL appears regular and elliptical for most normals. Thus, deviations from normal are more easily appreciated in the thickness map by the practitioner, and arcuate defects seen in the deviation map may be less likely to be due to anatomical variations.
Ganglion Cell Analysis

The analysis contains:

• Data for both eyes (OU)

• Thickness Map - shows thickness measurements of the GCL + IPL in the 6mm by 6mm cube and contains an elliptical annulus centered about the fovea.

• Deviation Maps - shows a comparison of GCL + IPL thickness to normative data.

• Thickness table - shows average and minimum thickness within the elliptical annulus.

• Sector maps - divides the elliptical annulus of the Thickness Map into 6 regions: 3 equally sized sectors in the superior region and 3 equally sized sectors in the inferior region. Values are compared to normative data.

• Horizontal and Vertical B-scans.
Ganglion Cell Analysis

Thicknes Map

Deviation Map

Deviation Map

Thicknes Map

Status:

ID Patent

Analysis

Finish
Guided Progression Analysis
Landscape of Medical Therapy

Persistence and Adherence With Topical Glaucoma Therapy

Poor patient compliance leads to diminished efficacy/disease progression

Difficulty in administration

Need for high drug concentrations

Preservatives can cause side effects

Advances in Medical Therapy

- Combination Medications
- Preservative Free Drug Alternatives
- Novel Drugs on Horizon
- Novel Drug Delivery Systems
Combination Medications

- Timolol-dorzolamide (Cosopt)
- Timolol-brimonidine (Combigan)
- Brinzolamide-brimonidine (Simbrinza)
Preservative Free Alternatives

- Ocudose Timolol
- Tafluprost (Zioptan)
- Timolol-dorzolamide (Cosopt PF)
- Compounded formulations
Drugs Under Investigation

- Nitric oxide-donating prostaglandins
- Rho-kinase (ROCK) inhibitors
Aqueous Humor Dynamics

IOP – A complex homeostasis

- Aqueous formation in ciliary body – passive diffusion, ultrafiltration and active secretion
- Conventional Outflow – Trabecular Meshwork → Schlemm’s Canal → Episceral Venous System
- Non-Conventional Outflow – Uveoscleral
AR-13324 (ROCK-NET Inhibitor) Triple-Action

3 Identified IOP-Lowering Mechanisms

- ROCK inhibition relaxes TM, increases outflow
- NET inhibition reduces fluid production
- ROCK inhibition lowers Episcleral Venous Pressure (EVP)
Quadruple-Action PG324 (ROCK-NET Inhibitor/latanoprost)

4 Identified IOP-Lowering Mechanisms

- ROCK inhibition relaxes TM, increases outflow
- NET inhibition reduces fluid production
- ROCK inhibition lowers EVP
- PGA receptor activation increases uveoscleral outflow
0.02% PG324 Achieved Statistical Superiority Over Individual Components at All Time Points (p<0.001)

Mean IOP at Each Time Point
Primary Efficacy Measure

PG324 Phase 2b, Intent to Treat
## PG324 (ROCK-NET Inhibitor/latanoprost)

<table>
<thead>
<tr>
<th></th>
<th>0.02% PG324 (n = 72)</th>
<th>0.005% latanoprost (n = 73)</th>
<th>0.02% AR-13324 (n = 78)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean</strong></td>
<td><strong>Mean</strong></td>
<td><strong>Difference</strong>*</td>
<td><strong>Mean</strong></td>
</tr>
<tr>
<td>Day 8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 AM</td>
<td>17.0</td>
<td>19.6</td>
<td>20.0</td>
</tr>
<tr>
<td>10 AM</td>
<td>15.6</td>
<td>18.3</td>
<td>18.0</td>
</tr>
<tr>
<td>4 PM</td>
<td>15.6</td>
<td>18.6</td>
<td>17.9</td>
</tr>
<tr>
<td>Day 15</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 AM</td>
<td>16.5</td>
<td>19.6</td>
<td>19.6</td>
</tr>
<tr>
<td>10 AM</td>
<td>15.8</td>
<td>18.3</td>
<td>18.7</td>
</tr>
<tr>
<td>4 PM</td>
<td>15.7</td>
<td>18.3</td>
<td>18.4</td>
</tr>
<tr>
<td>Day 29</td>
<td></td>
<td></td>
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<tr>
<td>8 AM</td>
<td>16.9</td>
<td>19.2</td>
<td>20.3</td>
</tr>
<tr>
<td>10 AM</td>
<td>15.9</td>
<td>17.7</td>
<td>18.6</td>
</tr>
<tr>
<td>4 PM</td>
<td>16.8</td>
<td>18.4</td>
<td>18.5</td>
</tr>
</tbody>
</table>

* Difference between 0.02% PG324 and latanoprost or AR-13324

- **0.02% PG324 superior to latanoprost by 1.6–3.2 mmHg (p<0.001)**
- **0.02% PG324 superior to AR-13324 by 1.7–3.4 mmHg (p<0.001)**
Most Common AE in PG324 Phase 2b was Conjunctival Hyperemia

Asymptomatic, Transient, Self Limited

80% of Hyperemia was graded Mild by Biomicroscopy
Summary

- Targets diseased tissue – Trabecular Meshwork
- Lowers EVP
- Reduces AH production
- + latanoprost (PG324) ↑ uveoscleral outflow

Positive Phase 2 Study Results

- AR-13324 0.02% QD
  - Consistent IOP reduction independent of baseline pressure
- PG324 0.02% QD
  - Significantly better IOP lowering than latanoprost or AR-13324 0.02%
- Hyperemia rates similar to prostaglandin analogs
Advances in Drug Delivery

- Injectable
- Contact lenses
- Punctal plug delivery
- Other implantable systems
Anecortave Acetate Injection
Drug Eluting Punctum Plugs

Expected Punctum Plug Benefits:

– Sustained delivery over time
– Improves compliance
– Vastly reduces dosing frequency
– Reduces patient burden
– May improve safety/efficacy

Graph showing:
- Topical Drops
- Drug Concentration
- Time
- Greatest risk of side effects
- Sustained delivery over time
- Therapeutic Levels
- Greatest risk of lack of efficacy
# Eluting Plugs Under Investigation

<table>
<thead>
<tr>
<th></th>
<th>Biodegradable Plugs</th>
<th>Classic Plugs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug capacity</strong></td>
<td>Higher capacity</td>
<td>Lower capacity &lt;sup&gt;(1)&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Drug release</strong></td>
<td>Adjustable, consistent release rate</td>
<td>High initial release rate which decreases over time</td>
</tr>
<tr>
<td><strong>Plug design</strong></td>
<td>Drug encapsulated in pliable hydrogel; incorporates fluorescent label for patient visualization</td>
<td>Drug core within hard plastic shell</td>
</tr>
<tr>
<td><strong>Patient experience</strong></td>
<td>Soft plug sits beneath punctal opening</td>
<td>Foreign body sensation due to protrusion of plastic cap</td>
</tr>
<tr>
<td><strong>Absorption</strong></td>
<td>Bioresorbable material</td>
<td>Non-absorbable material</td>
</tr>
</tbody>
</table>

1. Clinical trial required use of two plugs per eye to achieve clinically meaningful results, which caused epiphora.
Non-Absorbable Eluting Punctal Plug

Existing drugs

Proprietary plugs

Proprietary insertion tool
Biodegradable Eluting Plug

Product Design

• Disease-specific, tailored drug release and plug persistence

Procedure (1)

• Easy to insert, familiar procedure to physicians (2)
• Upon insertion, shrinks in length and expands in width
• Non-invasive
• Absorbable – no need for removal

1. Drug-eluting punctum plugs are investigational new drugs and not commercially available in the United States or other geographies
2. Based on clinical trials conducted and on physician experiences with commercially available punctum plugs for the treatment of dry eye
Replenish Intraocular Pump
Stores 3 to 9 months volume of drug molecule or biologic
Biocompatible materials
Minimally Invasive Implant uses established surgical procedures for glaucoma setons
Metered dose with +/- 5% accuracy
Anterior chamber or intravitreal drug delivery
Multiple year (5-10) lifetime of implant
Avoids systemic / local side effects of drug; fast mode of action
# Advances in Laser Technology

<table>
<thead>
<tr>
<th></th>
<th>ALT</th>
<th>SLT</th>
<th>MLT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Wavelength</strong></td>
<td>488/514 nm, 532 nm</td>
<td>532 nm</td>
<td>532 nm, 577 nm, 810 nm</td>
</tr>
<tr>
<td><strong>Mechanism</strong></td>
<td>Shrinkage of TM with adjacent stretching</td>
<td>Selective destruction of pigmented TM cells without thermal or collateral damage</td>
<td>Thermally effects - not destroys - pigmented TM cells without thermal or collateral damage</td>
</tr>
<tr>
<td><strong>Repeatable</strong></td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Treatment Endpoint</strong></td>
<td>Blanching (mild) to bubbles (intense)</td>
<td>Yes</td>
<td>None</td>
</tr>
<tr>
<td><strong>Post op inflammation</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>None</td>
</tr>
<tr>
<td><strong>Spot Size</strong></td>
<td>50 µm</td>
<td>400 µm</td>
<td>300 µm</td>
</tr>
<tr>
<td><strong>Complications</strong></td>
<td>PAS, IOP spikes</td>
<td>IOP spikes</td>
<td>Minimal</td>
</tr>
</tbody>
</table>
Why Laser Trabeculoplasty First?

• Medical Compliance
  – Forgetfulness
  – Side effects
  – Cost of topical medications

• Efficacy of Procedure

• Quality of Life
Glaucoma Laser Trial (GLT)

- Proposed ALT as initial glaucoma therapy
- 44% patients controlled IOP without meds at 2 years
- 70% patients controlled by ALT alone or with timolol at 2 years
- Results controversial
Pathophysiology of Trabeculoplasty

• Mechanical Theory
  – Opening of aqueous channels by TM tissue shrinkage (not supported by histologic studies)

• Cellular or Biologic Theory
  – Migration of macrophages may clear debris in TM
  – Trabecular cell division enhanced
  – Expression of IL-1 and TNF-α may increase expression of stromelysin in juxtacanalicular TM
  – Upregulation of TM matrix metalloproteinases
ALT Technique

- 50 µm spot, 0.1 sec/burst, 400-1000 mW
- 180 or 360° treatment
- 20-25 laser spots per quadrant
- Laser burns equally spaced at anterior half of TM
ALT Results

• No uniform definition for success
• 90% have IOP lowering at 1 yr; 50% at 5 yrs; 20-30% at 10 yrs
• Optimal IOP lowering effect occurs by 4 to 6 weeks
• Multiple factors affect success
ALT: CW Pulse
Laser exposures can create high thermal rise resulting in photocoagulation

MLT: Meshwork architecture remains intact without the signs of coagulation as seen with ALT
SLT: available space for more content if needed

MLT: available space for more content if needed
SLT Technique

- Fixed spot size (400 microns)
- Fixed time (3 nanoseconds)
- Treat TM (large spot size covers angle)
- Applications confluent, not overlapping
- Adjust power to a slight blanch of TM or just at bubble formation (0.8-1.2 mJ)
- Treat 180-360 degrees
MLT Technique

- 300 μm spot (smaller spot than SLT accesses narrow angles)
- 300 ms
- 1000 mW
- 15% duty cycle
- 360° confluent treatment
- No visual signs of treatment during or post treatment
- ? provides comparable IOP-lowering effects as ALT and SLT with less energy and inflammation
Retrospective MLT Study

• 13 of the 33 patients responded to MLT utilizing a power of 700 mW with a decrease in IOP at 4+ months
• The average decrease in IOP in these responders was 23.2% at 4+ months
• An additional 2 patients resulted in the same IOP at 4+ months after a decrease by 1 class of anti-ocular hypertensive medications
MLT Early Observations

• No postop IOP spikes observed
• No postop anti-inflammatory medication required
• No perioperative glaucoma medication required
• Likely need to treat with 1000 mW power in most patients
Laser Options for Angle Closure

- Laser Iridotomy
- Laser Iridoplasty
- Endocycloplasty
Laser Iridotomy

- Indications
- Contraindications
- Technique
Indications for LPI

• Acute angle-closure glaucoma
• Chronic angle-closure glaucoma
• Aphakic or pseudophakic pupillary block
• Malignant glaucoma
• Occludable narrow angles
• Nanophthalmos
• Pigment dispersion syndrome (?)
Contraindications for LPI

- Corneal opacification
- Flat anterior chamber
- ≥180 degrees of PAS
- Angle closure cause by primary synechial closure (uveitis, NVG, ICE)
Iridotomy Technique

• YAG laser generally preferred
• Contact lens required
  – Abraham lens (+66 D planoconvex)
  – Wise lens (+103 D button)
• Use 2% pilocarpine preoperatively
• Use apraclonidine or brimonidine perioperatively
• Use topical steroid postoperatively
Iridotomy Location

- Classically placed between 11:00 & 1:00
- Temporal/nasal locations reasonable alternative
- Choose site beyond lens equator
- Perform LPI in base of iris crypt
- Traditionally 150-200 um size
Laser Iridotomy Outcomes

• Success* after LPI
  – PACS → 100%
  – PAC → 97%
  – PACG → 53%
  – Follow up = 1-3 yrs

*Success=no further surgery and no vision loss

Laser Peripheral Iridoplasty

- Indications
- Contraindications
- Technique
Iridoplasty Indications

• Recalcitrant acute angle-closure glaucoma
• Plateau iris syndrome
• Angle closure related to lens size or position
• Adjunct to laser trabeculoplasty
• Nanophthalmos
Iridoplasty Contraindications

- Advanced corneal edema or opacification
- Flat anterior chamber
- Synechial angle closure
Argon Laser Iridoplasty Technique

- Pretreat with pilocarpine
- 500 µ spot, 0.5 sec/burst, 200-400 mW
- Place 20 to 24 spots over 360 degrees as peripherally as possible
- Leave 2 spot diameters between each spot
- Avoid large visible radial vessels
- Use topical steroids postoperatively
Laser Iridoplasty
Laser Iridoplasty

Effective in opening the angle in many cases

Laser Iridoplasty

• Should you perform this in all cases of narrow/closed angle after LPI?
  – We don’t know

• Risks
  – More PAS, IOP spike
  – Is it effective?
    • Angle opening?
    • Preventing glaucoma?
Laser Peripheral Iridotomy With and Without Iridoplasty for Primary Angle-Closure Glaucoma: 1-Year Results of a Randomized Pilot Study

XIA SUN, YUAN BO LIANG, NING LI WANG, SU JIE FAN, LAN PING SUN, SI ZHEN LI, AND WEN RU LIU

• Beijing Tongren Eye Center
Results

- LPI: 77 eyes (61 at 1 yr)
- LPI + Iridoplasty: 81 eyes (65 at 1 yr)

- IOP
  - LPI: Pre-op 26.2, At 1 yr 19.6
  - LPI + Iridoplasty: Pre-op 29.0, At 1 yr 21.3
Results

• IOP
  – No significant difference in IOP reduction between groups

• Corneal Endo Cell counts
  – No difference pre- and post-laser

• Complications
  – No significant difference between groups
Results

• PAS
  – LPI 4.5 clock hours 3 clock hours
  – LPI + Iridoplasty 5 clock hours 2 clock hours
  – Iridotomy → Iridoplasty
    • 3 clock hours → 2 clock hours
    • PREVENTION OF 1 CLOCK HOUR OF PAS
Endocycloplasty

• Endolaser of the ciliary processes—cause shrinkage and posterior rotation
  – Goal—allow iris to retract, thus opening angle
  – Procedure—laser posterior part of ciliary processes
  – Generally combined with cataract extraction
Endocycloplastasty

Posterior treatment

Pre-op

Post ECPL+Phaco

Tam D. Rev Oph 2013
Angle Closure Summary

• Laser iridotomy first line
  – Unless ≥180 degrees of PAS

• Laser iridoplasty in select patients
  – Data lacking

• Endocycloplasty may be helpful in plateau iris
  – But phaco alone may be sufficient
Case Studies Revisited

- Case 1. Consider cataract surgery combined with MIGS procedure as next step
- Case 2. Consider cataract surgery alone as next step. ECP can be nice alternative to filtration surgery, especially in patients with plateau iris syndrome
Conclusions

• Diagnostic technology continues to improve and may allow for better early glaucoma detection and assessment of glaucoma progression

• Novel drug delivery systems potentially will improve patient issues related to medical compliance

• Laser surgery provides an excellent alternative to medical and incisional surgical options in select patients

• MIGS procedures may be performed with good facility and may expand the role of surgery in the management of glaucoma

• Comprehensive cataract surgeon can now expand practice into surgical glaucoma
Thank You