Disclosures

I have no financial relationships or conflicts of interest with the manufacturers of any commercial products in this presentation.

Overview

Glaucoma Background
- Challenges
- Historical surgical options

Recent Surgical Options
- MIGS

Future Surgical Options
- New Glaucoma Medications
- Future Glaucoma Delivery Systems
Glaucoma Treatment Challenges

- **Medications:**
  - Patient compliance
  - Cost: generics vs. branded
  - Side effects/irritation
  - Refill issues

- **Surgical:**
  - Complications
  - Failure (initial trabeculectomy =60-80%, 5 year =almost 50%)
  - Asymptomatic Variability and Reliability

The Majority of Patients with Glaucoma Are Noncompliant

Across multiple studies, it has been shown that the majority of patients do not take their glaucoma medications as prescribed by their doctor.

- In a study of over 5,500 managed care patients, 90% were noncompliant and more than 50% of patients failed to refill their initial prescription in the 1st year.
- 25% of patients in a US government health plan, with minimal out-of-pocket costs, failed to fill their second glaucoma prescription.
- In a separate trial, patients, on average, took their glaucoma medications only 7 out of 10 days.
- In a hospital based trial, 41% of patients who are compliant indicated that they experience challenges in paying for their medications.

Noncompliance is the number one reason for drug therapy failure.

Surgical Options (Open Angle Glaucoma)

- Shunt (Molteno, 1966. Baerveldt and Ahmed 1990’s)
- Trabeculectomy (1968)
- Laser Trabeculoplasty (ALT, 1979, SLT, 2001)
- ECP: Endoscopic Cyclophotocoagulation (1992)
- Ex-PRESS shunt (2002)
- Trabectome (2005)
- Canaloplasty (2007)
- MIGS: Micro or Minimally Invasive Glaucoma Surgery (2012)
Primary Source of Resistance: Diseased Trabecular Meshwork

- Abnormality of the trabecular meshwork (TM) is the primary source of elevated intraocular pressure (IOP) in open-angle glaucoma.
- 50-75% of total resistance to aqueous humor outflow is found in the juxtacanalicular tissue of the TM.
- Bypassing the TM allows access to Schlemm's canal and the distal system in order to improve aqueous outflow through the conventional outflow pathways.

Micro-Invasive Glaucoma Surgery (MIGS)
MIGS: Defined

- Ab-interno approach
  -- Clear corneal micro-incision (<2.0mm)
  -- Conjunctival sparing
- Minimally traumatic
  -- Negligible disruption of normal anatomy/physiology
  -- Excellent biocompatibility
- Efficacious
- Extremely high safety profile
- Rapid recovery


The iStent Trabecular Micro-Bypass Stent System

- 1st FDA approved MIG therapy (2012) :
  - Improves aqueous outflow through the natural physiologic pathway
    - Bypasses TM into Schlemm's Canal
- The iStent Trabecular Micro-Bypass Stent is indicated for use in adult patients with mild to moderate open-angle glaucoma for the reduction of intraocular pressure (IOP) in conjunction with cataract surgery

iStent Specifications

- Made of surgical-grade nonferromagnetic titanium
- Heparin-coated to promote self-priming

iStent is the smallest medical device known to be implanted in the human body and weighs just 60 µg
Microstenting Schlemm’s Canal
Advantages:

- Enhancement of natural physiological outflow
  - Decreases IOP and may reduce or eliminate medication burden
  - Decreases risk of IOP fluctuations
- Physiologic floor minimizes risk of hypotony
  (Natural episcleral venous pressure typically 8-11mm Hg)
- Lack of bleb or conjunctival manipulation
  - Does not preclude further glaucoma surgery if needed
- Minimal disruption of angle anatomy
  - Minimize risk related to cell damage, inflammation, fibrosis, PAS

Concomitant Cataract & Glaucoma Patients - US

3.5M US Cataract Procedures
One in Five Eyes with Cataract on OHT Medication
20.5% Cataract + Minimum of 1 OHT Med
79.5% Cataract Only


iStent Efficacy
Effect of Cataract Surgery on IOP Reduction

Chart review of 588 normotensive and OHT subjects
53% had a mean reduction of 1.6 to 2.5 mm Hg


Baseline IOP (mm Hg)

<table>
<thead>
<tr>
<th>IOP (mm Hg)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤23</td>
<td>18</td>
</tr>
<tr>
<td>24-25</td>
<td>274</td>
</tr>
<tr>
<td>26-27</td>
<td>8</td>
</tr>
<tr>
<td>28-29</td>
<td>0</td>
</tr>
<tr>
<td>≥30</td>
<td>0</td>
</tr>
</tbody>
</table>

iStent Pivotal US IDE Trial

Prospective, randomized, multi-centered study of POAG patients who underwent iStent + cataract surgery vs. cataract surgery (CE) alone.

290 subjects at 29 sites
240 randomized subjects with cataract and mild-to-moderate OAG
50 additional non-randomized subjects for safety

Patient population
Mild-to-moderate POAG (also PXE and PDS)
IOP ≤ 24 mm Hg on 1-3 medications
Post-medication washout IOP 22 – 36 mm Hg

Efficacy endpoints
Primary: IOP ≤ 21 mm Hg without medications at month 12
Secondary: IOP reduction ≥ 20% without medications at month 12
Follow-up through 2 years postoperative


Primary Endpoint
≤ 21 mm Hg IOP with no medications

18% more patients with CE plus iStent achieved target pressures of ≤ 21 mm Hg with no medications
17% more patients with CE plus iStent achieved ≥20% reduction in IOP with no medications.
Pre-operative Indications

- Concomitant cataract & glaucoma
  - Mild to moderate open angle glaucoma
  - Visually significant cataract to prevent examination
- Need to reduce medication burden
- Need for reduction of IOP fluctuations/better IOP control
- Need for preservation of future surgical options

Pre-operative Considerations

- Glaucoma workup
  - Visual field - Determination of severity of the glaucoma
  - Optic nerve head imaging/assessment
  - Pachymetry
  - IOPs
  - Gonioscopy - evaluating for synechia, iris processes, narrow anatomical angles, angle recession or any other abnormalities of the angle structure that may interfere with placement of the iStent
  - Anterior segment and Dilated fundus examination - rule out significant other ocular pathology

Contraindications:

- Closed/narrow angle
- Neovascular
- Angle recession
- Uveitic
- Anatomical variability
  - Lack of TM pigment making placement difficult
  - PAS, severe iris processes
Mechanism of Action: Anatomic Placement & Rationale

- Placed in inferonasal locations with high presence of collector channel congregations
- Designed to improve continuous, physiological outflow in the lower nasal quadrants
Complications:
- Microhyphema
- Tube positioning/stent obstruction (4%)
  - Iris blocking snorkel
  - Debris blocking stent
- IOP spike
- Treatment failure

Postop Management
- Same as with cataract surgery alone
  - Normal postop schedule (1 day, 1 week, 1 month)
  - Same postop medications
  - Hyphema—blurry vision
  - IOP spike/steroid responder—treated the same
  - Assessment of stent position—1 week gonioscopy
- “Final effect” on IOP not until 2-3 months postop

When do you consider discontinuing one or more glaucoma medications?
- Not until postop medications are finished
- 1-3 months
Suprachoroidal MIGS

- CyPass micro-stent (Alcon)- 6mm polyimide device, multiple fenestrations distal end
- iStent Supra (Glaukos)- 4mm device
- Good for pts with angle anomalies, easy to implant?

CyPass Micro-Stent (Alcon)

- Approved by FDA in August 2016
- 1st Suprachoroidal MIG
- Stent placed between the iris and scleral spur into the supraciliary space
- Advantages of stent in suprachoroidal space:
  - Large surface area = greater fluid absorption
  - Negative oncotic pressure = easier outflow from AC

CyPass Dimensions/Features

- 6.35 mm in length
- 510 µm in diameter
- Distal two-thirds fenestrated
COMPASS Study

- Number of U.S. sites: 24
- Patients: 565 enrolled, 480 completed
  - CyPass + cataract: 355
  - Cataract only: 125
- Follow-up: 2 years
- Primary endpoint:
  - Proportion of eyes with >20% reduction in IOP without medication at 2 years.

COMPASS Study Results:

<table>
<thead>
<tr>
<th></th>
<th>CyPass Micro-Stent + Cataract Surgery</th>
<th>Cataract Surgery Only</th>
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</thead>
<tbody>
<tr>
<td>Number of Participants Analyzed</td>
<td>374</td>
<td>131</td>
</tr>
<tr>
<td>Proportion of Eyes With ≥ 20% Decrease in Intraocular Pressure (IOP) From Baseline to the Hypotensive Medication-free 24-month Postoperative Examination</td>
<td>72.8</td>
<td>58.0</td>
</tr>
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COMPASS Study Results:

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<td>Number of Participants Analyzed</td>
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<td>131</td>
</tr>
<tr>
<td>Mean Change in IOP Between Baseline and Hypotensive Medication-free 24-month Postoperative Examination (units: mmHg)</td>
<td>-7.0 (4.53)</td>
<td>-5.3 (3.95)</td>
</tr>
</tbody>
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**COMPASS Study Results:**

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<td>Number of Participants Analyzed</td>
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<tr>
<td>Proportion of Eyes With Postoperative IOP ≥ 6 and ≤ 18 mmHg, as Measured by Goldmann Tonometry, at the Hypotensive Medication-free 24-month Postoperative Examination</td>
<td>61.2</td>
<td>43.3</td>
</tr>
</tbody>
</table>

**CyCLE study (Europe)**

- 136 Patients
- 15 sites
- 2 year follow-up data
- Two groups:
  - >21 mm Hg and on medication (uncontrolled) with CyPass + CE (51)
  - ≤21 mm Hg and on medication (controlled) with CyPass + CE (85)
- No Control group of CE alone
- 21% had prior surgical intervention including 6% Trabeculectomy

**CyCLE study results: (24 months)**

- **Cohort 1 (>21 mm Hg, uncontrolled)**
  - Mean IOP reduction from 25.5 (baseline) to 16.4
  - Medication reduced from 2.2 meds to 1.0 meds
- **Cohort 2 (<21 mm H g, controlled)**
  - Mean IOP reduction from 16.4 (baseline) to 16.1
  - Medication reduced from 2.0 meds to 1.1 meds
Potential complications:

- Hyphema
- Hypotony (6%)
- Myopic shift
- IOP spike (both initially and post 30 days)
- Iritis (greater than 30 days post-op)
  - COMPASS study: CyPass + CE = 8.6%, CE only = 3.8%
- Tube obstruction 2’ to PAS
- Endothelial Cell loss
  - Company pulled it from the market in August.

Subconjunctival MIGS

- Xen gel implant (AqueSys)
- 6mm gelatin tube, lumen size 45 µm;
  - Tested 33 µm, 160 µm
- Bypasses natural drainage pathway by shunting fluid from AC to subconjunctival space
- Ab interno approach
- Potential for lower IOPs like trab/tube shunts while minimizing hypotony and post op wound leaks.
Subconjunctival MIGS

- **Indications:** Refractory primary open angle glaucoma in which the patient has failed previous glaucoma surgeries or is on maximum tolerated medical therapy. Medicare requires an IOP of >20.

- **Xen gel Stent Efficacy summary:**
  - 30-41% reduction from pre-surgical medicated IOP.
  - Approximately 70-90% of patients needed fewer topical medications post-operatively at 1 year.
  - Efficacy varied based on stand alone vs. with CE, and with or without MMC.
  - Stand alone Xen45 vs. Trabeculectomy both with MMC
    - 354 (n=185 Xen, 169 Trab) eyes with no prior filtering surgery
    - Efficacy, failure rate and safety were equivalent between groups.

- **Xen gel complications**
  - Tube erosions
  - Hypotony
  - Choroidal effusion
  - Conjunctival scarring
  - Up to 30% will need 5FU injections and/or bleb needling
  - Use of MMC at time of implant reduces this risk.
  - Aqueous misdirection
  - Endophthalmitis

What’s Next?

Trabecular Bypass MIGS

- iStent Inject: 2nd generation
  - Easier to insert
  - Multiple stents (2) in one injector to improve IOP lowering
  - iStent SA (Stand alone)—same as iStent inject without CE
  - iStent Infinitie—3 stents and also stand alone procedure.

iStent Inject Efficacy

- IDE pivotal study: 505 eyes (n=387 iStent, n=118 CE alone) for 2 years
  - 71.8% vs 61.9% (difference of 10%) had 20% or greater reduction in unmedicated IOP
  - 64% vs 47% (difference of 17%) for original iStent
  - Medication free mean IOP reduction was 7 mmHg vs 5.4 (difference of 1.6)
  - 63.2% were on no medications
  - Mean reduction in medications from 1.6 to 0.4

- 3 year data:
  - 37% reduction in mean IOP from medicated pre-operative IOP.
  - Medications reduced from 2.9 to 0.5
iStent Inject SA Efficacy

- One, two or three stents
- 119 eyes (n = 38, 41, 40)
- 37 month endpoint showed mean IOP (unmedicated):
  - 17.4 vs 13.8 vs 14.2 mm Hg (baseline was 25.0 for all three groups)


Trabecular Bypass MIGS

- Hydrus Microstent (Ivantis)
  - 8 mm long nitinol alloy
  - Placed through trabecular meshwork into Schlemm’s canal
  - Acts as a scaffold for 3 clock hours of Schlemm’s canal with end extending into the A/C
  - Recently approved Aug. 2018
  - For Mild to Moderate Glaucoma

Hydrus Microstent

- Results (Horizon Trial)
  - 331 patients (556 globally), for 2 years
  - Comparing Hydrus with CE vs. CE alone
  - 20% or greater reduction in IOP: 79% vs 55% (24% difference)
  - Mean IOP reduction (after medication washout):
    - 7.9 mm Hg vs 5.2 mm Hg (2.7 mm Hg difference)
  - Medication free: 79% vs 53%
Hydrus Microstent

- Hydrus vs 2 iStents:
  - 152 patients for 12 months
  - Stand alone procedure
  - 73% (Hydrus) vs 47% (iStent) had a 20% or greater reduction in IOP
  - 47% (Hydrus) vs 24% (iStent) were medication free
  - Medication reduced by 62% (Hydrus) vs 37% (iStent)


Complications:
- 3.8% PAS causing obstruction
- 2.7% IOP elevated significantly
- 1.1% transient hyphema
- No cases of hypotony

Subconjunctival MIGS

- MicroShunt (InnFocus—soon to be Santen)
  - Ab Interno Tube shunt
  - Poly(Styrene-b-isobutylene-b-Styrene) (SIBS)
  - Implanted in over 250 patients worldwide
  - 3 year data (22 patients):
    - Mean IOP reduction from 23.8 to 10.7 (55% reduction)
    - 60% achieved an IOP of <14 mm Hg
    - 65% on 0.3 meds or less (44% on no medications)
    - 2 patients had hypotony (<6mm Hg) and
    - 2 with choroidal effusion (resolved within 3 months)
Where do MIGS fit in?

Surgical Decision Making As a Function of Glaucoma Severity

| Glaucoma Intervention Spectrum | Pharmacotheraphy | Laser Trabeculectomy | Filtration Surgery +/- CE
|--------------------------------|------------------|---------------------|------------------------
| Glaucoma Disease Spectrum | MIGS | MIGS +/- CE | Severe |

New Glaucoma Medications

Vyzulta (Latanoprostene bunod)

- Metabolized into Latanoprost acid and Butanediol mononitrate
- Butanediol releases nitric oxide which relaxes the TM
- Mechanism of action:
  - Trabecular meshwork outflow
  - Uveoscleral outflow
Vyzulta Efficacy

- 20-25% IOP reduction
- VOYAGER (Vyzulta vs latanoprost)
  - Mean IOP reduction greater with Vyzulta compared to latanoprost group
- CONSTELLATION, APOLLO, JUPITER
  - Vyzulta vs timolol
  - In all three studies, Vyzulta lowered mean IOP greater than timolol
  - Improved diurnal ocular perfusion pressure with Vyzulta

- Use in normotensive patients?
  - Small study in Japan showed a 27% reduction in IOP in normotensive patients

Vyzulta side effects

- Same as prostaglandins alone
  - Hyperemia
  - Eyelash growth
  - Burning
  - Periocular pigment changes? maybe
  - Orbital fat loss? maybe

Rhopressa (netarsudil)

- Inhibits Rho kinase (ROCK) and Norepinephrine transporter (NET)
- Mechanism of action:
  - Increases aqueous outflow by increasing perfusion through TM
  - Other mechanisms as well?
  - Lower episcleral venous pressure (ROCK inhibition)
  - Decrease aqueous production (NET inhibition)
- Synergistic with prostaglandin
  - Future combo product with netarsudil and latanoprost
Rhopressa Efficacy

- **ROCKET 2 Study:**
  - Similar efficacy as timolol, about 20% (5mm Hg) reduction in IOP
  - 1 mm Hg worse than latanoprost
  - Baseline IOP > 25 mm Hg: timolol had greater effect
  - BID dosing showed slightly greater effect, but with increased side effects

- Roclatan:
  - Phase 2b study showed: 34% reduction in IOP
  - 2 mm Hg more than latanoprost group alone

Rhopressa side effects

- Hyperemia 50%
- Vortex keratopathy (Verticillata) 20%

Future Glaucoma Delivery Systems

- Sustained Release:
  - Intracameral implants
  - Intravitreal
  - Intracameral
  - Sub-conjunctival or Sub-Tenon's
  - Punctal plug implants
  - Contact lens-like polymer

- Goal: 3-12 months of continuous effect with minimal complications and ease of insertion/removal
Questions?


https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4734795/