Glaucoma Disease Progression
Role of Intra Ocular Pressure

Is “Good Enough”, “Low Enough”? 

Dr. Shabbir Hussain
Glaucoma Diseases Progression Key Considerations

- Good number of patients may be diagnosed only after some damage to the optic nerve.
- Even when 40% of the nerve fibers are lost, patients can retain normal visual field\(^2\).
- 56% of all newly diagnosed patients in the US present with moderate Glaucoma (already suffered optic nerve damage) at the time of diagnosis\(^3\).
- Rate of disease progression can vary from patient to patient.
- Predicting the disease progression course is difficult.
Glaucoma Diseases Progression
Key Considerations

- Landmark studies like AGIS, OHTS, EMGT illustrate the benefit of IOP reduction in all types of Glaucoma patients regardless of the severity of disease\(^1,4-6\)

- Lowering intraocular pressure can
  - Prevent further progression of existing field damage
  - Prevent optic-nerve damage from progressing to visual field damage
  - Prevent ocular Hypertension from progression to nerve damage
Glaucoma Diseases Progression
High Risk Groups

- Patients on beta-blocker therapy for long time and experiencing “Drift”
- Patients who do not respond sufficiently to Latanoprost
- Patients who have not achieved their target IOP with current medications
- Patients with some visual field damage
- Patients with some optic nerve changes
- Patients on multiple drug therapy
- Patients with high baseline IOP
- Patients having more than one risk factor like heredity, Diabetes, Hypertension
Glaucoma Treatment:
Aim to Achieve and Maintain Lower Target Pressures and prevent disease progression

- Evidence from controlled, prospective, randomized clinical trials:
  Reducing IOP to lower target pressures can prevent glaucoma and slow or stop progression
  - OHTS
  - EMGT
  - CIGTS
  - CNTG
  - AGIS
Objective: To determine the safety and efficacy of topical medication in delaying or preventing the onset of glaucoma

1636 participants randomized to:

Observation or topical glaucoma medication
Lowering IOP:
Delays or Prevents the Development of POAG

Proportion of Participants Developing POAG

Hazard Ratio 0.40
95% CI (0.27, 0.59)
$P < .001$

Kass, 2002
IOP Lowering in OHT Reduces the Incidence of POAG

Kass, 2002

Untreated

Treated to Achieve 20% IOP Reduction and Target IOP ≤ 24 mm Hg

Incidence of POAG

0%
4%
8%
12%

9.5%

4.4%
OHTS Results
Arch Ophthalmol 2002; 120: 701

- 5 years

- Cumulative probability of POAG
  medication group = 4.4% (N = 817)
  observation group = 9.5% (N = 819)

- Endpoint > 50% optic disc alone (no VF loss)
Development of POAG – Observation Group

Baseline IOP (mm Hg)

- ≤ 23.75
  - ≤ 23.75: 17%
  - >23.75 to ≤ 25.75: 12%
- >23.75 to ≤ 25.75
  - >23.75 to ≤ 25.75: 36%
- >25.75
  - >25.75: 6%

Central Corneal Thickness (microns)

- ≤ 555
  - ≤ 555: 17%
  - >555 to ≤ 588: 9%
  - >588: 2%
- >555 to ≤ 588
  - >555 to ≤ 588: 10%
- >588
  - >588: 7%

Gordon, 2002
Risk Factors for the Development of POAG in OHT

<table>
<thead>
<tr>
<th>Factor</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per decade)</td>
<td>1.22 (1.01, 1.49)</td>
</tr>
<tr>
<td>IOP (per mm Hg)</td>
<td>1.10 (1.04, 1.17)</td>
</tr>
<tr>
<td>CCT (per 40 µM thinner)</td>
<td>1.71 (1.40, 2.09)</td>
</tr>
<tr>
<td>PSD (per 0.2 dB greater)</td>
<td>1.27 (1.06, 1.52)</td>
</tr>
<tr>
<td>Horizontal C/D Ratio (per 0.1 larger)</td>
<td>1.27 (1.14, 1.40)</td>
</tr>
<tr>
<td>Vertical C/D Ratio (per 0.1 larger)</td>
<td>1.32 (1.19, 1.47)</td>
</tr>
</tbody>
</table>

Gordon, 2002
Early Manifest Glaucoma Trial (EMGT)

- Objective: To compare the effect of immediate therapy to lower IOP versus late or no treatment on the progression of newly detected open-angle glaucoma

- 255 patients randomized to:

  Laser trabeculoplasty plus topical betaxolol or to no initial treatment
In treated patients, IOP was reduced 25% from a baseline of 20.6 mm Hg to 15.5 mm Hg at month 3.

Treatment was well-tolerated but associated with increased incidence of lens opacities.

Heijl, 2002
Early Treatment Reduces and Delays the Progression of Glaucoma

*Similar findings in patients with baseline IOP < 21 or > 21 mm Hg

Heijl, 2002
Fewer Treated Patients Have Glaucoma Progression

Incidence of Progression

Untreated: 62%
Treated: 45%

*P = .007

Heijl, 2002
Benefit of 1 mm Hg Additional IOP Lowering

- Each incremental 1 mm Hg decrease in IOP was associated with a:

  10% decrease in the risk of glaucoma progression

*Heijl, 2002*
Objective: To determine if newly diagnosed patients with open-angle glaucoma are better treated initially with medication or filtration surgery

- Medication group: n = 307
- Surgery group: n = 300
Medical Management vs Surgery
Both Lower IOP

Mean IOP (mm Hg)

Time in Months

Lichter et al, 2001
Medical Management vs Surgery
Both Effectively Prevent Visual Field Loss

Patients With ≥3 Unit Decrease in VF Score (%)

Time in Months

Lichter et al, 2001
Implications of EMGT and CIGTS:
Optimal Treatment for Early Glaucoma

- Patients with any field loss should be treated aggressively to reach low pressures that reduce the risk of progression

- Both medical treatment and surgery effectively reduce IOP and the risk of progression
  
  - No change in usual approach at this time (medical treatment first for most patients)
Objective: To determine if IOP-lowering treatment is effective in reducing the progression of normal-tension glaucoma

140 eyes randomized to:

Medical or surgical treatment (target 30% below baseline) or no Tx
Lowering IOP Reduces the Risk of Vision Loss in NTG

Mean IOP = 16.0 mm Hg
Mean IOP = 10.6 mm Hg

CNTG, 1998
Advanced Glaucoma Intervention Study (AGIS) 7

- **Objective:** To determine the effects of surgical and laser IOP-lowering procedures in glaucoma patients with IOP uncontrolled on medications

- **789 eyes**

- Analyses of IOP lowering and progression:
  - **Predictive:** Does IOP during first 1.5 years predict later visual field loss?
  - **Associative:** Are consistently low pressures associated with stable visual fields?
Consistently Low IOP Reduces Vision Loss in Advanced Glaucoma

AGIS, 2000

Mean IOP
- 0 to 50% of Visits < 18: 20.2 mm Hg
- 50 to 75% of Visits < 18: 16.9 mm Hg
- 75 to 100% of Visits < 18: 14.7 mm Hg
- All Visits < 18: 12.3 mm Hg
Low Target Pressure: Better Prognosis for Glaucoma Management

- Patients with IOP < 18 mm Hg (mean 12.3): no mean change in visual fields over 8 years
- Aggressive treatment had a more favorable outcome
  - Pressures in the low normal range may be needed for some patients who already have field loss
Management of Glaucoma

- Do corneal thickness testing on patients with: ocular hypertension or glaucoma
- Recognize: lower IOP = better prognosis
- Set a target pressure based on risk factors
- Prescribe therapy likely to reach the target pressure
- Monitor patients with serial visual field testing and optic nerve examination
Conclusions

- Reducing IOP can prevent, slow, and stop glaucoma.
- Decision to treat in OHT based on evaluation of the risk of glaucoma vs the risks and costs of treatment.
- Individualization of care necessary for setting a target IOP.
  - Include corneal pachymetry.
Conclusions

- The lower the IOP, the less the risk of glaucoma and field loss
  - Just 1 mm Hg additional IOP lowering can improve the prognosis
  - Multiple medications or surgery may be needed to reach target pressures

- Optimal glaucoma management:

  Treat early, treat aggressively, and, think long-term
Implementing What We Have Learned

Dr. Maj. Avinash Mishra
Choosing Glaucoma Therapy

- **Efficacy** = IOP lowering
  - Amount
  - Consistency
- **Safety**
  - Systemic side effects
- **Tolerability**
  - Local ocular effects
## In the Real World—What Therapy Should I Start First?

<table>
<thead>
<tr>
<th>Options</th>
<th>Advantage</th>
<th>Concern</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Beta-blocker</td>
<td>Tolerability</td>
<td>Safety</td>
</tr>
<tr>
<td>– Alpha agonist</td>
<td>Safety</td>
<td>Allergy</td>
</tr>
<tr>
<td>– Hypotensive lipid</td>
<td>IOP, Safety</td>
<td>Hyperemdia</td>
</tr>
<tr>
<td>Laser trabeculoplasty</td>
<td>Safety</td>
<td>Duration</td>
</tr>
<tr>
<td>Filtration surgery</td>
<td>IOP</td>
<td>Safety</td>
</tr>
</tbody>
</table>
Choosing Medical Therapy:
Monotherapy (Single Drug) Preferred

- If a single medication can get you at or below target without side effects, what is the advantage of getting to the same place with multiple medications?
- Are there disadvantages of multiple drug therapy?
Choosing Medical Therapy:
Monotherapy (Single Drop) Preferred Patient Considerations

- Convenience
  - Fewer drops to instill
  - No need to wait between instillation of multiple drops
- Less chance for mistakes
- Simple regimen enhances compliance
- Possible cost savings
Choosing Medical Therapy:
Monotherapy (Single Drug) Preferred Treating Physician Considerations

- Fixed combinations and 2-drug regimens have combined side effects of 2 medications
  - $1 + 1$ may even be $> 2$
  - If a problem—which agent responsible?
- Fewer drug interactions
- Less preservative corneal toxicity
Choosing Medical Therapy:
Monotherapy (Single Drug) Preferred Disease Considerations

- >30% reductions in IOP are possible
- Fewer medications means fewer potential side effects
- If on multiple agents and efficacy is inadequate, it is much more difficult to determine the contribution of each individual medication to the total.
Considerations in Choosing Monotherapy

- Efficacy
  - Mean IOP drop
  - Ability to get patient to target pressure
  - Responder rate

- Safety

- Tolerability

- Convenience

- Compliance

- Cost
Once-Daily Hypotensive Lipids Lower IOP Most Effectively

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Medication</th>
<th>Mean IOP Reduction*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha2 adrenergic</td>
<td>Brimonidine BID</td>
<td>4-6 mm Hg</td>
</tr>
<tr>
<td>Beta-blocker, NS</td>
<td>Timolol BID</td>
<td>[~ 6 mm Hg]</td>
</tr>
<tr>
<td>Beta-blocker, Sel</td>
<td>Betaxolol BID</td>
<td>4-5 mm Hg</td>
</tr>
<tr>
<td>CAI</td>
<td>Dorzolamide TID</td>
<td>3-5 mm Hg</td>
</tr>
<tr>
<td>Combination</td>
<td>Timolol / dorzolamide BID</td>
<td>More than either alone, less than dual therapy</td>
</tr>
<tr>
<td>Once-Daily Lipids</td>
<td>Latanoprost QD</td>
<td>6-8 mm Hg</td>
</tr>
<tr>
<td></td>
<td>Travoprost QD</td>
<td>7-8 mm Hg</td>
</tr>
<tr>
<td></td>
<td>Bimatoprost QD</td>
<td>7-8 mm Hg</td>
</tr>
</tbody>
</table>

*Values given in package insert prescribing information, PDR, or from clinical trials
Hypotensive Lipids Are Superior to Timolol in Lowering IOP

Values from FDA website
http://www.fda.gov/cder/foi/nda/index.htm
More Patients Reach Target Pressures With Bimatoprost Monotherapy

* $P \leq .010$ vs Timolol

Higginbotham et al, 2002
<table>
<thead>
<tr>
<th></th>
<th>Bimatoprost (Lumigan®)</th>
<th>Timolol / Dorzolamide (Cosopt®)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ocular AEs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conjunctival hyperemia</td>
<td>31 (34.4%)</td>
<td>15 (17.2%)</td>
<td>0.009</td>
</tr>
<tr>
<td>Burning eye</td>
<td>2 (2.2%)</td>
<td>12 (13.8%)</td>
<td>0.004</td>
</tr>
<tr>
<td>Stinging eye</td>
<td>2 (2.2%)</td>
<td>9 (10.3%)</td>
<td>0.025</td>
</tr>
<tr>
<td><strong>Non-ocular AEs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taste perversion</td>
<td>0 (0.0%)</td>
<td>5 (5.7%)</td>
<td>0.027</td>
</tr>
</tbody>
</table>

*All treatment-related AEs with incidence >5% and a significant between-group difference*
Bimatoprost Monotherapy Is as Effective as Timolol / Latanoprost

- Crossover study design
  - Patients received each regimen for 60 days

88 patients

Timolol / Latanoprost

83 patients

Bimatoprost Monotherapy

Day 0

Day 60 (Baseline)

Day 74

Day 120

Dirks et al, AGS, 2002
No Change in Mean IOP at 8 AM After Switching to Bimatoprost Monotherapy

Dirks et al, AGS, 2002
Equivalent Clinical Success With Bimatoprost Monotherapy and Timolol / Latanoprost

Timolol Gel and Latanoprost: 82.9%
Bimatoprost: 82.3%

Dirks et al, AGS, 2002
Summary

- Bimatoprost monotherapy controlled IOP in most patients previously treated with timolol gel / latanoprost
- Most patients were clinically successful after switching to bimatoprost monotherapy
- Both treatments were well-tolerated
- Bimatoprost monotherapy is an effective alternative to dual therapy with timolol gel and latanoprost

Dirks et al, AGS, 2002
Safety of Hypotensive Lipids

*Adverse event defined as:*

- Any untoward medical occurrence – whether or not related to the use of an investigational agent
- Product label includes adverse events based predominantly on frequency of occurrence
  - Includes treatment-related and non treatment-related adverse events based on clinician’s assessment
- If FDA has potential concern, information placed under “Warnings and Precautions”
## Systemic Adverse Events

<table>
<thead>
<tr>
<th>Bimatoprost</th>
<th>Latanoprost</th>
<th>Travoprost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection (cold, URI)</td>
<td>URIs (infection / flu)</td>
<td>Angina pectoris</td>
</tr>
<tr>
<td>Headache</td>
<td>Chest pain</td>
<td>Chest pain</td>
</tr>
<tr>
<td>(Abnormal LFTs)</td>
<td>Angina pectoris</td>
<td>Hypercholesterolemia</td>
</tr>
<tr>
<td>Asthenia</td>
<td>Muscle / joint / back pain</td>
<td>Bradycardia</td>
</tr>
<tr>
<td>Hirsutism</td>
<td>Rash / allergic skin reaction</td>
<td>Depression</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Headache</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Urinary incontinence</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prostate Disorder</td>
</tr>
<tr>
<td></td>
<td></td>
<td>UTIs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Infection, cold syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anxiety</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Arthritis, back pain, pain</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dyspepsia, GI Disorder</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypertension</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypotension</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Accidental injury</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sinusitis, bronchitis</td>
</tr>
</tbody>
</table>

- **Systemic Adverse Events**

- **Bimatoprost**
  - Infection (cold, URI)
  - Headache
  - (Abnormal LFTs)
  - Asthenia
  - Hirsutism

- **Latanoprost**
  - URIs (infection / flu)
  - Chest pain
  - Angina pectoris
  - Muscle / joint / back pain
  - Rash / allergic skin reaction

- **Travoprost**
  - Angina pectoris
  - Chest pain
  - Hypercholesterolemia
  - Bradycardia
  - Depression
  - Headache
  - Urinary incontinence
  - Prostate Disorder
  - UTIs
  - Infection, cold syndrome
  - Anxiety
  - Arthritis, back pain, pain
  - Dyspepsia, GI Disorder
  - Hypertension
  - Hypotension
  - Accidental injury
  - Sinusitis, bronchitis
Once-Daily Hypotensive Lipids Are Systemically Safe

- No effects on cardiorespiratory function
- Pregnancy category “C”
- Travoprost should not be used in women who are or might become pregnant
Once-Daily Hypotensive Lipids Are Well-tolerated

- Low rates of discontinuations from clinical trials due to adverse events
- Most side effects are ocular
- Common side effects:
  - Conjunctival hyperemia (trace to mild)
  - Changes in irispigmentation
  - Eyelash changes
- Incidence of allergy is low
Conclusions

- “Good Enough” IOP control may not always be “Low Enough” to prevent disease progression
- Patients should be treated with monotherapy whenever possible
- Monotherapy with once-daily hypotensive lipids provides the best IOP lowering
  - Lowers IOP more effectively than timolol
  - Lowers IOP as effectively as combined timolol / dorzolamide
  - Allows more patients to reach low target pressures
Conclusions (Continued)

- Patients on timolol / latanoprost can be switched to bimatoprost monotherapy with no loss in IOP-lowering efficacy

- Benefits of hypotensive lipids
  - Efficacy
  - Systemic safety
  - Once-daily convenient dosing
Achieving the New Targets Set by These Trials

Dr. Rahul Shukla
Evolution in the Medical Treatment of Glaucoma in India

- Timolol still remains the mainstay because of cost considerations
- Pilocarpine gradually getting replaced with Brimonidine after price revisions by major brands
- Bimatoprost and Latanoprost still considered “Expensive”, however tertiary Institutes and leading Consultants consider them as preferred option to surgery
Beta Blockers Some Limitations

- May not achieve target pressures in many patients
- Efficacy at night is not proven, hence may not help prevent early morning Spikes.
- Not desirable in patients with COPD, Hypertension, Diabetes, Depression, hyperlipidemia etc
Timolol Vs Bimatoprost

LUMIGAN offers superior IOP lowering efficacy

![Graph showing mean IOP at 10 AM (mm Hg) over time for Timolol BID (n=241) and LUMIGAN® QD (once daily) (n=474). The graph illustrates a significant difference (*P < .001) in IOP reduction between the two groups.](image-url)
Timolol Vs Bimatoprost

Lumigan offers superior diurnal control

![Graph showing mean IOP (mm Hg) over time for timolol BID (n = 241) and LUMIGAN® QD (n = 474). The graph indicates significantly lower IOP at 8 AM and 4 PM for LUMIGAN® QD compared to timolol BID. The significant difference is marked with an asterisk (*P ≤ .001).]
Timolol Vs Bimatoprost

Replace timolol with Lumigan for more IOP reduction

Beta-blocker monotherapy to LUMIGAN® monotherapy (n = 587)
Beta-blocker baseline = 20.9 mm Hg

*P < .001
Timolol Vs Bimatoprost

Lumigan efficacy maintained for over 2 years

**Graph:**
- **Mean IOP at 10 AM (mm Hg)**
- **X-axis:** Months
- **Y-axis:** Mean IOP at 10 AM (mm Hg)
- **Legend:**
  - Timolol BID (n=81)
  - LUMIGAN® QD (once daily) (n=167)

**Statistics:**
- *P < .001
- **P < .006

**Note:**
- *P < .001
- **P < .006
Timolol Vs Bimatoprost

Lumigan achieves superior IOP reduction to Timolol over 24 hours

Mean IOP (mm Hg)

Timolol QD (once daily) (n=39)
LUMIGAN® QD (once daily) (n=38)

Day 28
Day 29

*P ≤ .037
Latanoprost Vs Bimatoprost

**Lumigan® demonstrates IOP reduction**

*Vs Latanoprost*

![Graph showing IOP reduction comparison between Latanoprost and Lumigan®](image)

- *P < .001

**Graph Details:**
- **Mean IOP (mm Hg)**
  - Latanoprost QD (n = 136)
  - Lumigan® QD (n = 133)
Latanoprost Vs Bimatoprost

Lumigan® demonstrates diurnal control Vs Latanoprost

![Graph showing comparison between Latanoprost and Lumigan®](graph.png)
Latanoprost Vs Bimatoprost

Lumigan® demonstrates better response rate Vs Latanoprost

Percentage of patients achieving defined response

% Reduction from baseline

*P < .001

Latanoprost QD (n = 133)
baseline 23.3 mm Hg

LUMIGAN® QD (n = 136)
baseline 24.0 mm Hg
Latanoprost Vs Bimatoprost

Switch Latanoprost non-responder to Lumigan®

![Graph showing mean IOP (mm Hg) over time]

- **latanoprost QD**
- **LUMIGAN® QD (Once daily)**

(n = 15)

*P = .0001

* indicates significance.
Lumigan® demonstrates IOP reduction Vs Latanoprost over 24 hours

- Latanoprost QD (n = 38)
- Lumigan® QD (n = 38)
Bimatoprost Monotherapy Lowers IOP More Effectively Than Latanoprost: A 6-Month Randomized Clinical Trial

- Multicenter, randomized, investigator-masked trial
- Adult patients with OHT or chronic glaucoma
- Treatment groups:
  - Bimatoprost 0.03% qPM, n = 133
  - Latanoprost 0.005% qPM, n = 136
- Efficacy outcome measures:
  - Mean change from diurnal baseline IOP (1° endpoint)
  - Mean IOP
  - Percentage of patients reaching
    - Specific target pressures
    - 15% and 20% reductions in IOP

Noecker et al, AJO, 2003
Significantly Greater Mean IOP Reductions With Bimatoprost at All Time Points

Noecker et al, AJO, 2003
Bimatoprost Superior to Latanoprost in Primary Endpoint: Mean Change From Baseline IOP

- Bimatoprost superior to latanoprost at every time point, every visit
- All differences statistically significant
- Difference between groups ranged from 1.2 mm Hg to 2.2 mm Hg in diurnal measurements at month 6
Efficacy of Latanoprost Consistent With Reported Literature Values

- IOP reduction from baseline at 8 AM:
  7.1 mm Hg at month 3 and 6.0 mm Hg at month 6

- Similar to morning IOP reduction measured in other studies:
  - 5.5 mm Hg at month 3 and 6.0 mm Hg at month 6 (Suzuki et al, 2000)
  - 6.2 mm Hg at month 3 (Mishima et al, 1996)
Bimatoprost Also Superior to Latanoprost in All Other Efficacy Measures

- Mean IOP
  - Significantly lower with bimatoprost at all 3 diurnal measurements at all 4 follow-up visits

- Percentage of patients reaching specific target pressures
  - Significantly more bimatoprost patients reached low target pressures at all time points at month 6

- Responder rates
  - Significantly more bimatoprost patients responded to treatment with $= 15\%$ and $= 20\%$ reductions in IOP

Noecker et al, AJO, 2003
Both drugs were well-tolerated

No treatment-related, serious AEs

Most common side effects:
  - Hyperemia (bimatoprost 44.4%; latanoprost 20.6%)
  - Eyelash growth (bimatoprost 10.5%; latanoprost 0.0%)

Similar rate of discontinuations due to AEs
  - Bimatoprost: 4.5% overall, 2.3% for hyperemia
  - Latanoprost: 3.7% overall, 0.0% for hyperemia

Uveitis: 1 patient in latanoprost group; no CME

Noecker et al, AJO, 2002
Bimatoprost Is Consistently Better Than Latanoprost in Lowering IOP

- 3 published head-to-head trials (1-month, 3-month, 6-month) with IOP follow-up measurements at 24 time points
- Mean IOP lower with bimatoprost at 22 time points, tied at 2 time points, **NEVER** lower with latanoprost
- Mean IOP reductions greater with bimatoprost at 23 time points, tied at 1 time point, **NEVER** greater with latanoprost
Primary Therapy Comparison: Bimatoprost vs Latanoprost

- Bimatoprost lowers IOP 1-2 mm Hg more than latanoprost
- The incidence of hyperemia is approximately twice as high with bimatoprost

Noecker et al, AJO, 2002
Mean Hyperemia Scores
With Bimatoprost

Abelson et al, In press
Respective Phase III Trial Results:
Lower Incidence of Iris Pigmentation Changes With Bimatoprost

- Increased iris pigmentation reported for 16.1% of patients treated with latanoprost QD for 1 year

- Increased iris pigmentation reported for only 1.5% of patients treated with bimatoprost QD for 1 year
  - No new reports of iris pigmentation during the second year of bimatoprost treatment
Bimatoprost Reduced Mean IOP in Latanoprost Nonresponders

- 66% of IOP measurements were $\leq 18$ mm Hg on bimatoprost

* $P < .001$ vs baseline and latanoprost

Gandolfi et al, ARVO 2002
Most Latanoprost Nonresponders Responded to Bimatoprost

<table>
<thead>
<tr>
<th>Prostaglandin</th>
<th>Responders</th>
<th>Nonresponders</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bimatoprost</td>
<td>13</td>
<td>2</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Latanoprost</td>
<td>0</td>
<td>15</td>
<td></td>
</tr>
</tbody>
</table>

Definition of Responder: \( \geq 20\% \) IOP Reduction

Gandolfi et al, ARVO 2002
Relative Disadvantages of the Hypotensive Lipids

- Change in iris pigmentation
- Eyelash changes
- Hyperemia
- Eyelid skin darkening
- Macular edema in susceptible patients?
- Exacerbation of uveitis?
- Exacerbation of herpetic keratitis?
- Expense
Primary Advantage of the Lipids: Efficacy

- Excellent, sustained IOP lowering
  - 30%-35% reduction in IOP
  - Greater efficacy than nonselective beta-blockers

- Effective in the black population, which shows reduced responsiveness to some therapies
  - As monotherapy, lower IOP as effectively as combinations of other drug classes
  - Flat diurnal curves
  - No known tachyphylaxis
Other Advantages of Lipids

- Convenient, once-daily drugs
- Side effects mostly local
  - Tolerability rather than safety issues
  - Contrasts with serious systemic effects of beta-blockers
- Low incidence of topical allergies
- Mechanism of action
  - Enhance outflow to counteract physiological deficit that causes high IOP
Pros and Cons of Bimatoprost as First-Line Therapy

- Important to maximize efficacy to reduce the risk of progression

- Bimatoprost lowers IOP better than all other medications
  - Bimatoprost is as great an improvement over latanoprost as latanoprost was to timolol
  - Best chance of getting patient to target IOP

- Conjunctival hyperemia is more common with bimatoprost than latanoprost
Manage Tolerability to Maximize Efficacy

- Safety is an issue for the physician, but tolerability will ultimately be decided by the patient.
- The physician can have a large influence on how the patient views tolerability issues.
- Patient education is key:
  - Side effects of treatment should be weighed against possible loss of visual function.
  - Side effects that are expected and transient may be best tolerated.
Conclusions

- Hypotensive lipids should be used as first-line therapy for glaucoma
- Bimatoprost patients are more apt to reach low target pressures with bimatoprost than with latanoprost
- Many patients who fail to respond adequately to latanoprost may be successfully switched to bimatoprost
- Tolerability issues with the lipid agents can be addressed with patient education
Reaching the Difficult Target Pressures

Dr. Rahul Shukla
Goal: Reach Target Pressure

- Goal to reach target on initial monotherapy
- If target not reached, choices:
  - Switch to more effective primary therapy
  - Add another medication
Benefits of Replacement Therapy

- Single medication preferable to using multiple medications
  - Safety, tolerability, compliance
- Eliminate medications no longer effective
  - Reverse therapeutic trial
    - One-eye trial
    - Stop medication weeks prior to next scheduled visit
    - Easy way to determine whether medication still effective
Bimatoprost Monotherapy in Patients Previously on Dual Timolol/Latanoprost

Mean IOP at 8 AM (mm Hg)

83 Patients

- Timolol gel + Latanoprost
- Bimatoprost

Day 0
Day 14
Day 60
Day 74
Day 120

60-Day Crossover Design

Dirks et al, AGS, 2002
Lumigan Indian Experience

The India Lumigan Early Experience Data (L.E.E.D.) Study Group

Data on file Allergan India Pvt. Ltd.
Objective and Trial Design

- To evaluate the response to Bimatoprost in “real-life” clinical practices
- Open-label, 2-month surveillance trial
  - In glaucoma or ocular hypertension patients who need additional IOP lowering, or who are intolerant of other medications
  - Bimatoprost was used as monotherapy, replacement therapy or adjunctive therapy at physicians’ discretion

Data on file Allergan India Pvt. Ltd.
Patient Population

- 571 patients from 72 clinical sites in India
  - 6.4% lost to follow-up
- 74.2% equal to or older than 50
- 38.5% female and 61.5% Male
- 97.6% Asian
- 90.2% with open-angle glaucoma and 9.8% with ocular hypertension

Data on file Allergan India Pvt. Ltd.
Baseline Characteristics

Based on “Difficulty to Control”

(\(n=444\)- All patients who completed at least one follow-up)

Data on file Allergan India Pvt. Ltd.
Medications at Baseline and During Study

- No Medications at Baseline: N-92
- Bimatoprost Replacement Therapy: N-168
- Bimatoprost Adjunctive Therapy: N-216

Data on file Allergan India Pvt. Ltd.
Lumigan lowers IOP as first-line, replacement & adjunctive therapy

Overall Mean IOP Patients who completed at least One follow-up

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Baseline</th>
<th>Visit 2</th>
<th>Visit 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Medications at Baseline</td>
<td>24.5</td>
<td>17.6*</td>
<td>16.6</td>
</tr>
<tr>
<td>N=92</td>
<td></td>
<td>-34.8%</td>
<td>-38.5%</td>
</tr>
<tr>
<td>Bimatoprost Replacement Therapy</td>
<td>21.9</td>
<td>16.0*</td>
<td>15.5*</td>
</tr>
<tr>
<td>N=168</td>
<td></td>
<td>-25.2%</td>
<td>-27.4%</td>
</tr>
<tr>
<td>Bimatoprost Adjunctive Therapy</td>
<td>25.6</td>
<td>18.2*</td>
<td>16.9*</td>
</tr>
<tr>
<td>N=216</td>
<td></td>
<td>-25.6%</td>
<td>-28.7%</td>
</tr>
</tbody>
</table>

* P < 0.001 as compared to Baseline

Data on file Allergan India Pvt. Ltd.
Lumigan enables more patients to reach Target IOPs

- Baseline
- Visit 2
- Visit 3

Data on file Allergan India Pvt. Ltd.

*p<0.001 compared to baseline*
Lumigan brings about significant IOP reduction irrespective of the base line

Mean IOP by Baseline IOP  Patients who completed at least one visit considered

Data on file Allergan India Pvt. Ltd.
Lumigan further lowers IOP in all category of patients

Mean IOP by “Difficulty to Control” N=444

Data on file Allergan India Pvt. Ltd.
Lumigan as a replacement therapy further reduces IOP

Mean IOP by Number of Medication(s) in Patients whose prior medications have been replaced with Bimatoprost Monotherapy.

Data on file Allergan India Pvt. Ltd.
Replacement of Beta-blockers / Latanoprost with Lumigan resulted in an additional IOP reduction.

Data on file Allergan India Pvt. Ltd.
Majority of the patients rated Lumigan as a comfortable therapy

Data on file Allergan India Pvt. Ltd.
Lumigan was rated as good or excellent by ophthalmologists involved in the study.

Physicians' Overall Evaluation: Bimatoprost® vs. Other Medications (n=30)

Data on file Allergan India Pvt. Ltd.
Adverse Events

- Bimatoprost was safe and well tolerated
  - Very few adverse events were observed (13.2%)
  - The reported adverse events are
    - Conjuntival hyperemia (2.7%)
    - Conjectival congestion (1.3%)
    - Redness (2.5%)
    - Pain (1.1%)

Data on file Allergan India Pvt. Ltd.
Thank you!