Medical Management of Glaucoma

Michael Chaglasian, OD, FAAO
Illinois Eye Institute
Illinois College of Optometry
mchaglas@ico.edu

Outline

- Early Glaucoma Cases
  - photos, VF, OCT, pachs, etc
  - Identify findings that indicate treatment
- Options for Treatment
  - Medication Overview
    » PGAs, CAIs, AA, BB and FC
    - Pros and Cons
    - Diurnal Effect
    - Nocturnal Control
    - Neuroprotection?
- Goals of Treatment
  - Target IOP
- Normal Tension Case
  - Identify related risk factors
- Monocular Trials
- Cases
- Q and A

Decision Making In The Management Of Glaucoma

“*To treat or not to treat*?”... that is the 1st question!
“*How to treat*?”... that is the next question!
“*How to modify treatment*?”... that’s another good question!

CASE EE

IOP 22-25 mmHg OD, OS
CCT 525

Disclosure

- Michael Chaglasian, OD is a paid advisor, consultant or researcher for the following commercial/industry groups:
  - 1. Advisory Boards:
    - Allergan, Inc., Alcon Labs, Bausch+Lomb, Carl Zeiss Meditec, Merck, Sucampo
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Outline

Disc Photos

Visual Fields

Discussion

Prostaglandin Analogs

TRAVATAN Z

Lumigan

Xalatan

Travatan Z: Non BAK option

Unique Ionic Buffer System

When TRAVATAN Z solution comes in contact with the positively charged ions in the tear film, the ionic buffered preservative system becomes inactive, providing a solution that is safe and gentle on the eye.
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Travoprost: Sustained IOP Lowering

Lumigan 0.01%

New Preservative Free PGA: Zioptan (Tafluprost)

- Efficacy similar to all other PGAs
- Unit dose vials
- Not on many formularies
- Merck no longer has sales force but product is still available

Rescula (unoprostone 0.15%)

- Prostone Class
  - related to PGAs but different in several ways
  - fewer topical SEs
  - BID dosing
  - 3-4 mmHg IOP lowering
    - Baseline of 22mmHg
  - ? Additive to PGAs
- MOA
  - Increases the outflow of aqueous humor through the trabecular meshwork.
  - Via effect on BK (Big Potassium) and ClC-2 chloride channels
  - exact mechanism is unknown at this time

Prostiones

- Prostiones act locally to restore normal function in cells and tissues, and because they are quickly metabolized to an inactive form, their pharmacologic activity can be targeted to specific organs and tissues.
- They possess a unique mechanism of action as highly potent and selective ion channel activators.
- Ion channels are integral parts of cell membranes that regulate the flow of specific ions into and out of cells.
- This regulation is key to the functioning of cells, such as metabolic processes and cell survival.

Rescula

- Established ocular and excellent systemic safety profile
  - Hyperemia incidence similar to timolol
  - Eyelash length/density changes similar to timolol
  - No deleterious effects on CV or pulmonary function in clinical studies
  - No labeled drug-drug interactions

Sucampo Care on File. Integrated summary of clinical safety. Sucampo Pharmaceuticals, Inc.
Rescula

Potential Niche:
- PGA intolerant
- Beta Blocker contraindicated
- Brimonidine Allergy
- CAI alone with TID dosing
- Patients with OHTN and/or Early Glaucoma who don’t need 30% IOP reduction

- Adjunctive Role?
  » No significant published data on adjunctive use with PGAs

CASE MZ

IOP in high teens
CCT= 560

Discussion

Latanoprost Generic

- March 2011
  » Expected Availability April
- Fast change over during reminder of year
  » Branded Xalatan to Latanoprost generic
  » Managed Care Formulary contracts go through December 2011
- Multiple Suppliers
  » Including Pfizer/Greenstone and Falcon
  » Unknown questions about efficacy and side effects

Generic Latanoprost

Facts and Myths about Generic Drugs

- Currently, what percentage of filled prescriptions are for generics?

3 out 4 prescriptions filled in the United States are for generic drugs.
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Myths about Generics

- Don’t work as well as brands
- Have more variability
- Have different ingredients
  - Active
  - Inactive
- Hard to duplicate
- Aren’t as stable

Benefits of Brand Products:

- Comfort and reliability
  - medication itself
  - bottle familiarity
  - No changes between generic manufacturers
- Sample support from Company
- Patient Assistance Programs
- Web site information
- Support to Pharma Company that supports your profession

CASE CM

38 yo
GAT= 22 OD 25 OS
Was on Xalatan in Past
? of side effects and/or poor response

Discussion

Case LH

57 yo, W, F
-7.50 Myopia
GAT: 19-23 / 18-23
CCT= 562, 571

American Glaucoma Society

Questions about generic ophthalmic medications from AGS members, answered by Willy Chambers, M.D., FDA Deputy Director for the Division of Transplant and Ophthalmic Products, March 2011.

Q: Can you explain the FDA policies for generic ophthalmic medications and what kind of clinical testing is performed?

Dr. Chambers: For ophthalmic products, the formulation of a generic product often depends on when the innovator product and generic product were approved. Prior to 1992, the FDA used to permit changes in inactive ingredients for ophthalmic generic products without testing. In 1992, that policy was changed. Currently, generic ophthalmic solutions, such as latanoprost are expected to have the same active and inactive ingredients in the same concentrations (both active and inactive). If they are not the same, then a study comparing the clinical bioequivalence has to be performed. If the product is anything other than a solution, where manufacturing issues could potentially make a difference, the generic has to have a study demonstrating equivalence, even if the actives and inactives are the same. It is therefore important to distinguish between old ophthalmic generics (before 1992) and newer ophthalmic generics.
Management Issues

- Initiate Therapy -
  - Evaluate two to four weeks
    - (Sooner in high initial pressure)
- Target pressure important
  - Range 25-45% reduction
  - Write it down in the chart
- Use a step or ladder approach to therapy
- Monitor every 3-4 months

Discussion

Topical CAIs

Currently available:
- Brinzolamide 1% (Azopt)
- Dorzolamide 2%
  - Generic availability
- Consistent, moderate, mono-therapy IOP reductions
  - 15-20%, ~4 to 6 mm Hg
- FDA Labeled as TID agents

Azopt shows Nocturnal IOP Lowering:


Alpha Agonists

- Alphagan-P 0.1% (Allergan)
  - BAK→ Purite (↓ toxicitiy)
  - Less ocular allergy
- Aqueous suppressant and:
  - ↑ uveoscleral outflow
  - ? Neuroprotection?
- Bid vs. Tid dosing
- NO Neuroprotection!

No Nocturnal IOP Lowering with Brimonidine 0.1% TID

Brimonidine Neuroprotective?

Overview:
- To compare brimonidine to timolol maleate in preserving visual function in low-pressure glaucoma.
- Randomized, double-masked, multicenter clinical trial.

Outcome:
- Low-pressure glaucoma patients treated with brimonidine who do not develop allergy are “less likely to have field progression than patients treated with timolol.”

Issues with Data/Conclusions
- Failure rate of beta blockers:
  - Much higher than our collective clinical experience: EMGT, OHTS.
  - Extrapolating the Kaplan-Meier survival graph to 5 years would predict a 100% progression rate for the patients taking timolol.
- Side effect rate of brimonidine:
  - ~30% drop out due to side effects (0.2%).
- Degree of IOP lowering in treatment groups:
  - Approximately the same between the 2 drugs.

Generic Brimonidine
- 0.2%
- 0.15%
- Significant Cost Differences

Advantages of Fixed Combinations
- Dosing—1 drop vs 2 drops
- Convenience
- Potential to improve compliance¹
- No risk of washout from second drug²
  - Washout impedes absorption, thereby reducing efficacy³
- Possible cost savings
  - Only 1 copay

Generic Timolol

Timolol Fixed Combinations
- Cosopt®
  - Dorzolamide hydrochloride/timolol maleate solution
- Generic dorzolamide / timolol maleate ophthalmic solution
Fixed Combination: Combigan

- Combigan (Allergan)
  - Brimonidine 0.2%
  - timolol 0.5%
  - BID dosing
- Less allergy than brimonidine alone
  - timolol is a buffer

New: Cosopt PF

SIMBRINZA™ Suspension (Brinzolamide/Brimonidine)

- Additional 1-3 mm Hg IOP-lowering compared to the individual components
- Delivers 21-35% IOP-lowering efficacy
- Only fixed-combination without a beta blocker
- Adverse events profile consistent with those of its individual components
- Creates new treatment possibilities for lowering IOP

SIMBRINZA™ Suspension Has Two Active Compounds with Complementary MOAs

CASE DB

- 75 WF
  - 2006 Glaucoma Suspect
    - Diabetic, HTN
  - GAT 2002-2010
    - 17-23 OD and OS
  - Pachs: 550/551
    - large cupping, HRT, VF
- 2008/2010
- 2011
  - GAT: 21 / 21, VF #2
- 2012
  - GAT 17 / 17
  - VF #3
- 2013
  - GAT 25 / 26
  - Cirrus RNFL and GCA

Initiating Glaucoma Therapy: Monocular Trial
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Joe Glaucoma
- Small notch to inferior NRR in OD
- Corresponding visual field defect
- GAT: (Goldmann Applanation Tonometry)
  - 30 mmHg OD
  - 28 mmHg OS
- Start (PGA) therapy qhs OD only
- RTC 4 weeks

Assumptions we rely on for the Monocular Trial to hold true:
1. IOP fluctuation is the same between right and left eyes
2. Diurnal curve is the same over time
3. Medication has no crossover effect
4. Each eye responds the same to a medication
5. Patients have good compliance

What is the Evidence?
- Uniocular Trials Don’t Work (initial evidence)

Why?
- IOP fluctuation is the same between right and left eyes: False
- Diurnal Curve Is The Same Over Time: False
- Medication has same effect on each eye? Not Always

Conclusion:
The Monocular Trial Does Not Work.

Well Studied and Reported

Conclusion:
The Monocular Trial Does Not Work.

So, What Do I Do Now?
- Initiate Treatment in both eyes.
- Don’t judge the effect of therapy based upon a single pre-treatment value nor a single on-treatment value.
- Must obtain multiple IOP readings on our patients and see if the average changes after treatment is initiated
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What I Still Can’t Tell You.

- Exactly how often and with what frequency should the timing of these multiple IOP readings be.
- What do we need to accurately characterize a patient’s IOP response to medical therapy:
  - More is better.
  - Be patient, glaucoma is a slow process

Target Pressures and their Relevance

Michael A. Chaglasian, OD, FAAO
Chief of Staff / Illinois Eye Institute
Associate Professor / Illinois College of Optometry
mchaglas@ico.edu

Background

- Paul Chandler ~1950s
  - American Academy of Ophthalmology
    - Preferred Practice Patterns 1992
- American Optometric Association
  - Clinical Practice Guidelines
  1. “Determine an appropriate target pressure and readjust when necessary.”

Goals of Treatment

- Stable optic nerve and RNFL
- Stable visual fields
- Controlled IOP ??
  - “IOP safety threshold”
    - highly variable

Putting into Action

- In estimating the initial target pressure, the clinician can use knowledge about the
  - existing damage to the ON,
  - the degree of VF loss,
  - the patient’s age and
  - highest IOP,
  - along with clinical experience.

Why use target pressure?

- Identify a measureable goal of the treatment plan
- Benchmark the treatment plan
- Communicate to patient

Optometric Practice Guidelines Care Of The Patient With Open Angle Glaucoma AOA 2007
Target IOP in Clinical Practice

1. The target IOP is the IOP range at which the clinician judges that progressive disease is unlikely to affect the patient’s quality of life.

Comment: The burdens and risks of therapy should be balanced against the risk of disease progression.

Target IOP in Clinical Practice

2. The determination of a target IOP is based upon consideration of the amount of glaucoma damage, the IOP at which the damage has occurred, and the life expectancy of the patient, and other factors including status of the fellow eye and family history of severe glaucoma.

Comment: At present, the target IOP is estimated and cannot be determined with any certainty in a particular patient.

Comment: There is no validated algorithm for the determination of a target IOP. This does not, however, negate its use in clinical practice.

Target IOP in Clinical Practice

3. It is recommended that the target IOP be recorded so that it is accessible on subsequent patient visits.

4. The use of a target IOP in glaucoma requires periodic re-evaluation.

There are two clinically useful empirical observations about POAG:

- Past damage predicts future damage, unless the IOP is lowered.

- Damage in one eye is associated with a significantly increased risk of future damage in the other eye.

Kass MA. Arch Ophthalmol 1976

Setting a Target Pressure

Two Methods:

- Absolute Value

- Percentage decrease from baseline value

Amount of reduction is dependent upon “Stage” of glaucoma
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**Outline**

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### What Pressure Reduction is Required?

Randomized Clinical Trials provide some of the Evidence and Guidelines

**Note:** Differences between populations

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### Lowering IOP Halts or Delays Disease Progression: OHTS, EMGT, CNTGS

<table>
<thead>
<tr>
<th>Study</th>
<th>IOP</th>
<th>Progression (Tx/No Tx)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OHTS¹</td>
<td>20% reduction</td>
<td>4.4% / 9.5%² (5 years)</td>
</tr>
<tr>
<td>EMGT²</td>
<td>25% reduction³</td>
<td>45% / 62%⁴ (6 years)</td>
</tr>
<tr>
<td>CNTGS³</td>
<td>30% reduction</td>
<td>12% / 35%⁴⁵ (7 years)</td>
</tr>
</tbody>
</table>

¹ Kass MA et al. 2002. ² Heijl A et al. 2002. ³ CNTGS. 1998. ⁴ Average. ⁵ Patients (%) meeting computer-generated perimetric progression criteria based on VF and optic disc outcomes. ⁶ Patients (%) developing glaucomatous optic disc progression or VF loss.

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### Lowering IOP Halts or Delays Disease Progression: CIGTS, AGIS

<table>
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<tr>
<th>Study</th>
<th>IOP</th>
<th>Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIGTS (med)</td>
<td>35% reduction</td>
<td>No Progression</td>
</tr>
<tr>
<td>CIGTS (surg)</td>
<td>48% reduction</td>
<td>No Progression</td>
</tr>
<tr>
<td>AGIS</td>
<td>&lt;18 all visits</td>
<td>No Progression</td>
</tr>
</tbody>
</table>


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### Target IOP

- Established based upon ONH and visual field status + pre-treatment IOP
- More advanced disease requires lower target IOP:
  - Mild: 20% Reduction
  - Moderate: 25-35% Reduction
  - Advanced: 45% + Reduction

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### Risk Factors that will Modify the Target Pressure

- Presence and severity of damage to involved or fellow eye
- Family history predisposing to early onset disease or severe disease
- African ancestry
- Age and life expectancy
- High myopia
- Vascular risk factors: disc hemorrhage, nocturnal hypotension, migraine, Raynaud’s disease, diabetes mellitus, previous vein occlusion
- Large fluctuation or instability in IOP
  - Large fluctuations of IOP e.g., IOP spikes, exfoliation syndrome
- Poor follow-up

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### Debate on Using Target IOP

- All agree that lower IOP is better
  - IOP lowering slows the disease process
  - How low to go is the key question
- Every treatment has risk and a benefit
  - Benefit must exceed the cost
- Look at the “Costs” of treatment:
  - Side effects of medications
  - Complications of procedures

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Use of a target IOP range in glaucoma management.

Kuldev Singh, MD @ www.clinicalpodcast.com
### Rules for Target Pressure

- Use a range of IOP and not just a single number
- Be flexible, evaluate against the evidence of progression (or lack of)
- **Target is not the IOP, the PATIENT is the target**
  - If the patient is stable the IOP doesn’t matter

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### Rules for Target Pressure

- If glaucoma is diagnosed early, have plenty of time to adjust therapy and get more aggressive upon evidence of progression
- **Goal:**
  - Treatment patients just enough to maintain their ADLs and have a good QOL.
  - Balance the Costs and Benefits

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### Rules for Target Pressure

- Don’t over treat the easy/mild patients
- Don’t under treat the hard/difficult patients
  - Most practitioners get into trouble by not recognizing this
- **Don’t watch the IOP to the exclusion of the other data**