Medical Management of Glaucoma

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Disclosure of Relevant Financial Relationships

<table>
<thead>
<tr>
<th>Commercial Interest</th>
<th>What was received?</th>
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<td>Allergan Inc.</td>
<td>Honorarium</td>
<td>Advisory Board/Speaker</td>
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<td>Carl Zeiss Meditec</td>
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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?

Outline

- 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!

The Glaucoma Decision Making “Scale”
CASE EE

IOP 22-25 mmHg OD, OS
CCT 525

Disc Photos

Visual Fields

Visual Fields #2
Medical Management of Glaucoma

Discussion

Case EG

- 67 yo, AA male, Retired school teacher
- Good health, no medications
- + Family History of glaucoma
- OHTN/Early Glaucoma
- CCT = 567, 571
- Pre-Tx IOP ~ 30 mmHg OD, OS
- With PGA:
  - Always 20-23 mmHg x 5+ yrs
  - Good Compliance

Photos (initial)

SAP VFs
Can you see the change?

Two Years Later

Photos (5 yrs later)
Medical Management of Glaucoma

Forum Combined Report

Case EG Discussion
- Is this progression?
- Other things you’d like to see/do?
- Options for adjunctive treatment?
Prostaglandin Analogs

**TRAVATAN Z**

**Lumigan**

**Xalatan**

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**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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**Clinical Ophthalmology**

Sustained intraocular pressure reduction throughout the day with travoprost ophthalmic solution 0.004%

**Travoprost: Sustained IOP Lowering**

Clinical Ophthalmology 2012;6:525–531

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**Lumigan 0.01%**

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LUMIGAN® 0.01% and LUMIGAN® 0.03% 12-Month Trial

Mean Diurnal IOP Over 12 Months

[Graph showing mean diurnal IOP over 12 months for Lumigan 0.01% and 0.03%]

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M. Chaglasian, O.D.
The Only: Preservative Free PGA

Zioptan

- A Preservative Free prostaglandin analog
  - Introduced in 2003
  - Tafluprost 0.015%
  - Single use vial delivery

- Same PGA side effects:
  - Iris/Periorbital Pigmentation, Hyperemia, Deepening Orbital Sulcus, etc.

http://www.zioptan.com/zioptan/consumer/secure/index.html

CASE MZ

IOP in high teens
CCT = 560

Visual Fields

Disc Photos
Discussion

Branded Travatan Z

**Effect of Switching to Travoprost Preserved With SofZia in Glaucoma Patients With Chronic Superficial Punctate Keratitis While Receiving BAK-preserved Latanoprost**

Mahmoud Alshaar, MD; Padhi Ratak; MBBS; Ilia Meziane, MD

Objectives: To determine the safety and efficacy of switching from branded Xalatan (BAK-preserved Latanoprost) to a generic version of Latanoprost that is preserved with SofZia in patients with chronic superficial punctate keratitis (CSPK) who are receiving BAK-preserved Latanoprost.

Methods: A prospective, randomized, single-center, single-arm, clinical trial was conducted. Patients were randomized to switch from branded Xalatan to a generic version of Latanoprost preserved with SofZia. The primary outcome was the incidence of adverse events during the 12-week study period.

Results: The incidence of adverse events was similar between the two groups. There were no significant differences in visual acuity, IOP, or other variables measured during the study period.

Conclusions: Switching from branded Xalatan to a generic version of Latanoprost preserved with SofZia is safe and effective in patients with CSPK who are receiving BAK-preserved Latanoprost.

Branded Lumigan

Generic Ophthalmics

- **Prostaglandins**
  - Latanoprost
  - Travoprost
  - Bimatoprost 0.03%

- **Alpha Agonist**
  - Brimonidine 0.2, 0.15%

- **Carbonic Anhydrase Inhibitors**
  - Dorzolamide 2%

- **Beta Blockers**
  - Timolol
  - Levobunolol

- **Fixed Combination**
  - Dorzolamide/timolol

- 80% of all Rxs

- “In 2010 alone, the use of FDA-approved generics saved $158 billion, an average of $3 billion every week.”

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

What’s the Next Generic?

Travoprost (not Travatan Z)

Bitmatoprost 0.003% (not 0.01%)

http://www.accessdata.fda.gov/scripts/cder/ob/docs/queryai.cfm

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.

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

“Back Engineering”

Dr. Chambers: Back engineering is not difficult when you have a complete list of the ingredients. In the case of topical ophthalmics, by regulation, all of the ingredients, active and inactive are required to be listed in the package insert. Most of the time, a potential new manufacturer can figure out exactly how to make a copy. Additional incentives to make an exact copy come from the desire to have the generic be considered interchangeable with the innovator. The most common reason for a proposed generic to differ from the innovator is usually due to patent protection of the formulation. It is very rare for a company to deviate from the original, unless they are blocked by a patent.
Tolerance

Dr. Chambers: The concentration of the active is always measured in the stability studies. Typical time points cover the entire proposed shelf life period and often include baseline, months 3, 6, 9, 12, 18, and 24. The acceptable tolerance is +/- 10% for both innovators and generics. For latanoprost, this would mean that the concentration could vary from 0.004596% to 0.005596%. Since degradation is usually temperature dependent, the accelerated stability studies (i.e., studies at higher temperatures than permitted on the labeling) will typically show a problem well before that recommended temperature conditions. The FDA also looks for trends, so if the projected degradation line will fall outside the acceptable parameters before the intended shelf life, the shelf life is shortened to make sure this would not happen.

Stability

Dr. Chambers: Stability studies are required of generics. Stability studies are designed to simulate a representative portion of different lots of the drug product throughout the full shelf life, although the time of approval, only the first part of these studies may have been completed. When full shelf life data is not available, stability studies under accelerated conditions (studies at higher temperatures) are expected. Stability studies under accelerated conditions will generally predict the stability of a drug product at later time points under normal storage conditions. This is also true of the innovators, which rarely have completed stability studies at the time of approval.

Cap Color

Dr. Chambers: If you notice a generic (or innovator) not following the color code, please let me know. There was a period of time when it was missed on some applications, the review is supposed to catch them now.

For further questions, Dr. Chambers can be contacted at Wiley.Chambers@fda.hhs.gov

Compiled by Cynthia Matovu, M.D. Clair, AGS Patient Care Committee. Reviewed by Dr. Chambers, September 2011.

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

Facts

- FACT: Research shows that generics work just as well as brand name drugs.
- FACT: When it comes to price, there is a big difference between generic and brand name drugs. On average, the cost of a generic drug is 80 to 85% lower than the brand name product.

However, is there another “Cost”?

Impact of the Introduction of Generic Latanoprost on Glaucoma Medication Adherence

John D. Sun, MD, MS; Alberto Melman, MD, MPH; Nadeka taken, MD; Michael L. Sullivan, MD

Purpose: To assess possible changes in medication adherence to prostaglandin analogues (PAGs) after the introduction of generic PAGs among patients with open-angle glaucoma (OAG) after the introduction of generic PAGs.

Design: Retrospective cohort analysis.

Participants: Patients older than 65 years with OAG continuously enrolled in a nationwide managed care network using 2003-2013 claims data from PCS.

Methods: Multivariate logistic regression (MLR) for the 5 months before generic PAGs became available (July 2013-December 2013). The area was compared between patients who discontinued the nonswitching policy and those who did not. The area was compared between patients who discontinued the nonswitching policy and those who did not. The area was compared between patients who discontinued the nonswitching policy and those who did not.

Ophthalmology 2015;122:738-747
Improved Adherence when switched to Generics

**Conclusions:**
- Given that cost can significantly deter adherence, switching patients to generic medications may help improve patients' drug-regimen adherence.

“Patients on who stayed on Branded were 28% less likely to have improved adherence.”

Ophthalmology 2015;122:738-747

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**Case LH**

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

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**Disc Photos**

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**Visual Fields**

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**Discussion**
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

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

Agents Used in Combination with Prostaglandins: Effect on IOP

Azopt shows Nocturnal IOP Lowering:

Alpha Agonists

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

Generic Timolol

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

1. Razeghinejad et al. Expert Opin Pharmacother. 2010
Timolol Fixed Combinations

- **Cosopt®**
  - Dorzolamide hydrochloride/timolol maleate solution
- **Generic dorzolamide/timolol maleate ophthalmic solution**

Fixed Combination: Combigan

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

Cosopt PF

SIMBRINZA™ Suspension (Brinzolamide/Brimonidine)

- Additional 1.3 mm Hg IOP-lowering compared to the individual components1-3
- Delivers 21-35% IOP-lowering efficacy1-3
- Only fixed-combination without a beta blocker1-3
- Adverse events profile consistent with those of its individual components1-3
- Creates new treatment possibilities for lowering IOP

SIMBRINZA™ Suspension Has Two Active Compounds with Complementary MOAs4

- Brinzolamide
- Brimonidine
- Brinzolamide

SIMBRINZA™ Suspension is a fixed-combination that is beta blocker-free5-7

New and Upcoming Meds
Vesneo

VESNEO (latanoprostene bunod)

New Drug Application under review by the U.S. FDA. Approval data is due on Oct. 20, 2015.

Vesneo is a second-generation prostaglandin that provides a unique mechanism of action. It has been proven effective in a variety of therapeutic settings.

Rho Kinase Inhibitors

- “ROCK” Inhibitors: family of protein kinases
  - The enzyme and the pathway play a critical role in regulating the contractile tone of smooth muscle
  - Research in the last decade has identified ROCK as an important mediator of aqueous outflow through the trabecular meshwork
  - Lowers resistance to aqueous outflow in the trabecular meshwork
  - Potential of restoring normal TM function
  - No other medication works in this fashion

ROCK Inhibitors

- Aerie:
  - AR-12286 Rho Kinase Inhibitor.
    (Phase 2a)
  - Achieved a change in mean IOP of 28% (QD)
  - PG-286 Fixed Combination with Travoprost

Roclatan (Arie)

- Our Product Portfolio
- Table summarizing each of our existing product candidates, their mechanism of action, and their development status, as well as any intellectual property rights for these product candidates.

Trabodenoson (Inotek)

- Trabodenoson

The Helios Insert

- Maintenance of IOP Reduction with Single Dose of a Novel Topically Applied Bimatoprost Ocular Insert in Patients with Open-Angle Glaucoma or Ocular Hypertension

http://forsightvision5.com/products/helios-insert/
CASE EG2
66 yo, AAM
HTN, Cholesterol, Anxiety Disorder,
IOP = 27, 26 mmHg OD and OS
CCT = 550

2009 Photos

Unreliable VFs

Diagnosis / Treatment
• Early POAG OU
  – Unable to complete VF testing

• Initiate Travatan Z qAM OU
  – morning dosing for better compliance
  – same efficacy

• IOP = 20/21 mmHg over next year
Lost to Follow Up

- Missed several follow up visits over 3 years
- Returns:
  - “I just ran out of my medication, can you give me a sample. BTW, this medication is now costing me $100 per bottle. Is there anything else?”
- IOP = 27-25 mmHg
- Rx = latanoprost qAM OU

2013 Photos

Photo Comparison

Cirrus GPA

GPA Page 2
Management

- Reviewed treatment options, R & B of additional medical therapy vs. laser procedure. Discussed long term risks of vision loss and compliance related component.
- Patient elected medical therapy.
- Rx = dorzolamide/timolol BID OU
- IOP currently 17-18 OD/OS
- Continuing to recommend SLT for patient

Initiating Glaucoma Therapy: Monocular Trial

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?

- Unicocular 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

Well Studied and Reported
Conclusion:
The Monocular Trial Does Not Work.

OVER TEN YEARS OF RESEARCH

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*

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

CASE ML

47 yrs old
GAT = ~ 20-21 OD and OS
Asymmetric Cupping
CCT = 525 OD OS
Referred for Treatment

Baseline VF #1 (2009)

Baseline VF #2 (2010)
Medical Management of Glaucoma

Disk photos (2012 visit)

VF w/ Event Analysis (2012 visit)

VF w/ Trend Analysis (2012 visit)

OCT (2012 visit)

VF with Trend Analysis (2014)

Target Pressures and their Relevance

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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."

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 measurable goal of the treatment plan
- Benchmark the treatment plan
- Communicate to patient

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.

Target IOP

- Established based upon ONH and visual field status + pre-treatment IOP
- More advanced disease requires lower target IOP:
  - Mild: 20% Reduction
  - Not frequently chosen
  - Moderate: 25-35% Reduction
  - Advanced: 45% + Reduction

Randomized Clinical Trials provide some of the Evidence and Guidelines

Note: Differences between populations
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
  - e.g., IOP spikes, exfoliation syndrome
- Poor follow-up

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

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

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**