

Glaucoma: Practical Tips to get you started

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Introduction: Principles of Glaucoma Medical Therapy

- Balance benefits with risks
- Use least amount to achieve desired response with fewest side effects
- Individualize treatment
- Focus treatment on preserving vision and the optic nerve
- Consider patient compliance

Evolution in Primary Therapy

- Over the past 15+ years, clinicians have switched from topical B-blockers to prostaglandin agents
 - Prostaglandin analogues
 - Superior efficacy - 30-35% reduction (or more!)
 - Systemic safety
 - Diurnal control of IOP
 - Convenience / enhanced compliance
 - Relatively few side effects

Prostaglandins

- Latanoprost (Xalatan) Pharmacia- Aug 1996
- Unoprostone (Rescula) Novartis- Sept 2000
- Brimatoprost (Lumigan) Allergan- March 2001
- Travoprost (Travatan) Alcon- March 2001
- Tafluprost (Zioptan)* Merck-Feb 2012
- Vyzulta (latanoprostene bunod) B&L Nov 2017

Prostaglandin: pros

- Very few systemic side effects
- Once daily administration
- Long action with flattening of diurnal curve
- Few drug/drug interactions

Prostaglandins: cons

- Mild hyperemia
 - Subsides over time, 2 weeks or less
 - While 35-50% do reports some level of hyperemia, only 3% discontinued due to hyperemia
- Eyelash growth: low incidence 0.8%
- Iris color change: benign, cosmetic change
 - 2-3%

Prostaglandins: cons

- CME
- Iritis
 - Avoid in patients with h/o iritis, as can precipitate attack
 - Consider d/c while in post-op cataract period
- Re-activation of HSV
- Non-response: 8-9%
 - Similar or better than virtually all other classes

Generic Latanoprost

- March, 2011
- Several companies
 - Apotex, Inc.
 - Mylan Pharmaceuticals, Inc.
 - B&L Pharmaceuticals
 - Greenstone, Ltd.
 - Falcon Pharmaceuticals

Generic Latanoprost

- Few studies indicate if equivalent
- Indian J of Ophth 2007 Study
 - Xalatan group had slightly lower IOP reduction than generic, 38% vs. 25%
 - If switched from generic to trade, just under 1 mm decrease (16.98 to 16.09)
 - If switched from trade to generic IOP rose just over 1 pt (14.29 to 15.36)
 - Adverse effects: initial, 8/11 in trade name vs. 16/18 in generic; 11/11 switched to generic vs. only 6 of 18

Generic Latanoprost

- Bottom line:
 - Fairly similar IOP response
 - Maybe more adverse reaction in generic
 - Generics may need extra counseling etc.
 - Have back for IOP change after switch?
 - Difference among generics?
- May not have an option!!
 - Cost: Good RX 3/18
 - ≈\$11.24 for 2.5 ml vs. \$61.21 for trade, 81% less!!

Other Generic PGs

- Lumigan 0.03%
 - Generic, but not widely available
 - \$56.96 vs \$135.73, 58% less
 - Note: Trade name is now 0.01%
- Travatan 0.004% ≈\$27.33 (45% less)
 - Since 2013
 - Trade name no longer available
 - Only Travatan Z ≈\$60.66

Vyzulta (latanoprostene bunod 0.024%)

- B&L: approved Nov 2017
 - To lower IOP in patients with POAG or OC HTN
 - Once daily administration in evening
- PG analog
 - Combines PG with a nitrous oxide molecule for better efficacy
 - Dual action: increases aqueous outflow through the TM as well as uveoscleral outflow
 - In studies, IOP decreased 7.5 mm-9.1 mm
 - 1.23 mm lower than latanoprost
 - Good RX: \$375 for 5 ml

Vyzulta

- Side effects: similar to all PGs
 - Increased iris pigmentation
 - Darkening of eyelid skin
 - Eye lash changes, including increased length, thickness, and or direction
 - Use in caution in pts with h/o ocular inflammation
 - Macular edema, including CME, has been reported
 - Conjunctival hyperemia 6%
 - Eye irritation 4%
 - Eye pain 3%
 - Installation site pain 2%

Beta Blockers: pros

- Good IOP response
- Few ocular side effects
 - Inexpensive
 - Multiple generics
 - ≈\$4.00

Beta Blockers: cons

- Long term drift
 - After 2 years – nearly 50% change therapy
- Systemic side effects:
 - Breathing issues, pulse rate, depression, decreased libido, caution in diabetics etc.
- BID administration
- Many drug/drug issues
 - Systemic b-blockers, cardiac meds (digitalis, CA channel blockers)

Rhopressa (netarsudil 0.002%)

- Rho Kinase inhibitor for the reduction of elevated IOP in pts with OAG or OC HTN
- FDA approved Dec 2017: Aerie Pharmaceuticals
 - Not yet available in pharmacies
- Once daily in evening
- Increased outflow of aqueous through TM
- IOP decrease similar in studies to timoptic bid
 - 3.9mm -4.1 mm

Rhopressa

- Conjunctival hyperemia 53%
- Common (≈20%)
 - Corneal verticillata
 - Instillation site pain
 - Conjunctival hemorrhage
- Less common (5-10%)
 - Instillation site erythema
 - Corneal staining
 - Blurred vision
 - Increased lacrimation
 - Erythema of eyelid
 - Reduced VA

Try Switching first

- Clinical trials – adding prostaglandin to timolol monotherapy – 25% further IOP reduction
- Switching from timolol to prostaglandin – similar IOP reduction
 - Approximately 23%
- Different class of medication
- Different medication with class
 - Some evidence that pt may respond better to one PG vs. another

Why Switch?

- Fewer adverse effects
- Better compliance
 - Less meds=better compliance
- Lower cost
 - Less meds=less cost

What to add next?

- OHTS Study: at 60 mos, 49% of patients required 2 or more meds to reach target IOP
- So what is best additive to PG?
 - Beta-Blocker?
 - Alpha-agonist?
 - CAI?
 - Fixed combinations?

What to add next?

- “All 3 classes of meds are similarly effective in lowering mean diurnal IOP when used in combination with PGAs”

Adjunctive Therapy with Latanoprost

PURPOSE: To determine the additive IOP reduction of various topical IOP-lowering agents used adjunctively with latanoprost

METHODS:

- Retrospective evaluation of 73 eyes of 73 patients with glaucoma and inadequate IOP control on latanoprost alone
- Each patient received adjunctive treatment with an additional IOP-lowering agent (dorzolamide, brimonidine, timolol, or other beta-blockers) for 1 year

Brinzolamide vs. Timolol as Adjuncts to Latanoprost

PURPOSE: To compare the diurnal and nocturnal effects of brinzolamide and timolol on IOP in patients already receiving monotherapy with latanoprost

DESIGN: Prospective, open-label, and crossover clinical trial

METHODS:

- Baseline data of 24 hr IOP were collected in a sleep laboratory while patients were receiving latanoprost monotherapy
- Measurements were taken every 2 hrs in the sitting and supine positions during the 16-hr diurnal/wake period and in a supine position during the 8-hr nocturnal/sleep period
- Patients were randomly assigned to receive an add-on treatment with either brinzolamide 1% 3 times per day or timolol 0.5% gel forming solution once every morning for 8 weeks
- Cross over to receive the other add-on treatment

Brimonidine vs. Brinzolamide as Adjuncts to Travoprost

PURPOSE: To compare efficacies of adjunctive therapy with brimonidine 0.15% or brinzolamide 1% in combination with travoprost 0.004%

DESIGN: Three-month randomized, parallel-group, double-masked, multicenter clinical trial

METHODS:

- Patients were randomized to receive adjunctive therapy with brimonidine (N = 79) or brinzolamide (N = 84)
- Treatment efficacy was assessed after 1 and 3 months of concomitant therapy
- IOP was measured at 8:00 AM, noon, and 4:00 PM at baseline (on travoprost monotherapy) and after 3 months of concomitant therapy

What to add next?

- Alpha-agonist/CAI
 - Alphagan/Trusopt or Azopt
 - CAI/Alpha-agonist
 - Beta-blocker
 - Fixed combination as appropriate

FIXED COMBINATIONS

Benefits of Fixed Combinations for Glaucoma Management

- Dosing-one drop vs two drops
- Convenience may help patient compliance
- No risk of washout from second drug¹
- Possible cost savings (only 1 copay)

¹Choudhri et al. *Am J Ophthalmol*. 2000

Compliance with Eyedrops

- Once daily – 49%
- More than twice daily – 39%
- More than one kind – 32%

Current Fixed Combinations

- Dorzolamide hydrochloride-timolol maleate ophthalmic solution (*Cosopt*[®])
- Brimonidine tartrate/timolol maleate ophthalmic solution 0.2%/0.5% (*Combigan*[™])
- Brinzolamide 1%/brimonidine 0.2% (*Simbrinza*[™])

Cosopt

- 2% dorzolamide/0.5% timoptic
- BID
- 1st combo for glc (1998)
- Generic as well as trade name (Merck)
- Studies showed combo lowered pressure more than either timoptic or dorzolamide alone

Combigan

- Timoptic 0.5%/brimonidine 0.2% BID (Allergan)
 - October 2007
- IOP lowering effect of Combigan BID was slightly less than T 0.5% BID and brimonidine 0.2% TID concurrently
- BID administration
- Not approved as first line therapy at this time only as adjunctive

Simbrinza™

- Brinzolamide 1%/brimonidine 0.2% SUSPENSION by Alcon
 - SUSPENSION so needs to be shaken
- First combo without beta-blocker!!!
- FDA Approved: April 19, 2013
- Cost: ≈\$100 for 8 ml bottle

Simbrinza™

- Efficacy proven in 2 Phase 3 randomized, multi-centered, double-masked studies
 - IOP was reduced an additional 1-3 mm vs. individual components
 - IOP reduced 21-35% at month 3 (5 to 9 mm)
- Most frequent adverse effects (3-5%)
 - Blurred vision
 - Eye irritation
 - Dysgeusia (bad taste)
 - Dry mouth
 - Allergy
- Rate of discontinuation ≈ 11%
- Beware with sulfonamide allergies

PG/Beta Blocker?

- DouTrav available in Europe (Alcon)
- Xalacom (Pfizer) also in Europe
- To date, no PG combo FDA approved in US
 - Studies have not shown that combo qd is as good as separate components
 - Increased compliance alone is not enough for FDA
- Roclatan combo: Rhopressa (netarsudil 0.002%) with latanoprost perhaps 2nd Q 2018
 - Mercury 1 and 2
 - 1-3 mm lower than each agent separately

Zioptan (tafluprost 0.0015%)

- FDA approved Feb 13th, 2012
- First preservative-free PG
- Indicated for reducing elevated IOP in patients with open-angle glaucoma or ocular hypertension

Zioptan (tafluprost 0.0015%)

- FDA approval based on 5 clinical studies of 905 pts
 - IOP lowered 6-8 mm at 3 mos, 5-8 mm at 6 mos in pts with baseline IOP of 23 to 26 mm
- Dosed once daily in the evening
- Cost: ≈ \$197 for 30-day supply
 - Good RX 10/2017

Zioptan (tafluprost 0.0015%)

- Side effects:
 - Increased length, color, thickness and shape of lashes
 - Usually reversible upon d/c
 - Increased iris pigmentation
 - Redness of eyes

Cosopt PF

- Preservative-free Cosopt by Merck
 - Dorzolomide 2%/timoptic 0.5%
- FDA approved Feb 1, 2012
- Commercially available June, 2012
- 0.2 ml individual vials

Cosopt PF

- In a controlled study of 26 pts with IOP \geq 21mm, IOP lowering effect same as traditional Cosopt
- IOP effect of Cosopt PF bid was greater (1-3 mm) than either dorzolomide 2% tid or timoptic 0.5% bid alone
- Cost: \approx \$170 mos supply
 - Good RX 10/2017

TRY TO RELATE VF TO ONH APPEARANCE

KNOW WHEN TO REFER

When to refer

- Pt progressing despite adequate IOP
- Unable to get IOP to target despite several attempts
- Poor compliance despite several DOCUMENTED discussions
- Advanced disease
- Simply not comfortable
- BETTER TO REFER EARLY THAN LATE!!!
- **You do not want to be the last person a patient sees before he goes blind!!**