Glaucoma Pharmacology A-Z

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PGAs

- QHS dosing
- Long duration of action
- Flatten diurnal curve
- Effective on trough and peak IOP
- No systemic side effects
- Little tachyphylaxis

Selecting Therapy

- Goals of primary therapy
  - Achieve lowest IOP on monotherapy
  - High response rate—few to no nonresponders
  - Maintain consistent IOP lowering
  - Obtain patient compliance and adherence by meeting their goals and expectations
- Building-block approach to medical therapy
  - Establish the strongest foundation prior to resorting to adjunctive therapy

PGAs 2008

- Bimatoprost (Lumigan)
- Latanoprost (Xalatan)
- Travaprost, Travaprost Z (Travatan, Travatan Z)

Prostaglandin analogs

- Lower IOP by enhancing uveoscleral outflow
- They also reduce episcleral venous pressure
- PGAs work by causing up to a 26% reduction in resistance to outflow
- Breaks down collagen in the uveoscleral meshwork
- Create new channels for outflow

Prostaglandin Side Effects

- Conjunctival hyperemia: Severe hyperemia
  - Lumigan 3.5%
  - Travatan 1.5%
  - Xalatan <1%
  - Rescula 1%
- Is this a transient phenomenon?
- Is it an allergic conjunctivitis?
- Is it worth stopping the drop?

Conjunctival hyperemia

- PGAs have an effect on EP receptors which are vasodilators
- The stronger the drug binds to that receptor the more pronounced the vasodilation effect will be.
- Will switching from 1 PGA to another decrease the hyperemia effect?

Prostaglandins

- Oh sure, we know they are good, but just how good are they?
  - Average IOP drop of 34%
  - Improved compliance
  - Excellent safety profiles
- In general, PGAs are the initial therapy of choice.

Prostaglandin Side Effects

- Iris pigmentation
  - Is it reversible?
  - Is it pre-cancerous?
- Xalatan – 6.7% @ 6mths
  16% @ 12mths
- Travatan – 3% @ 12 mths
- Lumigan – 1.9% @ 12mths
- Rescula – 1 patient
- SO?

Clinical Comparison Trials of the Once-Daily Lipids

- Evaluation of intra-class differences in efficacy and safety
- Seven published, prospective, randomized, investigator-masked, parallel-group studies
- Trials varied in duration, patient selection and characteristics, and methods of data analysis

Other Prostaglandin side effects

- CME
- Uveitis
- Reactivation of HSK
- Hypertrichosis
- Periorbital skin darkening
- One must take into consideration the benefits of low IOP with the risks of the side effects

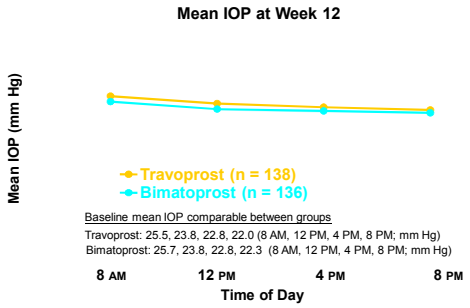
Bimatoprost and Travoprost

	Parrish et al, 2003*	Noecker et al, 2003†	Cantor et al, 2005
Sponsor	Pfizer	Allergan	Allergan
Length	12 weeks	3 months	6 months
Bimatoprost	n = 136	n = 16	n = 76
Travoprost (0.004%)	n = 138	n = 15	n = 81
Latanoprost	n = 136		

*Study also included arms for bimatoprost 0.1% and latanoprost 0.005%.
†Study was comprised of African-American patients.

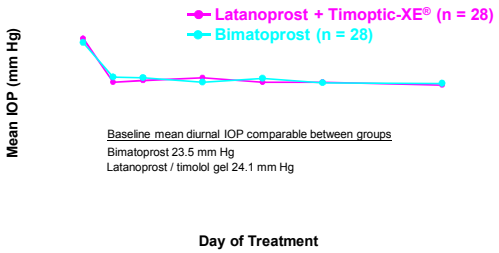
Parrish et al. *Am J Ophthalmol.* 2003;
Noecker et al. *Adv Ther.* 2003; Cantor et al. *Br J Ophthalmol.* 2006.

Bimatoprost and Travoprost: 12-Week Study



Parrish et al. *Am J Ophthalmol*. 2003

Bimatoprost and Latanoprost+Timoptic-XE®: 6-Month Study



Manni et al. *Graefe's Arch Clin Exp Ophthalmol*. 2004

Bimatoprost and Travoprost: 6-Month Safety Results

- Both medications were well tolerated
- Most common adverse event: ocular redness
  - 16 patients (20.8%) in the bimatoprost group and 12 patients (14.8%) in the travoprost group (*P* = .326)
- Ocular itching reported for 7.4% of travoprost patients and 2.3% of bimatoprost patients (*P* = .278)
- Treatment-related adverse events leading to patient discontinuations
  - 8 patients in the travoprost group exited early: 4 for lack of efficacy, 2 for ocular redness and lid erythema, 1 for ocular dryness and itching, and 1 for allergic symptoms
  - 2 patients in the bimatoprost group exited early: 1 for blurry

Noecker et al. *Adv Ther*. 2004;21(4):in press

Prostaglandins

- All decrease IOP by increasing uveoscleral outflow
- All are effective at squashing the diurnal curve
- They have either no effect or a positive effect on retinal perfusion
- But does 1 work better than the others?

Bimatoprost and Latanoprost: 6-Month Safety Results

- Most common side effects:
  - Hyperemia (bimatoprost 44.4%; latanoprost 20.6%)
- Similar rates of discontinuation due to AEs
  - Bimatoprost: 4.5% overall; 2.3% for hyperemia
  - Latanoprost: 3.7% overall; 0.0% for hyperemia
- Uveitis: One patient in latanoprost group; no cystoid macular edema

Noecker et al. *Am J Ophthalmol*. 2003

IOP reducing effect

- According to package inserts:
  - Latanoprost – 6.7mm
  - Unoprostone – 3-4mm
  - Bimatoprost – 8.1mm
  - Travaprost – 7.1mm

XLT Study – Parrish, Palmberg, et. al. (AJO, May 2003, Vol. 135, No.5)

- Multicenter study to compare IOP lowering efficacy of Bimatoprost vs Latanoprost vs Travaprost
- Also compared safety profiles of the 3 drugs
- Conclusions: All 3 drugs were comparable in their ability to lower IOP at all time periods.
  - Latanoprost exhibited greater ocular tolerability

Look at their failure rate:

- Percent of pxs who didn't reach their target IOP
  - Latanoprost – 14%
  - Bimatoprost- 6%
  - Travaprost – 8%
- SO?

Another way to look at efficacy:

- % of IOP reduction –
  - Latanoprost – 27%
  - Unoprostone – 15%
  - Bimatoprost – 33%
  - Travaprost – 28%
- FYI: Timolol 24%

What If:

- A patient failed on Xalatan?
- If switched to Lumigan, 57% achieved target IOP
- If switched to Travatan, 45.5% achieved target IOP
- SO?- Are all prostaglandins really created equal?

What is their ability to lower IOP <17mm?

- Latanoprost – 49.5% of pxs
- Bimatoprost – 64%
- Travaprost – 56.3%

Bournias, et.al , Journal of Ocular Pharmacology (2003)

- Replaced Xalatan w/ Lumigan
- Results:
  - IOP <15mm dropped from 11% to 36%
  - IOP <18mm dropped from 33% to 66%
  - Mean IOP decrease of 3.4mm

Final prostaglandin thoughts

- They are additive to other G drugs but not with each other
- Travatan and Lumigan maintain target IOP 36hrs after instillation and significant IOP drop up to 84 hrs after instillation
- Does one really work better than the others on African –Americans?
- What about BID dosing?

Beta-blocker side effects

- Respiratory-
  - Fatigue, bronchospasm, SOB!
- Cardiac –
  - Lethargy, bradycardia, lower pulse rate
- CNS depression-
  - Impotence, confusion
- But how common are they?

Beta-blockers

- 30 year history of successfully lowering IOP
- Reduces aqueous humor formation
- Adrenergic agonists
- Lowers IOP 22-28%
- Ocularly well tolerated

Lama study (AJO 11/02)

- Conclusions:
  - ...identifies no scientific studies supporting the development of worsening claudication, depression, hypoglycemia,sexual dysfunction or impaired neuromuscular transmission
  - Recommends careful medical history and checking pulse rate and rhythm
- So?

Beta-blockers

- Timolol maleate – Timoptic, Timoptic XE (1/2, 1/4 %)
- Carteolol – Ocupress 1% (Intrinsic sympathomimetic activity)
- Levobunolol – Betagan ½%
- Timolol hemihydrate – Betimol ¼, ½%
- Istalol ¼,1/2% - QD dosing indication
- Betaxolol ¼% - cardioselective, safer?

Beta-blocker side effects

- Cardiac problems
  - Bradycardia
  - Hypotension
  - Exercise intolerance
  - Heart block
- Respiratory problems
  - Bronchospasm
  - Status asthmaticus

Beta-blocker side effects

- CNS
  - Often overlooked
  - ACID
    - Anxiety
    - Confusion
    - Impotence
    - Depression
  - General decreased affect
- Diabetic problems
  - Decreased sense of caloric need due to depressed adrenergic surge

Adrenergic Agonists

- Dual mechanism of action
  1. Reduce aqueous production
  2. Enhance outflow mechanisms
- 22-28% IOP reduction
- Short duration of action
- TID dosage
- Avoid in kids

Beta-blocker side effects

- 22% of pxs have contraindication to or significant side effect from beta-blocker
- Question, query and query some more!
- Be specific
- Remember the dose relationship so:
  - ¼% rather than ½%
  - QD rather than BID
- They are real (may be anecdotal)

Mechanism of Action of Brimonidine-PURITE®

- Complements lipids because it decreases aqueous production
- Complements timolol because it increases uveoscleral outflow

Beta-blocker debate

- Are they still useful?
- As initial therapy?
- QD or BID?
- 0.25% or 0.5%?
- Gel or drop?
- Monocular therapy?
- How bad are the side effects really?
- Do systemic beta-blockers affect the efficacy of the drops?
- Tell me something good about beta-blockers!

Brimonidine Formulation Comparison

	ALPHAGAN® P		ALPHAGAN®
Concentration of Brimonidine	0.1%	0.15%	0.2%
pH	7.7	7.2	6.3-6.5
Preservative	PURITE®		BAK
Viscosity agent	Carboxymethylcellulose		Polyvinyl alcohol
Electrolytes	Potassium chloride, calcium chloride dihydrate, magnesium chloride hexahydrate		–

Brimonidine-PURITE® Development Strategy

- Improved formulation
  - –Enhance tolerability
  - –Maintain efficacy
  - –Alternative preservative to BAK
  - –Vehicle based on artificial tear technology

Effect of Brimonidine-PURITE® 0.15% Formulation on Safety

- Ocular surface exposed to 25% less drug with new formulation
  - –Less allergy, redness, irritation
- Lower concentration also means fewer systemic effects as less drug enters nasolacrimal duct

Katz. *J Glaucoma*. 2002.

Preservative Composition of Glaucoma Agents

Products that contain a gentle preservative, such as PURITE®, may pose less risk to the ocular surface.

ALPHAGAN® P	**Allergan, Inc.**	**50 ppm PURITE®**
ALPHAGAN®	**Allergan, Inc.**	**.005% BAK**
BETAGAN®	**Allergan, Inc.**	**.005% BAK**
LUMIGAN®	**Allergan, Inc.**	**.005% BAK**
Cosopt®	Merck & Co., Inc.	.0075% BAK
Trusopt®	Merck & Co., Inc.	.0075% BAK
Azopt®	Alcon	.01% BAK
Betoptic® S	Alcon	.01% BAK
Timoptic®	Merck & Co., Inc.	.01% BAK
Timoptic XE ®	Merck & Co., Inc.	.012% BDD
Rescula®	Novartis	.015% BAK
Travatan	Alcon	.015% BAK
Xalatan®	Pharmacia	.02% BAK

BAK: benzalkonium chloride; BDD: benzododecinium bromide

Brimonidine side effects

- 10-20%
  - Hyperemia
  - Allergic conjunctivitis
  - Ocular pruritis
- 5-9%
  - burning sensation,
  - conjunctival folliculosis,
  - ocular allergic reaction,
  - oral dryness,
  - visual disturbance

- Do these worsen with time?
- How do you know if the drops are the culprit?

Benzalkonium Chloride (BAK)

- Most commonly used preservative in glaucoma products
- BAK can accumulate and remain in ocular tissue
  - –Has been shown to cause cytotoxic effects on the ocular surface in numerous studies (DeSaint, 2000; Gasset et al, 1974; Noecker, 2004)

DeSaint et al. *Curr Eye Res*. 2000; Gasset et al. *Am J Ophthalmol*. 1974; Noecker et al. *Cornea*. 2004.

Alphagan systemic side effects

- Dry mouth (~20%)
- Fatigue (1-2%)
- Drowsiness
- Decreased BP

- This drug can cross blood-brain barrier, esp in older and younger pxs

Brimonidine questions

- What is the correct dosage?
- Which of the 3 products should be prescribed?
- Can it be used as stand alone therapy?
- Effect on diurnal curve?

CAI Side Effects

- ***Stinging***
- **Dryness**
- HA
- Bad taste
- Sulfa drug so:
  - Aplastic anemia?
  - Renal stones?
- What about Cosopt?

Carbonic anhydrase inhibitors

- Lower IOP by reducing aqueous production
- Reduce IOP by 16-22%
- Sulfa drugs!!
- Dosage question – BID or TID?
- Are they useful as stand alone drugs?

Oral CAI side effects

- Paresthesia
- Depression
- Kidney stones
- Metallic taste
- Diarrhea
- Aplastic anemia
- These are virtually non-existent with drops

CAI directory

- Trusopt – Dorzolamide 2%
- Azopt - Brinzolamide 1%
- Oral CAI
  - Acetazolamide – Diamox 250, 500mg
  - Methazolamide – 25, 50mg

CAIs make wonderful partners

- Feldman, et al 2006 –
- 1.5-1.8 mm lower IOP as compared to brimonidine 0.15% when added to travaprost
- This significance was present at all time points
- BID dosing

Companion study #2

- When compared to brimonidine 2% adding them to Travaprost...
- IOP lowered by 13% w/ brimonidine
- IOP lowered by 23% w/ brinzolamide

Combination drugs

- Cosopt – timolol-dorzolamide
- Timolol ½%, Dorzolamide 2%
- This drop works better than either timolol or dorzolamide does on their own
- Cosopt is not as effective as if you were using both timolol and dorzolamide
- Same side effects as beta-blockers and CAIs
- Capice? Kapeesh?

Companion study #3

- Stewart et al, 2006
- Compared to timolol 0.5% as additive to travaprost
- No difference at all between the 2 drugs
- CAI is effective at controlling night IOP spikes (TID?)

New Combo Drugs

- Extravan – Travaprost 0.004%/Timolol 0.5%
- Combigan – Bimatoprost/Timolol 0.5%
- What do we know about these?

Oral CAI

- Is there still a place for them?
- What is the correct dosage?
- Are there precautions we need to take?

Extravan

- Dosed QD – generally in AM
- Barneby study-
  - Lowered IOP 2-3mm more than T ½ alone
  - Lowered IOP 1-2mm more than Trav alone
  - Statistically significant in 7 0f 9 time points

Extravan

- Schuman Study
  - QD dosing in AM
  - Lowered IOP 7-9mm
  - Similar IOP drop if used Travatan and T ½ concommitantly
  - Consistent throughout day and for 3 months
  - Hyperemia – 14.3% w/ Extravan
  - - 23.4% w/ T ½ and Trav concommitantly

The Glaucoma Treatment Universe 2008

- Prostaglandins
- Alpha –agonist
- CAI
- Combo drugs
- Ginkgo , etc
- Beta-blockers
- Cardioselective beta-blockers
- ALT/SLT
- Trabeculectomy
- Nutrition issues

Eric's 7 Simple Rules For Treatment

1. Choose 30% IOP decrease as initial target
2. Squash the diurnal curve (Keep IOP peak <18mm)
3. Assess risk factors for progression and rate of progression
   (CT<555, IOP >26,C/D 0.5)

Regarding Prostaglandins:

- Generally the 1st line of treatment
- There are interindividual differences in efficacy
- Are there racial differences?
- If at first one fails; try, try , try again (with another prostaglandin)
- Why wouldn't you use a prostaglandin 1st?

Eric's Rules cont.

4. If you are going to treat; treat aggressively
5. KISS
6. Be mindful of perfusion issues
7. Above all, do no harm

Treatment paradigm – Step 2

- Prostaglandins 1st
- If not successful – try another agent by itself: Brimonidine bid or timolol
- If neither of these get IOP to desired level then add

Many Patients Require Adjunctive Therapy

- Ocular Hypertension Treatment Study (OHTS)[1]
  - 817 patients with OHT; target pressure reduction = 20%
  - At month-60 visit, 39.7% of patients in the medical treatment group required 2 or more medications to reach the target IOP
- Collaborative Initial Glaucoma Treatment Study (CIGTS)[2]
  - 307 newly diagnosed patients with mild to advanced glaucoma; aggressive target pressures set per formula
  - After first 2 years, >75% of patients required 2 or more medications to reach target IOP
- Even patients on the most powerful IOP-lowering medications often require adjunctive therapy[3]

1. Kass et al. *Arch Ophthalmol.* 2002; 2. Lichter et al. *Ophthalmology.* 2001. 3. Robin et al. *AGS.* 2003.

Treatment paradigm, part IV

- If on 2 meds and target IOP not met…
  - 1. Consider 3rd drop (Betoptic S or CAI)
  - 2. Substitute Combo drug for least successful drop
  - 3. Consider ALT or SLT
- What is maximum medical therapy nowadays?
- SLT/ALT and trabeculectomy should not be considered weapons of last choice or last chance

Consider Mechanism of Action (MOA) When Adding Medications

- Best chance of additivity by combining medications with different mechanisms
- Hypotensive lipids lower IOP by increasing aqueous outflow (uveoscleral/trabecular)
- Complement a hypotensive lipid by adding a drug that inhibits aqueous production
  - Brimonidine
  - CAI
  - Beta-blocker

Treatment Paradigm, Part III

1. Prostaglandins alone
2. Brimonidine or beta-blocker alone
3. Prostaglandin + beta-blocker or brimonidine or CAI (unless 1 of these absolutely sucked!)
4. Consider Cosopt or Combigan if (3) is not successful