Prostaglandin Analogs (PGs)

- **Mechanism of action:** increase uveoscleral outflow
- **Effect:** excellent (25-35% reduction)
- **Dosing:** once daily (doesn’t matter am/pm)
- **Side effects:**
  - Minimal systemic
  - Ocular:
    - Hyperemia
    - Hypertrichiasis
    - Hyperpigmentation – iris and periorbital skin
    - Prostaglandin-induced orbitopathy
Incidence of Prostaglandin-Induced Orbitopathy

Glaucma - Prostaglandins

• When to Use
  – POAG
  – Pigmentary glaucoma
  – Pseudoxfoliation glaucoma
  – Normal tension glaucoma
  – Ocular Hypertension
Glaucma - Prostaglandins

- When to reconsider:
  - Acute rise in IOP
  - Acute angle closure
  - Posner-Schlossman syndrome
  - Post-surgical spike
  - Pt with history of CME or risk of CME
  - Unilateral therapy
  - Pregnancy
  - Uveitic glaucoma (???)
  - Neovascular glaucoma (???)

UVEITIS

Flare-up rate with bimatoprost therapy in uveitis glaucoma.

Frankart, C., Velazquez Castañeda, B., Bhut, D., Dorey, D.


Abstract

PURPOSE: To evaluate the flare-off rates in patients with uveitic glaucoma treated with topical bimatoprost and to assess its effect on intraocular pressure (IOP) in the control eye.

METHODS: A retrospective case series of 12 patients with a diagnosis of uveitic glaucoma who received topical bimatoprost therapy for at least 6 months. The primary outcome measure was the flare-off rate, defined as a two-fold increase in IOP.

RESULTS: Of the 12 patients, 10 were identified. Of these, 10 patients had a flare-off rate of 100% (10/10). The flare-off rates were higher in patients with a history of CME or risk of CME compared to patients without such history. The flare-off rate was significantly higher in eyes with a history of CME compared to eyes without such history (p = 0.001).

CONCLUSION: These data suggest that bimatoprost as an adjunct to anti-glaucoma therapy in patients with uveitic glaucoma can slow or stabilize the flare-off rate in eyes with a history of CME or risk of CME.
The Use of Prostaglandin Analogs in the Uveitic Patient

Michael B. Horsley and Teresa C. Chen
Glaucoma Service, Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston, MA, USA


SUMMARY

The use of prostaglandin analogs in uveitic patients remains controversial. A causal relationship has yet to be established between prostaglandins and the reactivation of anterior uveitis, the development of cystoid macular edema, or the reactivation of HSK.

Due to the efficacy of prostaglandins in lowering IOP in patients with uveitis and the small likelihood of developing these rare complications, prostaglandin analogs should remain in the treatment algorithm of uveitic glaucoma patients.
Cystoid Macular Edema
**following cataract surgery**

Clinically Significant Diabetic Macular Edema???
Glaucoma - Prostaglandins

**Drugs:**
- latanoprost (Xalatan® and generic, Xelpros®)
- travoprost (Travatan-Z® and generic)
- bimatoprost (Lumigan® 0.01% and generic 0.03%)
- tafluprost (Zioptan®)

**How do they compare?**
- Efficacy
- Side effects
- Cost

(NEW DRUG)
Latanoprostene Bunod (Vyzulta®, B&L)

- Latanoprostene = latanoprost
  - Increases uveoscleral outflow
- Bunod modification donates NO
  - Exerts its effect in trabecular smooth muscle
  - Activating cyclic guanosine monophosphate signaling pathway
  - Resulting in trabecular relaxation and increased conventional outflow

**Mechanisms would be expected to be additive**

Bunod modification

Latanoprost moeity
Latanoprostene Bunod vs Timolol: APOLLO and LUNAR Trials

- Study design
  - Randomized (2:1 [LBN:timolol]) phase 3, multicenter, double-masked, parallel-group studies
- 2 treatment groups
  - LBN, 0.024%, qhs
  - Timolol, 0.5%, bid


APOLLO LUNAR

<table>
<thead>
<tr>
<th>Number of subjects</th>
<th>APOLLO</th>
<th>LUNAR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean baseline IOP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LBN</td>
<td>26.7 mm Hg</td>
<td>26.6 mm Hg</td>
</tr>
<tr>
<td>Timolol</td>
<td>26.5 mm Hg</td>
<td>26.4 mm Hg</td>
</tr>
</tbody>
</table>

APOLLO: Efficacy and Safety

- IOP reductions
  - 8 to 9 mm Hg for LBN (n = 264)
  - 6.5 to 7.5 mm Hg for timolol (n = 123)
- Adverse events
  - Similar rates between groups
  - Most common:
    - Eye irritation
    - Conjunctival hyperemia

* P ≤ .002 vs timolol

Phase 2 Study of Latanoprostene Bunod vs Latanoprost: VOYAGER

- N = 413 (intent to treat)
- At highest doses, LBN lowered IOP 1 to 1.5 mm Hg more than latanoprost
- Most common adverse event: pain upon instillation
- Conjunctival or ocular hyperemia:
  - LBN: 7.0%
  - Latanoprost: 8.5%
new info, inc citation

Cynthia, 7/14/2016
Glaucoma – beta-adrenergic antagonists (beta blockers)

- Mechanism of action: decrease aqueous production
- Efficacy: very good (25-30% reduction)
- Dosing: once vs twice daily
- Side effects:
  - Minimal ocular side effects
  - Systemic:
    - Bradycardia
    - Bronchial constriction
  - **CHECK EXISTING MEDS, VITALS
- Short term escape & long term drift

Glaucoma – beta blockers

- When to use:
  - First line therapy for patients with contraindications to prostaglandins
  - Need rapid lowering of IOP
  - Cost (generic is cheap)
  - Added drug for prostaglandin users
    - Different mechanism of action
- When to reconsider:
  - Symptomatic bradycardia
  - CHF patient
  - Patient on oral bb (+/-)
  - Normal tension glaucoma
**Glaucoma – beta blockers**

- Available drugs:
  - timolol maleate (Timoptic®, Timoptic-XE®, Timoptic PF®, generics, Istaol ®)
  - timolol hemihydrate (Betimol ®)
  - levobunolol (Betagan ® and generic)
  - metipranolol (Optipranolol ® and generic)
  - carteolol (Ocupress ® and generic)
  - betaxolol (generic solution, Betoptic-S ®)

**Glaucoma – alpha-adrenergic agonist**

- Mechanism of action:
  - Decrease in aqueous production
  - Increase in uveoscleral outflow
- Efficacy: good (20-25% reduction)
- Dosing: tid vs bid
- Side effects:
  - Systemic:
    - Somnolence
    - Dry mouth
    - Dizziness/fainting
  - Ocular:
    - allergy

**Glaucoma - brimonidine**

- Allergy:
  - Original brimonidine ® 0.2% generic
    - 30%+ allergy rate
  - Alphagan-P 0.15% (only available in “generic” with Polyquad ® preservative)
    - 20% allergy rate
  - Alphagan-P ® 0.1% (Purite ® preservative)
    - 10-15% allergy rate
  - Combigan ® (0.2%, with 0.5% timolol, BAK)
    - 5% allergy rate (?)
  - Simbrinz® (0.2% with 2% dorzolamide, BAK) -- ??? Allergy rate
Glaucoma - brimonidine

- **When to use**
  - Excellent additivity with prostaglandin
  - Good additivity with beta-blocker
  - Rapid IOP lowering (esp in combo)
  - Preservative toxicity/allergy
  - Category B pregnancy (D/C in breastfeeding)

- **When to reconsider**
  - Monotherapy (dosing)
  - Hx of allergy (any form of brimonidine)
  - CHILDREN (contraindication)

---

LoGTS

- Randomized, double-masked clinical trial to compare brimonidine 0.2% vs timolol 0.5% in preserving visual function in normal tension glaucoma patients
  - brimonidine 0.2% bid
  - timolol maleate 0.5% bid
  - Followed with VF every 4 months for minimum of 4 years

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**A Randomized Trial of Brimonidine Versus Timolol in Preserving Visual Function: Results From the Low-pressure Glaucoma Treatment Study**

THEODORE KLUPIN, JEFFREY M. LEHMANN, DAVID S. GREENFIELD, ROBERT BENCE, AND STEUBER CARLSON, ON BEHALF OF THE LOW-PRESSURE GLAUCOMA STUDY GROUP

*American Journal of Ophthalmology*

April, 2011
LoGTS

• Results:
  – No significant difference in IOP
  – Significant dropout in brimonidine group (allergy)
  – Significant/dramatic difference in visual field progression
    • 9% for brimonidine group
    • 39% for timolol group
• Question: what does this mean?

Glucoma – carbonic anhydrase inhibitors

• Mechanism of action: decreased aqueous production
• Efficacy: excellent (oral – 40-50%+); good (topical – 15-20%)
• Dosing: bid – tid
• Side effects:
  – Topical:
    • Bitter taste
    • Stinging
    • Hyperemia
    • Corneal endothelium

Glucoma - CAIs

• When to consider:
  – Good addition to prostaglandin
  – Brimonidine allergy
• When to avoid:
  – Fuchs corneal endothelial dystrophy
  – Pregnancy
  – Sulfa allergy (???)
• Available:
  – Dorzolamide (Trusopt® and generic)
  – Brinzolamide (Azopt®)
  – dorzolamide/timolol (Cosopt®, Cosopt PF®, and generic)
  – dorzolamide/brinzolamide (Simbrinza®)
Glaucoma - acetazolamide

- Typically used in emergency/acute situations rather than long term due to systemic side effects:
  - Paresthesia
  - Kidney stones
  - Metabolic acidosis
  - Blood dyscrasia
- Typical use:
  - Post-surgical IOP elevation
  - Acute angle closure (NON-PUPILLARY BLOCK ONLY)
  - Extremely elevated IOP
- Dosing:
  - 250 mg tablets qid (generic)
  - 500 mg time-released capsules (Sequels ®, generic) bid
(NEW DRUG)
Rho-Kinase Inhibitors

- netarsudil (Rhopressa®, Aerie) FDA approved in December 2017, in pharmacies Spring 2018
  - Inhibits the enzyme Rho kinase
  - Also inhibits norepinephrine transporter (increases adrenergic activity)

- Potentially lowers IOP by 3 mechanisms
  - Increasing trabecular meshwork outflow
  - Reducing episcleral venous pressure
  - Reducing aqueous production (via norepinephrine transporter inhibition)

\[ \text{IOP} = \frac{\text{PRODUCTION}}{\text{OUTFLOW}} + \text{EVP} \]


Netarsudil (Rhopressa®)

- Dosing is once daily (p.m.)
- Side Effects:
  - Hyperemia
    - 50-60% of patients
  - Sporadic
    - Conjunctival hemorrhages (small)
    - Corneal verticillata
    - Intracellular phospholipids
    - Asymptomatic
    - Did not decrease visual function

Netarsudil (Rhopressa)

- Lowered IOP approximately 5-7 mmHg, irrespective of starting IOP
  - May be best suited for those with lower IOP (?)
- Current development plan is in combination with latanoprost
  - netarsudil, 0.02%, plus latanoprost fixed combination lowered IOP more than latanoprost (P < .0001) or netarsudil, 0.02% (P < .0001), did in a completed phase 2b trial
  - Hyperemia: 14% latanoprost, 40% netarsudil, 40% fixed combination
NEW DRUG!!!!
latanoprost + netarsudil (Rocklatan)
• First available fixed combination in US with a pga
• First available fixed combination with once daily dosing (night)
• May be particularly effective in patients with lower starting IOP
• FDA approved March 2019

Glaucma - pilocarpine
• Mechanism of action – increase trabecular outflow
• Efficacy: good (25%)
• Dosing: qid
• Side effects:
  – Accommodative spasm
  – Browache
  – Bronchial constriction
• Use: acute angle closure with pupillary block (low concentration)

IOP-Lowering Drugs: Sites of Action
**Fixed Combination Medications**

- dorzolamide/timolol (Cosopt® and generic; Cosopt PF®)
  - Bid dosing
- brimonidine/timolol (Combigan®)
  - 5% allergy rate
  - Bid dosing
- brinzolamide/brimondine (Simbrinza®)
  - First non-beta blocker fixed combination
  - BAK-preserved
  - TID dosing
- Netarsudil/Latanoprost (Rocklatan®)
  - First pga fixed combo in US
  - Qhs dosing

**Other Fixed Combinations**

- Imprimis Pharmacy:
  - Compound multiple formulations of off-patent ophthalmics in a multi-dose preservative-free bottle, sell directly to patient (no insurance)
  - Potential Advantages:
    - No preservatives
    - Multiple drugs in one bottle = better adherence
    - Potential cost savings
    - Eliminates third-party dictated prescribing

**Generic Grab Bag**

- timolol maleate, other BBs
- latanoprost —or— travoprost — or — bimatoprost 0.03%
- brimonidine 0.15% -or- 0.2%
- dorzolamide
- (dorzolamide/timolol)

**Generic MMT:**

- Latanoprost or travoprost or bimatoprost
- Brimonidine 0.15% or 0.2%
- Dorzolamide/timolol combo
To gain FDA approval, a generic drug must:
- Contain the same active ingredient
- Be identical in strength, dose form, and route of administration
- Be bioequivalent (80-120% of branded product)
  - Not the same thing as therapeutic effect
- Have the same indications for use
- Meet the same batch requirements for identity, strength, purity, and quality
- Have a similar shelf life

We don't know about:
- Loss of control with long term use
- Tolerability
- Efficacy
- Multiple companies can make a generic; differences may not be apparent on bottle
- Cannot know for sure which company the pharmacy will have
- Patient’s confidence in generics varies
- Somewhat difficult to understand efficacy due to slow nature of disease
BAK-free Grab Bag

- Timoptic PF®
- Travatan-Z®, Xelpros® or Zioptan®
- brimonidine 0.15% -or- Alphagan-P® 0.1%
- Cosopt PF®

- BAK-free MMT:
  - Xelpros, Travatan Z, or Zioptan
  - Brimonidine 0.15% or 0.2%
  - Cosopt PF

Preservative-free Grab Bag

- Timoptic PF®
- Zioptan®
- Cosopt PF®
- (Compounded Drugs)

- Preservative-free MMT
  - Cosopt PF
  - Zioptan

Medication Follow-Up Questions

1. Is patient using drug?
2. Is patient tolerating drug?
3. Is there a therapeutic effect?
4. Am I reaching target IOP?
TYPICAL DRUG STEPPING

• Start with PGA
  – If good therapeutic effect but NOT reaching target, add timolol, brimonidine, or topical CAI
    • If good therapeutic effect with 2nd drug but still NOT reaching target, switch 2nd drug to combo
    • ***Here is where Vyzulta or Rocklatan could work
  – If PGA not having a good therapeutic effect
    • Consider non-adherence; re-try for another month
    • Consider switch to branded if using generic
    • Consider switching class (BB)
      – Can easily switch BB to combo if need additional therapy
  – If multiple meds don’t work - COMPLIANCE
Example: Guillermo

- 61yo healthy HM
- High risk ocular hypertension
  - IOPs range 28-32 OD, OS (multiple visits)
  - CCT 500 OU
  - C/D 0.4 OD, OS; normal, no RNFLDO
  - VF normal OU
  - OCT normal OU
- Goal IOP: 20% reduction from highest = under 25mmHg
- Initial therapy: latanoprost qhs OU

Example: Guillermo

- Follow-up:
  1. Is patient using drug? YES, claims excellent compliance
  2. Is patient tolerating drug? YES, minor redness, otherwise fine.
  3. Is there a therapeutic effect? NO – 20% minimum expected from first line med. His IOP on follow-up is 28mmHg
  4. Meeting target? (NO)
Example: Guillermo

- Tried additional time: No change in IOP
- Switched to branded: No change in IOP
  - COMPLIANCE CHECK!!!!
    - Pt adamant that he is using properly
    - Observe drop instillation = good technique
- Switched to timolol: IOP 21mmHg OD, 18mmHg OS

Example: Natalie

- 62yo Indian female with moderate POAG
  - IOP range 23-27mmHg OU
  - C/D ratio 0.8 OD, OS
  - Mild VF defect consistent with disc appearance
  - Ocular history also includes mild Fuchs corneal endothelial dystrophy
  - Medical history unremarkable
  - GOAL IOP: 35% reduction from highest = 17mmHg or less (mid teens)
  - Initial therapy: latanoprost
Example: Natalie

- **Follow-up:**
  1. Is patient using drug? YES, claims excellent compliance
  2. Is patient tolerating drug? YES
  3. Is there a therapeutic effect? YES – 20% minimum expected from first line med (<21). Pt’s IOP on meds = 20
  4. Meeting target? NO – Target is 17mmHg or less

- **Choices:**
  - Add
    - CAI (but remember Fuch’s)
    - BB
    - Brimonidine
  - Switch
    - PGA + timolol
    - Timolol alone
    - Other single or FDC
  - We went with brimonidine
    - On return, IOP 18mmHg
Glaucoma Drugs: What’s Next?

- Drug Delivery System (DDS)
  - Contact lens delivery
  - Punctal plug delivery
  - Insertable
  - Injectable
    - Sub-conjunctival
    - Anterior chamber
    - Vitreous
Where Does Laser Fit In?

SELECTIVE LASER TRABECULOPLASTY

- Specially designed laser used to treat pigmented trabecular meshwork cells
- Application of laser is same technique as for Argon Laser Trabeculoplasty (ALT)
- Differences:
  - Very short pulse (3 nanoseconds)
  - Eliminates collateral “burn” damage
  - Mechanism appears to be cytokine-mediated macrophage recruitment
  - Can be repeated

SELECTIVE LASER TRABECULOPLASTY

ALT  SLT
SELECTIVE LASER TRABECULOPLASTY

• Post-Op Care
  – Similar to ALT (? Steroid, ? NSAID)
• Complications:
  – Similar to ALT
  – Include:
    • Corneal abrasion
    • Uveitis
    • Scattered PAS
    • Transient IOP rise

“Selective Laser Trabeculoplasty as Primary Treatment for Open Angle Glaucoma” (Archives Ophthalmology July 2003)

– 45 eyes treated with SLT as primary treatment
– Mean IOP decrease: 7.7 mmHg (+/- 3.5)
– 4% non-response to treatment
– 3 eyes required meds at end of 18 month follow up
– Complications: redness, IOP spike


• Retrospective chart review of 120 eyes of 120 patients undergoing 90° SLT
• Primary measure: time to failure
• Results:
  – Average time to failure: 18 months
  – Success at 12 months: 62%
  – Success at 24 months: 34%
  – Success at 36 months: 28%
  – Success at 48 months: 24%
Predictors of Success in Selective Laser Trabeculoplasty for Chinese Open-angle Glaucoma

J Glaucoma • Volume 23, Number 5, June/July 2014

Aim: To investigate the determinants of success of selective laser trabeculoplasty (SLT) in Chinese open-angle glaucoma patients.

Conclusion: The positive predictors of SLT success included: higher pre-SLT IOP, use of topical CAI, thinner RNFL, and lower day 1 IOP. Using 3 anti-glaucoma medications was associated with failure.
Newly diagnosed OAG and OHTN (treatment-naïve)

Two groups:
- Medicine 1st
- Laser 1st

Compared
- HRQoL
- Clinical Efficacy
- Cost effectiveness

Followed for 36 mo
**LiGHT Trial**

- 356 SLT-1
- 362 Med-1

**LiGHT Trial Results**

- 91% patients completed 36 months
  - No difference in HRQoL
  - Proportion of patients at target IOP:
    - SLT-1 93% (0 patients requiring surgery)
    - Med-1 91% (11 patients requiring surgery)
  - SLT-1 provided medicine-free treatment for at least 36 months in 74% of group

**SELECTIVE LASER TRABECULOPLASTY**

- Consider when:
  - Non-compliance is an issue
  - There are undesirable or intolerable side effects from medications
  - Patient is on maximum tolerated medical therapy (?)
  - Surgical intervention is contraindicated
Is There Another Bag?

Surgery Indications

• Progressive visual field loss or optic nerve/nerve fiber layer loss despite maximum tolerated medical therapy
• Problems with adherence, allergies, intolerance to medications

Trabeculectomy

• Goal: Create fistula between anterior chamber and subconjunctival space
• Success is dependent on surgery but also highly dependent on post-surgical care
• Advantages:
  – No devices ($$)
  – Can achieve very low IOP
• Disadvantages:
  – Complications up to 40% cases
  – Failure up to 50% at 5 years
  – Cataract formation
Filtration Surgery - Complications

- Early
  - Hyphema
  - Inflammation
  - Low IOP
  - IOP spike
    - Deep AC
    - Shallow AC
  - Endophthalmitis (rare in early post-op period)

Filtration Surgery Complications

- Late Complications:
  - Bleb leak
  - Hypotony
  - Blebitis/Endophthalmitis
  - Scarring of ostomy

Alternatives to Trabeculectomy: Ex-Press Mini Shunt

- Non-valved, MRI compatible stainless steel device with 50micron lumen
- Originally placed under the conjunctiva (complications), now placed under a scleral flap
- Lower incidence of hypotony compared to trabeculectomy
- Similar results with fewer early complications
Alternatives to Trabeculectomy: Tube Shunts

- AKA Glaucoma Drainage Device
  - Historically used in patients with previous trabeculectomy failure or secondary glaucomas
  - Now more common as initial surgical choice
  - TVT study
    - Early post-op complications:
      - Tube: 21%  Trab: 37%
    - Late post-op complications:
      - Tube: 34%  Trab: 36%
    - Reoperation for surgical complications:
      - Tube: 22%  Trab: 18%
Minimally Invasive Glaucoma Surgery (MIGS)

- Aim to lower IOP with a better safety profile than filtration surgery
- Often termed “blebless” surgery
- Generally rapid recovery (same as cataract surgery) with minimal impact on quality of life
- Typically indicated for mild/mod POAG

Typical MIGS Features

- Ab interno
- micro incision
- Minimal trauma
- Efficacy
- High safety profile
- Rapid recovery

MIGS – Ab Interno

- Usually performed under gonioscopic view, usually through side port incision
- Most commonly performed at the same time as cataract surgery
  - Trabectome OR KDB (TM unroofing with blade)
  - Trabecular microbypass stent (iStent)
  - Suprachoroidal microbypass stent (iStent Supra)
  - Xen gel
  - Endocyclophotocoagulation (ECP)
Trabectome
• Bipolar cautery on a handpiece inserted into the AC through the cataract incision
• Ablates and removes a portion of the TM to increase aqueous outflow
• Typical IOP goal is mid-teens
• Complications include hyphema, inflammation
• KDB (similar)

iStent
• Very small titanium device implanted through TM into Schlemm’s canal
• Goal is to improve aqueous outflow through conventional path (bypass TM directly into Schlemm’s canal
• FDA trials compared cataract surgery alone with cataract/iStent; at 12 months:
  – 68% cataract/iStent patients IOP ≤21 without meds
  – 50% cataract surgery alone IOP ≤21 without meds
• IOP not lowered as much as with trabeculectomy
• Fewer complications/less hypotony
Xen Gel Stent (Allergan)

- Creates communication between anterior chamber and the subconjunctival space from the inside of the eye

Other Stents

- CyPass Microstent (Alcon) - WITHDRAWN
- Hydrus Micro Stent (Ivantis) – Schlemm’s Canal Scaffold

Endocyclophotocoagulation

- Endoscopic viewing system with laser, inserted through corneal incision and used to selectively ablate ciliary processes (decrease aqueous production)
- Mean decrease over 2 years = 7.1mmHg
- Not dependent on open angle/TM visualization
ICE Procedure

Other Procedures – Ab Externo
- Canaloplasty
  - Circumferential catheterization with suture tensioning of Schlemm’s canal

How Do MIGS Compare to Trab?
- Few reports, somewhat difficult to compare
- Different complications
- Typically less IOP reduction with MIGS than with filtration
- Often seen as an intermediate step in glaucoma management
- Appeal: procedure at same time as cataract surgery
MIGS – Final Point

• Since MIGS performed at time of cataract surgery, OD must be proactive in seeking surgeon who is experienced and willing to perform
• Don’t miss the opportunity!

Thank you for your attention!

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