




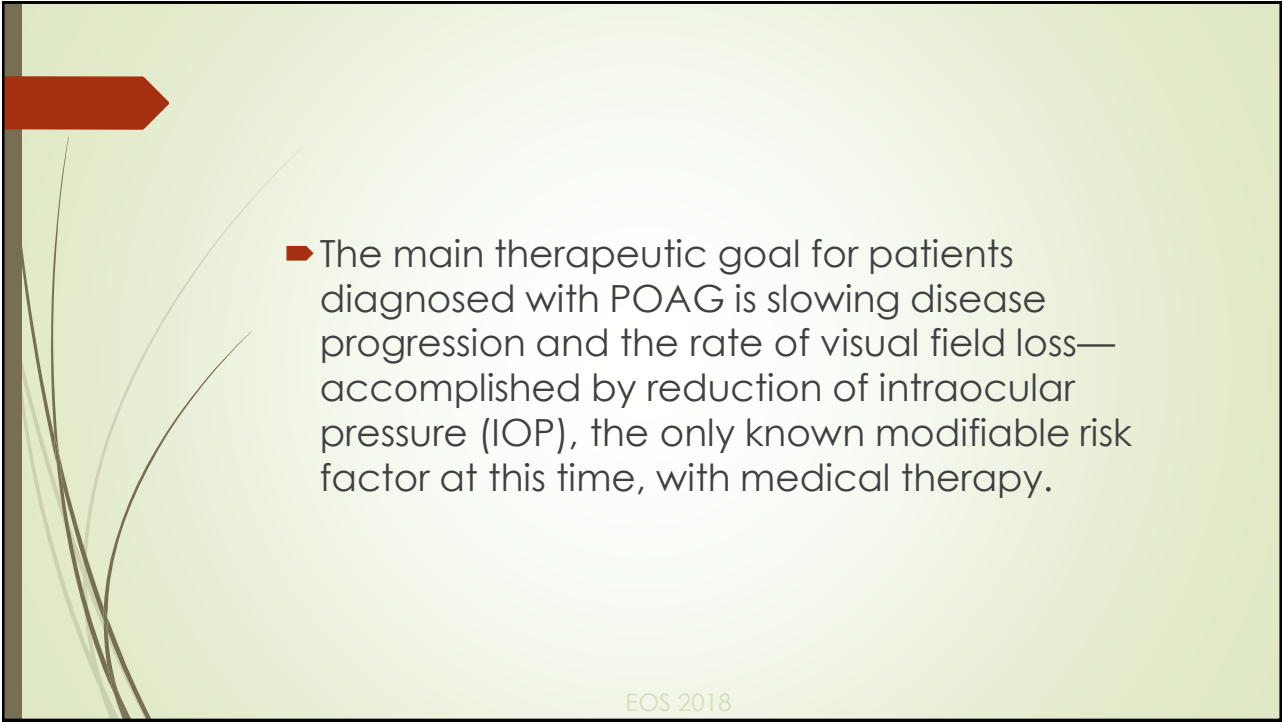
Here Comes the Rock

An Update on Current and Near Future Medical Therapy in POAG

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- ▶ primary open-angle glaucoma (POAG), a leading cause for blindness in the world, is estimated to affect around 80 million people worldwide by the year 2020.

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- ▶ The main therapeutic goal for patients diagnosed with POAG is slowing disease progression and the rate of visual field loss—accomplished by reduction of intraocular pressure (IOP), the only known modifiable risk factor at this time, with medical therapy.

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The ideal drug for treatment of POAG

- ▶ effectively lower IOP
- ▶ no adverse effects or systemic exacerbation of disease
- ▶ inexpensive with once-a-day dosing.

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Available Classes of Medical Therapy

- ▶ Beta-adrenergic blockers
- ▶ Alpha2 Agonists,
- ▶ Carbonic anhydrase inhibitors (CAIs)
- ▶ Prostaglandin analogs (PGAs)
- ▶ Miotic agents (parasympathomimetics)
 - ▶ Pilocarpine ophthalmic (Isopto Carpine)

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Beta-adrenergic blockers *decrease aqueous humor production*

- ▶ Timolol
- ▶ Levobunolol (Betagan)
- ▶ Betaxolol ophthalmic (Betoptic)

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Alpha2 Agonists

decrease aqueous production

- ▶ Brimonidine (Alphagan-P)
- ▶ Apraclonidine (Iopidine)

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Carbonic anhydrase inhibitors (CAIs)

Reduce secretion of aqueous humor

- ▶ Dorzolamide (Trusopt)
- ▶ Brinzolamide (Azopt)

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Prostaglandin analogs (PGAs)

Increase uveoscleral outflow of aqueous.

- ▶ Latanoprost (Xalatan)
- ▶ Bimatoprost (Lumigan)
- ▶ Travoprost (Travatan-Z)
- ▶ Tafluprost (Zioptan)
- ▶ Latanoprostene bunod ophthalmic (Vyzulta)

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Together we are strong



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Combination Therapy

- ▶ Less daily dosing simplifies a patient's treatment plan, avoids medication washout, decreases preservative exposure and, in many cases, decreases ocular effects without affecting IOP-lowering efficacy

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Combination Therapy

- ▶ **B-blocker/CAIs** *Cosopt, Azarga*
- ▶ **B-blocker/alpha agonists** *Combigan*
- ▶ **B-blockers/PGA** *Xalacom, Duotrav*
- ▶ **CAI/alpha agonists** *Symbrinza*
 - ▶ a good alternative treatment for those who cannot take B-blockers or wish to avoid PGAs due to ocular, especially with monocular treatments

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Where do we begin

ANDY WILLIAMS Where Do I Begin? (Love Story)



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- ▶ PGAs are often first-line treatment for IOP reduction in POAG and ocular hypertension, often enough to achieve and maintain adequate IOP control
- ▶ Depending on the target IOP another monotherapy or a combination therapy can be added

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Near Future...



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latanoprostene bunod 0.024% (*Vyzulta* B&L)

- Compound of latanoprost and a nitric oxide (NO) donor
- reduces IOP by increasing aqueous outflow through both the trabecular meshwork/Schlemm's canal and uveoscleral pathways.
- In phase III trials, once-daily use of this drug performed better than both twice-daily timolol and once-daily latanoprost. Mild punctate keratitis and ocular hyperemia are the most common ocular side effects

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Here comes the ROCK

New Medications in the near horizon



Rho kinase (ROCK)

- ▶ ROCK (Rho kinase) signaling regulates a wide spectrum of fundamental cellular events, such as cell adhesion, motility, proliferation, differentiation, and apoptosis
- ▶ is involved in a variety of pathological conditions, including vascular disease, cancer, asthma, insulin resistance, kidney failure, osteoporosis, neuronal degenerative disease, and **glaucoma**



ROCK inhibitors in Glaucoma

- ▶ destabilize filamentous actin, leading to more empty space in trabecular meshwork and improving outflow.

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ROCK inhibitors for Glaucoma

- ▶ One ROCK inhibitor have been approved for use in the clinical setting.
- ▶ **Ripasudil** (Glanatec, Kowa), approved in Japan in 2014 already **second-line drug for glaucoma treatment in Japan** in an eye drop form to increase the outflow of the aqueous humor as a treatment for glaucoma and ocular hypertension

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ROCK inhibitors for Glaucoma

NOW FDA APPROVED

- ▀ phase III clinical trial was completed in 2016.
- ▀ **Netarsudil** (*Rhopressa*, Aerie Pharmaceuticals) is both an RHO-kinase inhibitor and norepinephrine transporter inhibitor
- ▀ It has two mechanisms of action aimed at IOP reduction: increasing trabecular meshwork outflow (**ROCK-I**), and decreasing aqueous production (**norepinephrine transporter inhibitor**)

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And now combine the old and new..



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And combine the ROCK.. **Roclatan**

- currently in phase III clinical trials
- a combination of netarsudil 0.02% and latanoprost 0.005%. It is administered once daily to act on both the trabecular meshwork and the uveoscleral outflow

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“ Some of these new drugs are already in use in Japan for some years, and they very recently got FDA approval. They would hit the world market and our practices soon after.. ”

Horizons will remain open for more and more potent agents for the control of this dreadful sight threat; glaucoma



WHAT'S NEXT?

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That mighty cell!

- ▶ promote nerve health
 - ▶ neuroprotective agents
- ▶ Regenerative Medicine
 - ▶ neurotrophic factors and growth factors that could help the cells regenerate
- ▶ RGC Implantation
 - ▶ Animal studies: growth of both dendrites into the retina and axons along the retinal nerve fibre layer and across the optic chiasm



Annie Cavanagh image

Treating the brain

- ▶ glaucoma as a disorder of the entire visual system
 - ▶ IOP rise affects not only the RGCs and nerve fibres, but also extends to major vision centres in the brain!
 - ▶ Possible intrinsic distress in areas of the brain that process vision



The Gene Connection, *Pharmacogenetics*

- ▶ Phenotyping and genotyping to guide a pharmacogenetic approach, offering a more personalized care.
- ▶ Treatment of specific genetic defects with an appropriate individual therapy.



Gene Therapy; *promising animal studies*

- Introducing genes to the back of the eye that can inhibit apoptosis and encourage neurotrophic factors to preserve RGCs.
- Development of therapeutic constructs that target the cytoskeleton of the trabecular meshwork



“The understanding and management of Glaucoma, this vision threatening disease has made huge leaps in the past few decades, yet one eyes a still brighter future culminating in its true treatment...”



future
from here.

