What's New in Glaucoma Treatment! (TPG)

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Introduction

Glaucoma is the leading cause of irreversible blindness worldwide, affecting over 65 million people and projected to reach 79.6 million by the year 2020.1 The main modifiable and recognized risk factor for glaucoma is the intraocular pressure (IOP). The goal of any current treatment option is focused on lowering IOP to prevent or reduce damage to the optic nerve. In recent years, emerging technologies have led to a vast array of new treatment modalities for glaucoma and more continue down the pipeline.

Therapeutics*:*

Rho kinase (ROCK) inhibitors are a potential novel class of drugs that are currently in FDA trials in the US. Multiple studies have indicated that ROCK and Rho GTPase inhibitors induce reversible modifications to cell morphology and cell interactions in the trabecular meshwork (TM) and juxtacanalicular regions. This facilitates greater outflow of the aqueous humor resulting in a lower IOP. In addition to their ocular hypotensive properties, inhibitors of both ROCK and Rho GTPase have been shown to enhance ocular blood flow, inhibit postoperative scarring, and promote retinal ganglion cell survival and axon regeneration in animal models.2-3

RhopressaTM (Aerie Pharmaceuticals, US) is the first to approach regulatory submission in the US. Rhopressa is a small-molecule inhibitor of both ROCK and norepinephrine transporter (NET) and is thought to reduce IOP by increasing aqueous outflow through the TM and decreasing episcleral venous pressure4. In rabbit studies, the third mechanism of action includes norepinephrine transporter inhibition which decreased the total amount of fluid produced5. Currently, Rhopressa is in Phase III studies which started in July 2014 with Rocket 1 and Rocket 2. Jason Bacharach, M.D. presented the results at the recent American Glaucoma Society Meeting. In Rocket 1, the primary goal of the trial was to demonstrate non-inferiority of Rhopressa 0.02% dosed daily compared to timolol 0.5% dosed BID. Rhopressa did not meet the primary endpoint. In Rocket 2, 756 patients were enrolled and randomly assigned 1:1:1 to receive Rhopressa 0.02% QD, Rhopressa 0.02% BID, or timolol 0.5% BID; the primary endpoint was non-inferiority to timolol with subjects with baseline IOP > 20 mmHg and <25 mm Hg. Rhopressa demonstrated non-inferiority to timolol and met the primary endpoint analysis with minimal side effects. Bacharach et al. also had a double-masked randomized clinical trial that compared two concentrations of Rhopressa 0.01% QD, Rhopressa 0.02% QD to latanoprost QD. The study showed that both concentrations produced clinically and statistically significant reductions in IOP, the 0.02% concentration was less effective than latanoprost by 1mmHg, and both concentrations of Rhopressa was associated with a higher incidence. Of note, Rhopressa 0.2% maintained similar efficacy regardless of baseline IOP, whereas latanoprost was less effective at baseline IOPs of 22 - 26 mmHg. The company is expecting to file for a new drug application in 2016.

Aerie Pharmaceuticals also developed RoclatanTM, a once-a-day drug combination of Rhopressa and latanoprost. Currently, Mercury 1, the first phase III, 12 month 3-arm safety study evaluating Roclatan vs. Rhopressa QD vs. latanoprost monotherapy is expected to have an interim report in late 2016. The study goal is to demonstrate superiority of RoclatanTM compared to each of its two components. Additionally the second phase III, Mercury 2, a 90-day efficacy trial is expected to be completed in 2017.

Visneo (Latanoprostene bunod ophthalmic solution 0.024%), licensed by Nicox to Bausch + Lomb (US), is a novel nitric oxide (NO)-donating prostanoid FP receptor agonist that is rapidly metabolized in the eye into latanoprost acid and butanediol mononitrate. Latanoprost acid reduces IOP by increasing aqueous humor outflow through the uveoscleral pathway (non-conventional pathway). Meanwhile, the NO donors reduce IOP by causing relaxation of the TM and Schlemm's canal which result in increased aqueous humor outflow through the conventional pathway. The efficacy and safety of the drug were evaluated in two randomized phase III, double-masked, parallel-group studies called APOLLO and LUNAR. Each study compared latanoprostene bunod ophthalmic solution with timolol maleate ophthalmic solution 0.5% in subjects (N=831) with either primary open-angle glaucoma (POAG) or ocular hypertension (OHT). The main objective of these studies was to demonstrate that the mean IOP reduction over three months of treatment with latanoprostene bunod ophthalmic solution once daily (QD) was non-inferior to timolol 0.5% twice daily. A secondary objective was to demonstrate the superiority of latanoprostene bunod ophthalmic solution QD to timolol 0.5% BID. In both studies, latanoprostene bunod ophthalmic solution met the primary endpoint. The drug received its complete response letter as a new drug from the FDA in July 2016.6-7

Trabodenoson (Inotek Pharmaceuticals, US) is a novel eye drop that reportedly increases aqueous fluid outflow via the trabecular meshwork. The potent and highly selective adenosine mimetic drug targets the A1 receptor subtype causing an increase in metabolic activity that leads to digestion and removal of proteins that can block the healthy outflow of aqueous humor. In a phase II study, ocular doses of trabodenoson, from 50 to 500 mcg, were well tolerated and showed a dose-related reduction in IOP that was statistically significant and clinically relevant at 500 mcg in POAG or OHT with a baseline IOP = 24 mmHg (on no IOP lowering therapy). Inotek Pharmaceuticals has initiated their second phase II dose-ranging trial of a fixed- dose combination of trabodenoson and latanoprost. Additionally, a phase III MATrX-1, a randomized, double-masked, placebo-controlled safety and efficacy study is underway and is expected to be complete by 2017. The study's primary endpoint is reduction in intraocular pressure (IOP) in the trabodenoson treatment group during the study's 12 weeks of treatment, compared with the same measure in the placebo group. A timolol 0.5% study arm is also included for indirect comparison.

A common problem in disease management however, is low patient adherence to ocular medication administration. Factors contributing to decrease compliance include forgetfulness, cost of medications, poor understanding of glaucoma, difficulty with drop instillation, and difficulty with medication schedule.9 The bimatoprost insert (ForSight VISION5, US), a preservative-free ocular ring containing 13mg bimatoprost mixed into a silicone matrix and placed over an inner polypropylene support structure was designed to improve adherence. In 2015, the results of the phase II, prospective, randomized, double-masked, parallel-arm study showed that there was a reduction in IOP using the bimatoprost insert compared with twice-daily timolol 0.5% ophthalmic solution. The results demonstrated a clinically relevant sustained reduction in IOP of approximately 4 to 6 mmHg (≥20% reduction compared with washout baseline) for 6 months with no patients receiving rescue therapy. Of note, the bimatoprost insert group did have a higher ocular and non-ocular treatment-emergent adverse effects with a total of 9 patients (vs 1 in the timolol group) withdrawing from the study. The bimatoprost insert seemed to be safe, with an AE and tolerability profile similar to that of bimatoprost 0.03% ophthalmic solution. All participants in whom an insert dislodged fully were aware of the dislodgement and returned promptly to the clinic for a new insert. Larger confirmatory phase III studies are being planned.10

Another drug-delivery system includes the punctal plug delivery system. The Plug Delivery (QLT Inc, Canada) is designed to significantly reduce the IOP for 90 days using a proprietary punctal plug design. Although this design is the furthest along the research pipeline with the CORE Study, a phase II clinical trial, there has been no data reported since its initial press release in 2008. Ocular Therapeutix's (US) Sustained Release Travoprost (OTX-TP) uses a proprietary polyethylene glycol hydrogel technology to release the preservative free travoprost drug in punctual plug form. At the end of the treatment period the plug degrades without any need for removal. A recent clinical trial demonstrated feasibility of 1, 2 and 3-month sustained- release of

travoprost from these biodegradable punctal plugs and can deliver the drug into the tear fluid at therapeutic levels.12 A phase IIb study was recently completed but data has not been reported.

Surgical

Standard glaucoma surgeries (trabeculectomy and tube shunts) are major surgeries and although effective at lowering eye pressure, they have many potential complications. The minimally invasive glaucoma surgery (MIGS) groups of operations have been developed in recent years to reduce some of the complications of most standard glaucoma surgeries. Currently the Trabectome (NeoMedix Inc. US), iStent Trabecular Micro-Bypass Stent (Glaukos Corporation, US), and recently added CyPass Micro-Stent (Transcend Medical, US) have FDA approval in the US. However, a number of investigational implant devices including: XEN Gel Stent (AqueSys, US), InnFocus MicroShunt® (InnFocus, US), Hydrus™ MicroStent (Ivantis, US), and STARfloTM (iSTAR Medical, Belgium) are in the works with promising preliminary clinical trial data.

The Trabectome, FDA approved in 2006, was designed to reestablish access to the eye's natural drainage pathway by removing a 60–120° strip of the trabecular meshwork and the inner wall of Schlemm's canal via electrocautery. This ab interno approach is used to achieve direct flow of aqueous into the canal and then into the collector channels. Several studies have published its effectiveness in lowering eye pressure with minimal adverse effects. Kahook Dual Blade (DKB) (New World Medical, CA) is a novel dual blade device that uses precise micro-machining and laser cutting technology to remove trabecular meshwork while minimizing collateral damage to adjacent tissues. The dual blade device is designed with a taper at the tip to allow for smooth entry of the blade into Schlemm's canal. A key feature is that the instrument then elevates the TM tissue allowing for cleaner removal of the tissue, minimizing damage to adjacent structures. The single-use, disposable ophthalmic knife is FDA-registered in 2015 and commercially available throughout the US.

The iStent® is inserted into Schlemm's canal and provides an effective and safe procedure to treat coexisting primary open angle glaucoma and cataract cases. Most studies showed only a mild IOP reduction using iStent. Implantation of multiple iStents for better IOP control is currently being investigated.13 The second-generation iStent inject® preloaded with two stents is under clinical trials in the US as a standalone device or for use with cataract surgery. Fea et al. and Voskanyan et al. demonstrated significant reduction of IOP during the 12 months of follow up postoperatively.14 Glaukos also created the third- generation iStent Supra®, a 4mm tube made of polyethersulfone (PES) and titanium that is designed to reduce IOP by accessing the suprachoroidal space. One European study demonstrated that 98% of their patients (N= 42) met their primary endpoint of a 20% reduction in IOP after insertion of iStent Supra along with one medication and a mean IOP decrease of 47% from 20.8 mmHg to 13.2 mmHg.12 The company is anticipating FDA approval in 2018.

The CyPass Micro-Stent is a fenestrated microstent made of a biocompatible polyimide material that is placed by a curved guidewire into the suprachoroidal space. The guidewire helps the device to follow the curve of the sclera during implantation. The COMPASS clinical trial compared the safety and efficacy of CyPass Micro-stent with cataract surgery vs. cataract surgery alone. The study's primary endpoint was met demonstrating that the implantation of the CyPass Micro-Stent with cataract surgery resulted in a 20% or greater reduction in IOP from a medication-free baseline in a statistically significant higher proportion of eyes compared to cataract surgery alone at both the one- and two-year medication-free postoperative examinations. The device received FDA approval July 2016.

A biodegradable sustained-release bimatoprost implant, Bimatoprost SR (Allergan, US) is currently under phase III clinical trials and could potentially change the treatment paradigm for glaucoma. The implant is administered intracamerally using a prefilled, single-use applicator system. The implant can then be visualized in the inferior iridocorneal angle, where it slowly elutes the drug and then biodegrades. Results showed that the mean IOP reduction through week 16 ranged from 7.2 to 9.5 mm Hg with sustained effects through 6 months of follow-up. Rescue therapy was required in 4 study eyes (5.3%) through week 12 and in 6 study eyes (8%)

through week 16. There were no serious ocular adverse events in the study eye. The majority of the most common adverse events include conjunctival hyperemia, foreign body sensation, eye pain, and lacrimation increase were related to the injection procedure and graded as mild by the investigators. The interim positive results have led to the initiation of phase III studies in 2016. Another intracameral depot implant is ENV515 (Envisia Therapeutics, US). Envisia Therapeutics develops nanotechnology-based health care products and uses a proprietary system for molding nano- and microparticles called PRINT (Particle Replication in Nonwetting Templates). ENV515 is a biodegradable polymer drug delivery system that uses an extended-release formulation of travoprost and is marketed to potentially lower IOP for more than six months with a single dose. The three-month analysis in an ongoing 12-month safety and efficacy evaluation was released in May 2016 with results showing a -7.1 mmHg or 27% change from IOP baseline that was comparable to topical timolol 0.5% twice daily. ENV515 was well tolerated and there were no serious adverse events and no changes in corneal endothelial cell. The most common adverse event was early-onset transient related to the dosing procedure.

Cyclocoagulation

Although ciliary body destruction was first suggested as a way to lower IOP in the 1930's, the first cyclophotocoagulation (CPC) procedure was not performed until the 1970's and endocyclophotocoagulation (ECP) was not introduced until the 1990's. Contact transscleral CPC (TS-CPC) uses a continuous wave (CW) diode laser to destroy the ciliary body and has a high prevalence of significant post-surgical complications including hypotony, visual deterioration, and phthisis bulbi. It is therefore indicated for refractory glaucoma cases or in eyes with poor visual potential. ECP has been shown to have less adverse side effects as the endoscopic probe allows the surgeon to visualize and appropriately titrate the energy levels to ablate the ciliary processes. Newer treatment options include combined cataract extraction and ECP for moderate glaucoma cases.15

Micropulse laser was first introduced in the early 1990's. One decade later, it was adopted in the field of glaucoma. The pulsatile nature of the laser divides the laser emission into "on" time that targets ciliary epithelium and "off" time to allow heat to dissipate preventing collateral damage to the surrounding tissues. Current uses include micropulse laser trabeculoplasty (MLT) or micropulse transscleral photocoagulation (mTCP). Micropulse TCP has shown to be promising in different clinical trials. One study showed that patients with advanced glaucoma had a 73.7% success rate (defined as an IOP reduction of greater than 20% or IOP <21mmHg) after the initial treatment. Three patients (15.8%) underwent a second treatment, increasing the overall success rate to 89.5%.16

High-intensity focused ultrasound (HIFU) cyclocoagulation by EyeOP1 (EyeTechCare, France) has also gained popularity in glaucoma treatment and is currently undergoing clinical trials. The rapid sequential activation of the miniaturized transducers of the device delivers six focused ultrasound beams to induce partial and well-controlled lesions corresponding to six segments of linear tissue coagulation in the ciliary body. The procedure can be performed under local anesthesia in an outpatient setting. A pilot clinical study in 12 refractory glaucoma patients was conducted, showing a significant IOP reduction with no major intra- or postoperative complications, using 3- and 4-second treatment times. The EyeMUST1 Study also demonstrated effectiveness in decreasing IOP, particularly in patients with POAG.

In recent years, emerging technologies have significantly increased treatment options for glaucoma, both therapeutically and surgically. The common goal of all of these innovations is to lower the IOP while minimizing potentially devastating complications. In surgical cases these novel treatment modalities facilitate and expedite surgery time, decrease patient recovery time, and reduce patient dependence on topical medications. Although long-term follow-up to determine safety and efficacy of these new therapies is still needed, the modern era of glaucoma treatment remains very exciting as companies continue to innovate and challenge the current treatment paradigm for glaucoma.

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Name:_____ **License**:_____

1. Which of the following has Rho Kinase (ROCK) and Rho GTPase shown to do?

A. Decrease IOP
B. Enhance ocular blood flow
C. Inhibit scarring
D. Promote ganglion cell survival and axon regeneration
E. All of the above

2. Roclatan TM is a combination of:

A. Rhopressa and latanoprost
B. Rhopressa and travoprost
C. Rho GTPase and Rhokinase
D. Rho kinase and latanoprostene bunod

3. Which drug reduces IOP by increasing aqueous humor outflow through the uveoscleral pathway and through the trabecular meshwork & Schlemm's canal?

A. Rhopressa
B. Visneo (latanoprostene bunod)
C. Trabodenoson

4. Which two stent implants target the suprachoroidal space?

A. iStent Inject and Kahook Dual Blade
B. iStent Supra and CyPass Micro-Stent
C. iStent Supra and Trabectome
D. iStent Inject and XEN Gel Stent

5. The Bimatoprost Sustained-Release by Allergan delivers the drug via:

A. punctual plug
B. intracameral implant
C. laser therapy
D. ophthalmic drop

6. Micropulse laser is pulsatile and divides the laser into "on" time targeting ciliary epithelium and "off" time to allow heat to dissipate thereby preventing collateral damage

a. True
b. False.

7. Which MIGS is not FDA approved:

A. iStent
B. CyPass Micro-Stent
C. InnFocus MicroShunt
D. Trabectome

8. Which of the following is a potent adenosine mimetic drug that improves metabolic activity at the trabecular meshwork?

A. Trabodenosen
B. Latnoprostene bunod
C. Rhopressa
D. Roclatan

9. High-intensity focused ultrasound (HIFU) uses ultrasound beams to induce partial and well-controlled lesions corresponding to six segments of linear tissue coagulation in the ciliary body.

a. True
b. False

10. The bimatoprost insert is a preservative-free ocular ring that has been shown to be effective for up to 6 months in one study.

a. True
b. False

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