Ophthalmology Times®
CUTTING-EDGE ADVANCEMENTS
January 15, 2014 VOL. 39, NO. 2
CLINICAL DIAGNOSIS | SURGERY | DRUG THERAPY

OphthalmologyTimes.com
FOLLOW US ONLINE:

Clinical Diagnosis

WHY GLAUCOMA IN PREGNANCY BEARS DISCUSSION

MINNEAPOLIS :: **GLAUCOMA IS OFTEN** thought of as a disease of aging, but it can affect patients who are much younger and more interested in starting a family than planning for retirement. With women in this age group, ophthalmologists should take extra time before reaching for the prescription pad.

*(See story on page 15 : **Pregnancy**)*

Surgery

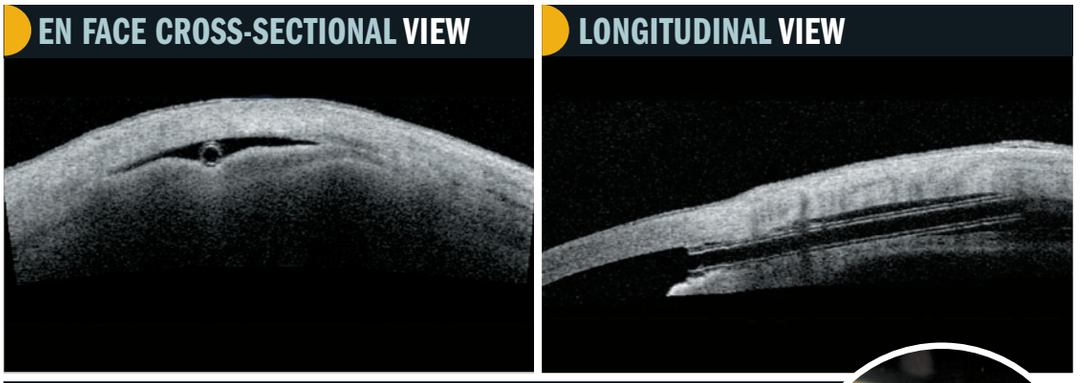
REDUCING IOP WITH DEEP WAVE TRABECULOPLASTY

AURORA, CO :: **DEEP WAVE TRABECULOPLASTY**—a novel non-invasive approach designed to lower IOP by enhancing aqueous outflow through the trabecular meshwork—has demonstrated promising efficacy and safety in both pre-clinical studies and an initial clinical trial. Based on encouraging results, a second study is now under way.

*(See story on page 8 : **Lower IOP**)*

Supraciliary micro-stent 2-year data positive

CyCLE trial sustains efficacy and safety profiles



IN VIEW: (Top, left) En face cross-sectional coherence tomography view of micro-stent (CyPass Micro-Stent, Transcend Medical) in situ in the supraciliary space. (Top, right) Longitudinal optical coherence tomography view of the device in situ in the supraciliary space. (Far right) Gonioscopic view of the device at 15 months in supraciliary space. *(Images courtesy of Tsontcho Ianchulev, MD, MPH)*

By Fred Gebhart;
Reviewed by Tsontcho Ianchulev, MD, MPH

SAN FRANCISCO :: **TWO-YEAR RESULTS** on the first ab interno micro-stent (CyPass Micro-Stent, Transcend Medical) designed to drain into the suprachoroidal space show good efficacy and safety profiles.

The 2-year data from the CyCLE multicenter trial in Europe show sustained efficacy and similar safety to the 1-year data.


Dr. Ianchulev

"The [micro-stent] creates additional outflow from the eye into the suprachoroidal space," said principal investigator Tsontcho Ianchulev, MD, MPH, associate clinical professor of ophthalmology, University of California–San Francisco and chief medical officer, Transcend Medical, Menlo Park, CA.

"The mechanism of action is very different from other micro-invasive glaucoma surgical (MIGS) devices which stent the trabecular pathway," Dr. Ianchulev said. "Instead, the [device] targets the suprachoroidal space, which has a much larger absorptive capacity and a negative oncotic pressure for increased outflow and IOP lowering."

The most current long-term data on the device were presented as a poster by Helmut Höh, MD, PhD, chief of ophthalmology at Dietrich-Bonhoeffer-Klinikum Neubrandenburg, Ernst Moritz Amdt University, Greifswald, Germany, at the recent meeting of the European Society of Cataract and Refractive Surgeons. The device has been approved for use in the European Union and Canada, but remains investigational in the United States.

The device—a biocompatible-but-nonresorbable polyimide tube that is 6.3 mm in length with a 510-µm external diameter—is implanted ab interno via a 1.5-mm corneal incision into the supraciliary space. The tube has proximal retention features designed for placement in the supraciliary space

*(Continues on page 11 : **Micro-stent**)*

NOW AVAILABLE LOTEMAX® GEL

UNIQUE FORMULATION DESIGNED TO CONTROL INFLAMMATION

FIRST IN CLASS* GEL DROP

Indications and Usage

- LOTEMAX® GEL is a corticosteroid indicated for the treatment of post-operative inflammation and pain following ocular surgery

Important Risk Information about LOTEMAX® GEL

- LOTEMAX® GEL is contraindicated in most viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal diseases of ocular structures
- Intraocular pressure (IOP) increase—Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. If this product is used for 10 days or longer, IOP should be monitored
- Cataracts—Use of corticosteroids may result in posterior subcapsular cataract formation
- Delayed healing—Use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation and occurrence of perforations in those with diseases causing corneal and scleral thinning. The initial prescription and renewal of the medication order should be made by a physician only after examination of the patient with the aid of magnification
- Bacterial infections—Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infection. In acute purulent conditions, steroids may mask infection or enhance existing infections
- Viral infections—Use of corticosteroid medication in the treatment of patients with a history of herpes simplex requires great caution. Use of ocular steroids may prolong the course and exacerbate the severity of many viral infections of the eye (including herpes simplex)
- Fungal infections—Fungal infections of the cornea are particularly prone to develop coincidentally with long-term local steroid application. Fungus invasion must be considered in any persistent corneal ulceration where a steroid has been used or is in use
- Contact lens wear—Patients should not wear contact lenses when using LOTEMAX® GEL
- The most common ocular adverse drug reactions were anterior chamber inflammation (5%), eye pain (2%) and foreign body sensation (2%)

Please see brief summary of full prescribing information on adjacent page.

*Ophthalmic corticosteroid.

References: 1. LOTEMAX GEL Prescribing Information, September 2012. **2.** Fong R, Leitritz M, Siou-Mermet R, Erb T. Loteprednol etabonate gel 0.5% for postoperative pain and inflammation after cataract surgery: results of a multicenter trial. *Clin Ophthalmol.* 2012;6:1113-1124. **3.** Data on file, Bausch & Lomb Incorporated.

LOTEMAX® GEL

loteprednol etabonate ophthalmic gel 0.5%

DISCOVER THE POWER OF GEL

BAUSCH + LOMB

BAUSCH + LOMB

LOTEMAX®

loteprednol etabonate
ophthalmic gel 0.5%

Brief Summary: Based on full prescribing information.

To report SUSPECTED ADVERSE REACTIONS, contact Bausch & Lomb at 1-800-323-0000 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

INDICATIONS AND USAGE

LOTEMAX is a corticosteroid indicated for the treatment of post-operative inflammation and pain following ocular surgery.

DOSAGE AND ADMINISTRATION

Invert closed bottle and shake once to fill tip before instilling drops.

Apply one to two drops of LOTEMAX into the conjunctival sac of the affected eye four times daily beginning the day after surgery and continuing throughout the first 2 weeks of the post-operative period.

CONTRAINDICATIONS

LOTEMAX, as with other ophthalmic corticosteroids, is contraindicated in most viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal diseases of ocular structures.

WARNINGS AND PRECAUTIONS

Intraocular Pressure (IOP) Increase

Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. Steroids should be used with caution in the presence of glaucoma. If this product is used for 10 days or longer, intraocular pressure should be monitored.

Cataracts

Use of corticosteroids may result in posterior subcapsular cataract formation.

Delayed Healing

The use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation. In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical steroids. The initial prescription and renewal of the medication order should be made by a physician only after examination of the patient with the aid of magnification such as slit lamp biomicroscopy and, where appropriate, fluorescein staining.

Bacterial Infections

Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions of the eye, steroids may mask infection or enhance existing infection.

Viral Infections

Employment of a corticosteroid medication in the treatment of patients with a history of herpes simplex requires great caution. Use of ocular steroids may prolong the course and may exacerbate the severity of many viral infections of the eye (including herpes simplex).

Fungal Infections

Fungal infections of the cornea are particularly prone to develop coincidentally with long-term local steroid application. Fungus invasion must be considered in any persistent corneal ulceration where a steroid has been used or is in use. Fungal cultures should be taken when appropriate.

Contact Lens Wear

Patients should not wear contact lenses during their course of therapy with LOTEMAX.

ADVERSE REACTIONS

Adverse reactions associated with ophthalmic steroids include elevated intraocular pressure, which may be associated with infrequent optic nerve damage, visual acuity and field defects, posterior subcapsular cataract formation, delayed wound healing and secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera.

The most common adverse drug reactions reported were anterior chamber inflammation (5%), eye pain (2%), and foreign body sensation (2%).

USE IN SPECIFIC POPULATIONS

Pregnancy

Teratogenic Effects: Pregnancy Category C.

Loteprednol etabonate has been shown to be embryotoxic (delayed ossification) and teratogenic (increased incidence of meningocele, abnormal left common carotid artery, and limb flexures) when administered orally to rabbits during organogenesis at a dose of 3 mg/kg/day (35 times the maximum daily clinical dose), a dose which caused no maternal toxicity. The no-observed-effect-level (NOEL) for these effects was 0.5 mg/kg/day (6 times the maximum daily clinical dose). Oral treatment of rats during organogenesis resulted in teratogenicity (absent innominate artery at ≥5 mg/kg/day doses, and cleft palate and umbilical hernia at ≥50 mg/kg/day) and embryotoxicity (increased post-implantation losses at 100 mg/kg/day and decreased fetal body weight and skeletal ossification with ≥50 mg/kg/day). Treatment of rats with 0.5 mg/kg/day (6 times the maximum clinical dose) during organogenesis did not result in any reproductive toxicity. Loteprednol etabonate was maternally toxic (significantly reduced body weight gain during treatment) when administered to pregnant rats during organogenesis at doses of ≥5 mg/kg/day.

Oral exposure of female rats to 50 mg/kg/day of loteprednol etabonate from the start of the fetal period through the end of lactation, a maternally toxic treatment regimen (significantly decreased body weight gain), gave rise to decreased growth and survival, and retarded development in the offspring during lactation; the NOEL for these effects was 5 mg/kg/day. Loteprednol etabonate had no effect on the duration of gestation or parturition when administered orally to pregnant rats at doses up to 50 mg/kg/day during the fetal period.

There are no adequate and well controlled studies in pregnant women. LOTEMAX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether topical ophthalmic administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Systemic steroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. Caution should be exercised when LOTEMAX is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

No overall differences in safety and effectiveness have been observed between elderly and younger patients.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment Of Fertility

Long-term animal studies have not been conducted to evaluate the carcinogenic potential of loteprednol etabonate. Loteprednol etabonate was not genotoxic *in vitro* in the Ames test, the mouse lymphoma tk assay, or in a chromosome aberration test in human lymphocytes, or *in vivo* in the single dose mouse micronucleus assay. Treatment of male and female rats with up to 50 mg/kg/day and 25 mg/kg/day of loteprednol etabonate, respectively, (600 and 300 times the maximum clinical dose, respectively) prior to and during mating did not impair fertility in either gender.

PATIENT COUNSELING INFORMATION

Administration

Invert closed bottle and shake once to fill tip before instilling drops.

Risk of Contamination

Patients should be advised not to allow the dropper tip to touch any surface, as this may contaminate the gel.

Contact Lens Wear

Patients should be advised not to wear contact lenses when using LOTEMAX.

Risk of Secondary Infection

If pain develops, redness, itching or inflammation becomes aggravated, the patient should be advised to consult a physician.

FOR MORE DETAILED INFORMATION, PLEASE READ THE PRESCRIBING INFORMATION.

Bausch & Lomb Incorporated
Tampa, Florida 33637 USA
US Patent No. 5,800,807

Swimming with snakes

Even when on vacation, scientific discoveries never cease to amaze

By Peter J. McDonnell, MD

director of the Wilmer Eye Institute, Johns Hopkins University School of Medicine, Baltimore, and chief medical editor of *Ophthalmology Times*.

He can be reached at 727 Maumenee Building
600 N. Wolfe St. Baltimore, MD 21287-9278
Phone: 443/287-1511 Fax: 443/287-1514
E-mail: pmcdonn1@jhmi.edu

A FEW WEEKS AGO, I escaped from the cold weather of Baltimore and went snorkeling with a friend off a beach in Costa Rica. One of the most beautiful and visitor-friendly countries in the world, this nation has protected the habitats of its native plants and animals. Sea turtles, monkeys, tree frogs, and orchids are all plentiful here.

On this sunny day, the warm, clear Pacific Ocean was teeming with colorful, interesting fish of all shapes and sizes, singly and in large schools. Most of them were just swimming around, while others were hard at working gnawing at the coral of the reef or plant life on the sea floor.

That's when I happened upon one more very colorful form of life—one that was about as welcome as Michael Jordan at a Hair Club for Men Convention (or, if the reader prefers, as a mosquito at a nudist colony). Cruising along the sea floor, just a few feet below me, was a very colorful sea snake, about 1 meter in length.

Having grown up on a beach along the Atlantic Ocean, where sea snakes do not live, all I knew about these creatures had come from books.

In the Pacific and Indian oceans, I knew, sea snakes are quite venomous. What I did not know was whether they were aggressive, whether they could swim faster than me with my flippers, and whether this particular species was poisonous.

Fortunately, while I pondered, this chap just ignored me and slithered beneath my floating body, headed off to do whatever business he or she had on her agenda for that day.

After a while, we were back on shore and my friend asked, "I saw snakes out there. Did you?"

We compared notes and learned that, based upon the coloring, we had actually seen different snakes.

"Are they poisonous?" she asked.

"I don't know," was my reply.

'IGNORANCE IS BLISS'

Sadly, the Internet reaches even to the pristine beaches of Central America, and quickly my snorkeling companion had researched this life form.

Thankfully, they are generally not aggressive, but are quick to defend themselves if molested. *Pelamis platurus*, extending from Pacific islands to Costa Rica and Panama, is indeed possessed of venom that can cause death. Based on LD50, the venom is more potent than that of any terrestrial snake in Costa Rica, but human fatalities are much less common. After 30 minutes to several hours, ptosis and paralysis of voluntary muscles occurs, followed by rhabdomyolysis, severe hyperkalemia, and cardiac arrest.

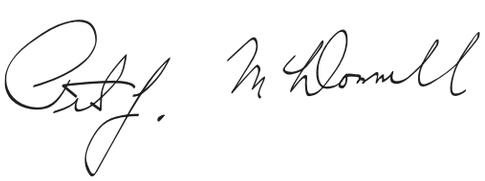
"I'm glad I didn't know this before I went snorkeling," my friend said.

"Ignorance is bliss" was all that occurred to me.

Even if, like me, you are creeped out by snakes, when you see them up close you have to admit they are very colorful. Equipped with their venom, they must feel no need to hide themselves.

Sea snakes have small eyes with round pupils. As a rule, they do not leave the water. That makes sense because presumably their eyes, adapted to see under water, would render them severely myopic on land.

Also, sea snakes like *Aipysurus laevis* have photoreceptors in the skin of their tails, allowing them to detect light. This ability is thought to let the snake know that it is completely hidden from prying eyes when it wants to be, or it might make it easier to avoid being surprised by creatures (like vacationing ophthalmologists) swimming above. ■



Reference

- Campbell JA, Lamar WW. 2004. The venomous reptiles of the Western Hemisphere. Comstock Publishing Associates, Ithaca and London.

Ophthalmology Times
JANUARY 15, 2014 ■ VOL. 39, NO. 2

Official publication sponsor of International Vision Expo & Conference New York / International Vision Expo & Conference Las Vegas

Ophthalmology Times EDITORIAL ADVISORY BOARD

How to Contact Ophthalmology Times

Editorial
24950 Country Club Blvd.,
Suite 200
North Olmsted, OH 44070-5351
440/243-8100
FAX: 440/756-5227

Subscription Services
Toll-Free: 888/527-7008 or
218/740-6477
FAX: 218/740-6417

Advertising
485 Route 1 South
Building F, Suite 210,
Iselin, NJ 08830-3009
732/596-0276
FAX: 732/596-0003

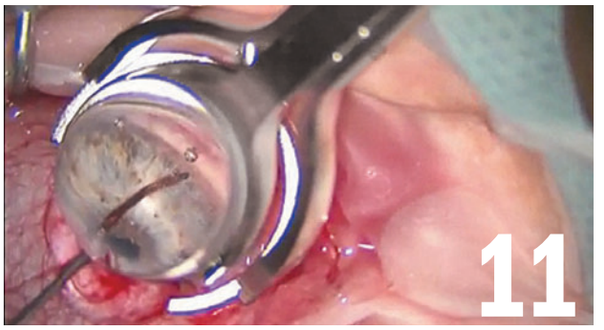
Production
131 W. First St.
Duluth, MN 55802-2065
800/346-0085
FAX: 218/740-7223,
218/740-6576

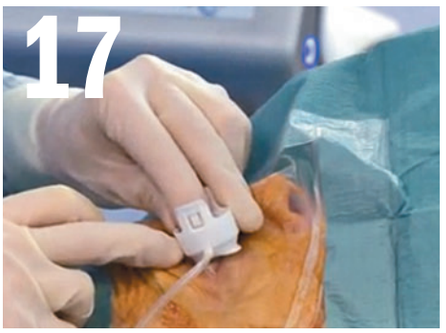
Ophthalmology Times *Mission Statement*

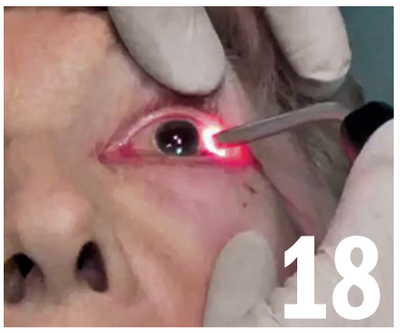
Ophthalmology Times is a physician-driven media brand that presents cutting-edge advancements and analysis from around the world in surgery, drug therapy, technology, and clinical diagnosis to elevate the delivery of progressive eye health from physician to patient.

Ophthalmology Times' vision is to be the leading content resource for ophthalmologists.

Through its multifaceted content channels, *Ophthalmology Times* will assist physicians with the tools and knowledge necessary to provide advanced quality patient care in the global world of medicine.







Special Report on page 8

CLINICAL DIAGNOSIS AND DRUG THERAPY IN GLAUCOMA

Drug Therapy

Technology

InDispensable

In Every Issue

On Twitter

Follow *Ophthalmology Times* on Twitter for the latest news and advancements in ophthalmology **@OphthTimes**

@OphthTimes Alimera ships first Iluvien orders in UK http://bit.ly/1fvcave http://t.co/E6ViGw21fv #ophthalmology #FDA

@OphthTimes approves ReSure Sealant http://bit.ly/KhiR5o #ophthalmology #eyes #eyecare

@OphthTimes Research Advancements Made in #Diabetes Induced #Blindness http://bit.ly/1gKN48e http://t.co/2xhF2lDtcx

@OphthTimes Zeiss broadens portfolio of #IOLs http://bit.ly/1eC6o66 http://t.co/auQV6heEDy #eyecare #eyes

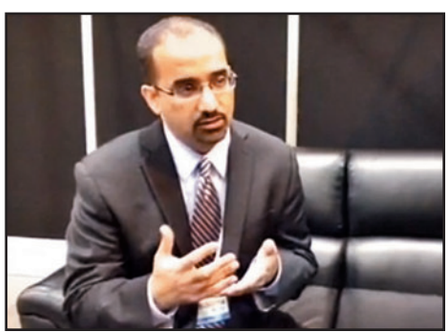
Digital App

Introducing the *Ophthalmology Times* app for iPad and iPhone. Download it for free today at *OphthalmologyTimes.com/OTapp.*

eReport

Sign up for *Ophthalmology Times*' weekly eReport at *http://bit.ly/XjksXX.*

Video



To learn more about the modular IOL design from Malik Kahook, MD, *go to http://bit.ly/1bUUjpG.*
(Video courtesy of Ophthalmology Times)

Facebook

Like *Ophthalmology Times* at **Facebook.com/OphthalmologyTimes.**

24 hours a day. 7 days a week.

Around the clock, SLT keeps your glaucoma patients' IOP under control.

Whether used as primary, adjunct or replacement therapy, SLT lowers IOP as effectively as medication, has a consistent safety profile, and – best of all – works 24 hours a day, 7 days a week, to keep IOP under control. Offering superior energy control, a sharp-edged aiming beam and the fastest firing rate at 3 shots per second, Ellex's proprietary SLT technology allows you to visualize the TM in greater detail, and to perform procedures faster and with improved accuracy.

SLT technology from Ellex now available in the USA! Learn more at ellex.com.

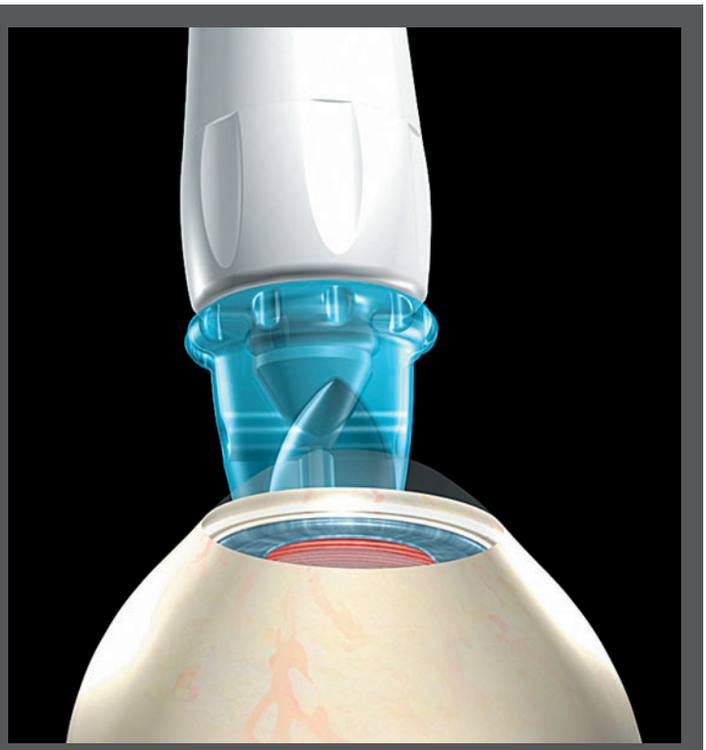
ellex

slt-ellex.com | 855 767-5784

REDUCING IOP WITH DEEP WAVE TRABECULOPLASTY

Investigational procedure modulates outflow using externally applied non-invasive mechanical energy

By Cheryl Guttman Krader; *Reviewed by Malik Y. Kahook, MD*



(FIGURE 1) The deep wave trabeculoplasty device applies non-invasive, focal, mechanical oscillation to the limbal region at a low amplitude and frequency—targeting the trabecular meshwork to restore outflow function. An anatomically conforming nose cone (translucent blue) ensures proper placement of the oscillating tip on the limbus and limits scleral deflection. *(Image courtesy of OcuTherix)*

AURORA, CO ::

Deep wave trabeculoplasty (DWT) (OcuTherix)—a novel non-invasive approach designed to lower IOP by enhancing aqueous outflow through the trabecular meshwork—has demonstrated promising efficacy and safety in both pre-clinical studies and an initial clinical trial.

Based on the encouraging results, a second clinical study is now under way.

DWT was invented by Malik Y. Kahook, MD, The Slater Family Endowed Chair in Ophthalmology and professor of ophthalmology, University of Colorado, Aurora, and inspired by evidence that IOP lowering following phacoemulsification surgery occurs secondary to ultrasound activation of a stress response in trabecular meshwork cells accompanied by the release of cytokines able to modulate outflow.

Dr. Kahook

DWT aims to trigger that tissue response using externally applied non-invasive mechanical energy, but at a much lower (sonic) frequency than phaco to avoid tissue trauma. In DWT, mechanical oscillations are delivered to the trabecular meshwork using a handheld instrument positioned along the limbal region that overlies the trabecular meshwork.

Results from pre-clinical testing performed in two animal models showed DWT lowered IOP 24% from baseline. In the clinical trial, DWT was associated with a 26% reduction in IOP from a mean of 24.27 mm Hg at baseline to 17.87 mm Hg at 3 months.

There were no remarkable safety findings in the pre-clinical studies, including no histological evidence of thermal or other tissue damage.

In clinical testing where DWT was performed under topical anesthesia, the procedure was well tolerated and caused no serious complications.

take-home

- **Deep wave trabeculoplasty reduced IOP by 26% in an initial clinical investigation and is being compared with sham and selective laser trabeculoplasty in a second clinical trial.**

"DWT would negate the issue of adherence to glaucoma medications and we anticipate it may be a more cost-effective option than topical drops," Dr. Kahook said. "The initial 'first in human' study showed promising IOP lowering in the majority of treated patients. The current clinical trial will allow us to learn more about the efficacy and reproducibility of the decrease in IOP compared [with] selective laser trabeculoplasty."

The University of Colorado holds the patent for DWT under Dr. Kahook's name and has licensed the technology to Ocutherix for commercial development.

DWT offers some very attractive attributes, explained Robert Atkinson, chief executive officer, OcuTherix.

"DWT would not require any capital equipment and could be offered as an efficient, in-office procedure that might successfully defer the use of other more invasive treatments for glaucoma without limiting their use as downstream options," Atkinson said.

The first human study of DWT included patients with primary open-angle glaucoma whose IOP was >23 mm Hg after a 1-month washout of existing medications. Participating patients underwent DWT in one eye—the procedure took about 5 minutes to complete—and the fellow untreated eye served as a control.

A significant decrease from baseline IOP was first observed at

Continues on page 11 : ***Lower IOP***

Monotherapy Maintained.

Proven IOP reduction[1]

•

Established tolerability with
low discontinuation rate[2]

On Your Terms.

Broad preferred coverage[3]

•

Comprehensive patient support

Indication: LUMIGAN® (bimatoprost ophthalmic solution) 0.01% is indicated for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

Important Safety Information

Warnings and Precautions: LUMIGAN® 0.01% causes changes to pigmented tissues, mostly increased pigmentation of the iris, eyelid, and eyelashes as long as LUMIGAN® 0.01% is administered. Iris color change may not be noticeable for several months to years. After discontinuation of bimatoprost, iris pigmentation is likely to be permanent, while eyelid and eyelash changes have been reported to be reversible in some patients. Patients should be informed of the possibility of increased pigmentation. The long-term effects of increased pigmentation are not known.

LUMIGAN® 0.01% should be used with caution in patients with active intraocular inflammation (eg, uveitis) because the inflammation may be exacerbated. Macular edema, including cystoid macular edema, has been reported with LUMIGAN® 0.01%. LUMIGAN® 0.01% should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema. LUMIGAN® 0.01% has not been studied to treat types of glaucoma other than open-angle glaucoma. Remove contact lenses prior to instillation of LUMIGAN® 0.01% and reinsert after 15 minutes.

Adverse Reactions: The most common (25%-45%) adverse event with LUMIGAN® 0.01% was conjunctival hyperemia. Approximately 0.5% to 3% of patients discontinued therapy due to conjunctival hyperemia. Other common events (> 10%) included growth of eyelashes and ocular pruritus.

Please see Brief Summary of the full Prescribing Information on adjacent page.

1. LUMIGAN® Prescribing Information. **2.** Katz LJ, Cohen JS, Batoosingh AL, Felix C, Shu V, Schiffman RM. Twelve-month, randomized, controlled trial of bimatoprost 0.01%, 0.0125%, and 0.03% in patients with glaucoma or ocular hypertension. *Am J Ophthalmol.* 2010;149(4):661-671. **3.** Managed Markets Insight & Technology, LLC, database, as of November 2013.

LUMIGAN® 0.01%
(bimatoprost ophthalmic solution) 0.01%

Allergan at your service

LUMIGAN® 0.01% AND 0.03%
(bimatoprost ophthalmic solution)

Brief Summary—Please see the LUMIGAN® 0.01% and 0.03% package insert for full Prescribing Information.

INDICATIONS AND USAGE

LUMIGAN® 0.01% and 0.03% (bimatoprost ophthalmic solution) is indicated for the reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension.

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

Pigmentation: Bimatoprost ophthalmic solution has been reported to cause changes to pigmented tissues. The most frequently reported changes have been increased pigmentation of the iris, periorbital tissue (eyelid) and eyelashes. Pigmentation is expected to increase as long as bimatoprost is administered. The pigmentation change is due to increased melanin content in the melanocytes rather than to an increase in the number of melanocytes. After discontinuation of bimatoprost, pigmentation of the iris is likely to be permanent, while pigmentation of the periorbital tissue and eyelash changes have been reported to be reversible in some patients. Patients who receive treatment should be informed of the possibility of increased pigmentation. The long term effects of increased pigmentation are not known.

Iris color change may not be noticeable for several months to years. Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery of the iris and the entire iris or parts of the iris become more brownish. Neither nevi nor freckles of the iris appear to be affected by treatment. While treatment with **LUMIGAN®** 0.01% and 0.03% (bimatoprost ophthalmic solution) can be continued in patients who develop noticeably increased iris pigmentation, these patients should be examined regularly.

Eyelash Changes: LUMIGAN® 0.01% and 0.03% may gradually change eyelashes and vellus hair in the treated eye. These changes include increased length, thickness, and number of lashes. Eyelash changes are usually reversible upon discontinuation of treatment.

Intraocular Inflammation: LUMIGAN® 0.01% and 0.03% should be used with caution in patients with active intraocular inflammation (e.g., uveitis) because the inflammation may be exacerbated.

Macular Edema: Macular edema, including cystoid macular edema, has been reported during treatment with bimatoprost ophthalmic solution. **LUMIGAN®** 0.01% and 0.03% should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema.

Angle-closure, Inflammatory, or Neovascular Glaucoma: LUMIGAN® 0.01% and 0.03% has not been evaluated for the treatment of angle-closure, inflammatory or neovascular glaucoma.

Bacterial Keratitis: There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface.

Use With Contact Lenses: Contact lenses should be removed prior to instillation of **LUMIGAN®** 0.01% and 0.03% and may be reinserted 15 minutes following its administration.

ADVERSE REACTIONS

Clinical Studies Experience: Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

In clinical studies with bimatoprost ophthalmic solutions (0.01% or 0.03%) the most common adverse reaction was conjunctival hyperemia (range 25%–45%). Approximately 0.5% to 3% of patients discontinued therapy due to conjunctival hyperemia with 0.01% or 0.03% bimatoprost ophthalmic solutions. Other common reactions (>10%) included growth of eyelashes, and ocular pruritus.

Additional ocular adverse reactions (reported in 1 to 10% of patients) with bimatoprost ophthalmic solutions included ocular dryness, visual disturbance, ocular burning, foreign body sensation, eye pain, pigmentation of the periocular skin, blepharitis, cataract, superficial punctate keratitis, periorbital erythema, ocular irritation, eyelash darkening, eye discharge, tearing, photophobia, allergic conjunctivitis, asthenopia, increases in iris pigmentation, conjunctival edema, conjunctival hemorrhage, and abnormal hair growth. Intraocular inflammation, reported as iritis, was reported in less than 1% of patients.

Systemic adverse reactions reported in approximately 10% of patients with bimatoprost ophthalmic solutions were infections (primarily colds and upper respiratory tract infections). Other systemic adverse reactions (reported in 1 to 5% of patients) included headaches, abnormal liver function tests, and asthenia.

Postmarketing Experience: The following reactions have been identified during postmarketing use of **LUMIGAN®** 0.01% and 0.03% in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The reactions, which have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to **LUMIGAN®**, or a combination of these factors, include: dizziness, eyelid edema, hypertension, nausea, and periorbital and lid changes associated with a deepening of the eyelid sulcus.

USE IN SPECIFIC POPULATIONS

Pregnancy: Pregnancy Category C

Teratogenic effects: In embryo/fetal developmental studies in pregnant mice and rats, abortion was observed at oral doses of bimatoprost which achieved at least 33 or 97 times, respectively, the maximum intended human exposure based on blood AUC levels.

At doses at least 41 times the maximum intended human exposure based on blood AUC levels, the gestation length was reduced in the dams, the incidence of dead fetuses, late resorptions, peri- and postnatal pup mortality was increased, and pup body weights were reduced.

There are no adequate and well-controlled studies of **LUMIGAN®** 0.01% and 0.03% (bimatoprost ophthalmic solution) administration in pregnant women. Because animal reproductive studies are not always predictive of human response **LUMIGAN®** should be administered during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether **LUMIGAN®** 0.01% and 0.03% is excreted in human milk, although in animal studies, bimatoprost has been shown to be excreted in breast milk. Because many drugs are excreted in human milk, caution should be exercised when **LUMIGAN®** is administered to a nursing woman.

Pediatric Use: Use in pediatric patients below the age of 16 years is not recommended because of potential safety concerns related to increased pigmentation following long-term chronic use.

Geriatric Use: No overall clinical differences in safety or effectiveness have been observed between elderly and other adult patients.

Hepatic Impairment: In patients with a history of liver disease or abnormal ALT, AST and/or bilirubin at baseline, bimatoprost 0.03% had no adverse effect on liver function over 48 months.

OVERDOSAGE

No information is available on overdosage in humans. If overdose with **LUMIGAN®** 0.01% and 0.03% (bimatoprost ophthalmic solution) occurs, treatment should be symptomatic.

In oral (by gavage) mouse and rat studies, doses up to 100 mg/kg/day did not produce any toxicity. This dose expressed as mg/m2 is at least 70 times higher than the accidental dose of one bottle of **LUMIGAN®** 0.03% for a 10 kg child.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility: Bimatoprost was not carcinogenic in either mice or rats when administered by oral gavage at doses of up to 2 mg/kg/day and 1 mg/kg/day respectively (at least 192 and 291 times the recommended human exposure based on blood AUC levels respectively) for 104 weeks.

Bimatoprost was not mutagenic or clastogenic in the Ames test, in the mouse lymphoma test, or in the *in vivo* mouse micronucleus tests.

Bimatoprost did not impair fertility in male or female rats up to doses of 0.6 mg/kg/day (at least 103 times the recommended human exposure based on blood AUC levels).

PATIENT COUNSELING INFORMATION

Potential for Pigmentation: Patients should be advised about the potential for increased brown pigmentation of the iris, which may be permanent. Patients should also be informed about the possibility of eyelid skin darkening, which may be reversible after discontinuation of **LUMIGAN®** 0.01% and 0.03% (bimatoprost ophthalmic solution).

Potential for Eyelash Changes: Patients should also be informed of the possibility of eyelash and vellus hair changes in the treated eye during treatment with **LUMIGAN®** 0.01% and 0.03%. These changes may result in a disparity between eyes in length, thickness, pigmentation, number of eyelashes or vellus hairs, and/or direction of eyelash growth. Eyelash changes are usually reversible upon discontinuation of treatment.

Handling the Container: Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye, surrounding structures, fingers, or any other surface in order to avoid contamination of the solution by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

When to Seek Physician Advice: Patients should also be advised that if they develop an intercurrent ocular condition (e.g., trauma or infection), have ocular surgery, or develop any ocular reactions, particularly conjunctivitis and eyelid reactions, they should immediately seek their physician's advice concerning the continued use of **LUMIGAN®** 0.01% and 0.03%.

Use with Contact Lenses: Patients should be advised that **LUMIGAN®** 0.01% and 0.03% contains benzalkonium chloride, which may be absorbed by soft contact lenses. Contact lenses should be removed prior to instillation of **LUMIGAN®** and may be reinserted 15 minutes following its administration.

Use with Other Ophthalmic Drugs: Patients should be advised that if more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes between applications.

APC70EN12 based on 71807US13.

Rx only

ALLERGAN®

MICRO-STENT

(Continued from page 1)

and distal fenestrations along the lower two-thirds designed to enhance outflow. Implantation ab interno leaves the patients with intact conjunctiva, sclera, and trabecular meshwork.

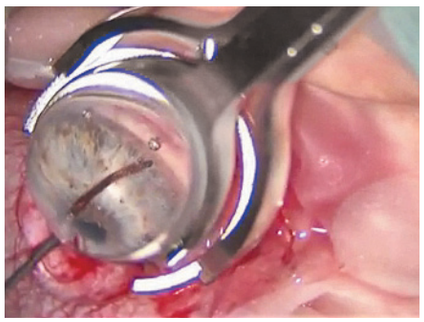
CYCLE STUDY

The CyCLE study includes 136 patients who had completed 2-year follow-up from fifteen centers in Europe. All patients had open-angle glaucoma and underwent phaco-cataract surgery and implantation with the micro-stent.

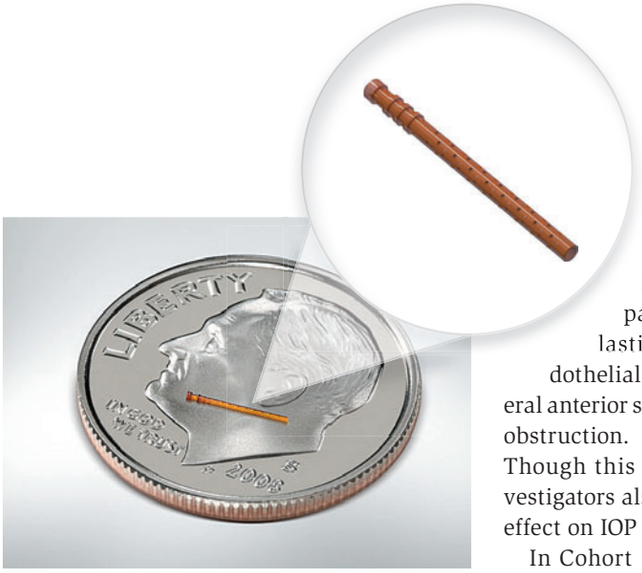
Patients were divided into two cohorts:

- **Cohort 1 (51 patients) had uncontrolled IOP of 21 mm Hg or greater at baseline.**
- **Cohort 2 (85 patients) had controlled IOP of less than 21 mm Hg.**

MICRO-STENT INSERTION



VIDEO For a video showing micro-stent insertion, go to **http://bit.ly/1dUm9Ua**.
(Video courtesy of Transcend Medical Inc.)



(FIGURE 1) The micro-stent—a biocompatible-but-nonresorbable polyimide tube that is 6.3 mm in length with a 510-µm external diameter—is implanted ab interno via a 1.5-mm corneal incision into the supraciliary space.
(Images courtesy of Transcend Medical)

The mean age of study patients was 74.3 years and 59.6 were female. Overall mean baseline IOP was 19.8 mm Hg. In Cohort 1, the mean baseline IOP was 25.5 mm Hg; in Cohort 2 it was 16.4 mm Hg.

Patients were taking a mean of 2.2 medications—2.2 medications in Cohort 1 and 2 medications in Cohort 2. Only 4% of patients were without medications, whereas 26% were taking 1 medication and 35% were taking either 2 medications or 3 or more medications.

Just under 6% of patients had a prior trabeculectomy and 14% had other prior glaucoma interventions.

"We saw safety comparable to other micro-stents and significantly better than conventional glaucoma procedures, such as trabeculectomy, which is the goal of MIGS intervention," Dr. Ianchulev said.

Adverse events included one explanted device, one repositioned device, one case of iritis lasting longer than 1 month, four patients with an IOP increase lasting longer than 1 month, two patients with transient hyphema lasting less than 1 month, five endothelial touches, and 12 cases of peripheral anterior synechia with partial or complete obstruction.

Though this was mainly a safety study, investigators also found there was a significant effect on IOP lowering, Dr. Ianchulev added.

In Cohort 1, the mean IOP dropped from 25.5 mm Hg at baseline to between 16.9 and 15.8 mm Hg at 24 months. Medication used dropped from a mean of 2.2 medications to 1 medication.

Cohort 2 showed stable IOP, from 16.4 mm Hg at baseline to a low of 15.2 at 6 months and 16.1 at 24 months. Medication use in Cohort 2 fell from a mean of 2 medications to 1.1.

Though trabecular stents have shown diminishing efficacy over 2 years, the sustained IOP effect with a supraciliary stent reflects the large absorptive area and capacity of the suprachoroidal space, Dr. Ianchulev said, as well as the physiology of the oncotic gradient across the stent.

The U.S.-based clinical trial of the micro-stent (COMPASS FDA clinical study)—the largest MIGS trial to date–is already fully recruited, randomized, and collecting data, Dr. Ianchulev said.

Initial data from 2-year follow up should be available in about 18 months. ■

TSONTCHO IANCHULEV, MD, MPH
E: *sianchulev@transcendmedical.com*
Dr. Ianchulev is an employee of Transcend Medical.

LOWER IOP

(Continued from page 8)

2 weeks post-DWT and persisted throughout the 3-month follow-up period. About 30% of DWT eyes were started on rescue IOP-lowering medication compared with 100% of the control eyes. Safety evaluations showed no evidence of anterior chamber inflammation.

The second clinical trial is randomly assigning patients to treatment with DWT, sham, or selective laser trabeculoplasty, with primary endpoints at 6 months and long-term follow-up out to 2 years.

"This second study is designed to give us stronger evidence about the efficacy of DWT and further insight on the durability of its IOP-lowering effect," Atkinson said. "It is known that IOP reductions after phacoemulsification can be maintained for 1 to 2 years or even longer, and we believe DWT may have a similar benefit, but that has yet to be demonstrated."

In the pre-clinical investigations, measurements of changes in matrix metalloproteinases (MMPs) and tissue inhibitors of MMPs provided surrogate evidence that DWT increased outflow facility.

However, in order to obtain more definitive evidence, W. Daniel Stamer, MD, Duke University, is planning studies to evaluate outflow function in human cadaveric eyes treated with DWT. ■

MALIK Y. KAHOOK, MD
E: *Malik.kahook@ucdenver.edu*
Deep wave trabeculoplasty was invented by Dr. Kahook.

The quest for a trabecular outflow drug

New class of glaucoma medicines is entering registration trials with dual-mechanism AR-13324

By Janet B. Serle, MD, and Casey C. Kopczynski, PhD, *Special to* Ophthalmology Times

IT HAS BEEN 20 years since a glaucoma drug with a new mechanism of action advanced to phase III clinical testing. That drug—latanoprost—went on to become the most widely prescribed treatment for glaucoma and ocular hypertension.

Enter a new class of drugs called ROCK/NET inhibitors that lower IOP through a dual mechanism of action, simultaneously inhibiting Rho kinase (ROCK) to increase fluid outflow through the trabecular meshwork and inhibiting the norepinephrine transporter (NET) to reduce fluid production.

The most commonly prescribed glaucoma medications do not address the physiologic cause of elevated IOP in glaucoma, the diseased trabecular outflow pathway.

The need for a trabecular outflow drug is what inspired David Epstein, MD, chairman, Department of Ophthalmology, Duke University; Eric Toone, PhD, professor of chemistry at Duke; and Casey C. Kopczynski, PhD, to start Aerie Pharmaceuticals in 2005. The company's novel glaucoma compound, AR-13324, is generating excitement in the eye-care community and on Wall Street. Aerie's recent IPO raised $77 million to fund phase III development of AR-13324 and phase II testing of PG324, a fixed-dose combination of AR-13324 and latanoprost.

"Targeting the diseased tissue to restore normal function is a fundamental tenet of medicine, yet no available glaucoma therapies do this," Dr. Epstein said. "We founded Aerie with the specific goal of bringing a safe and effective trabecular outflow drug to physicians and their patients."

TWISTS AND TURNS

"Innovation is rarely a linear process, especially in drug development," said Dr. Kopczynski, Aerie's chief scientific officer and a biotech start-up veteran. "In a start-up, you have to be focused, but more importantly you have to follow the data, even if it takes you in a different direction than originally planned."

The first potential trabecular outflow drugs Aerie pursued were ethacrynic acid and ticrynafen—compounds that Dr. Epstein's lab had studied for years. Since neither was a good drug candidate, Aerie's chemists generated related compounds with the goal of improving efficacy, tolerability, and solubility—a considerable challenge given that the biological targets for these drugs were unknown. After 6 months and little progress, the project was abandoned.

Committed to developing a trabecular outflow drug, Aerie initiated a new drug discovery program focused on inhibitors of Rho kinase, an enzyme that promotes actomyosin contraction in trabecular meshwork cells. At the time, Rho kinase inhibitors had been shown to relax trabecular meshwork cells, increase trabecular outflow in preclinical models, and lower IOP in healthy volunteers in the clinic.

However, the first ROCK inhibitor to reach the clinic required twice-daily dosing and caused significant hyperemia due to transient vasodilation of conjunctival blood vessels.

"Vasodilation is a pharmacological effect of Rho kinase inhibitors, but it is a transient effect," Dr. Kopczynski said. "Our strategy was to develop a more effective Rho kinase inhibitor that could be dosed once-daily with less hyperemia."

Aerie coupled medicinal chemistry, kinase profiling, and high-content cell-based screening to characterize more than 1,500 newly synthesized ROCK inhibitors. This extensive effort produced Aerie's first clinical stage trabecular outflow drug, a highly selective ROCK inhibitor with strong activity and a long duration of effect in pre-clinical models.

This agent also performed as designed in the clinic, providing the duration of action required to allow once-daily evening dosing. As a result, hyperemia during the day was minimal, similar to latanoprost in a phase IIb study. This observation confirmed that the transient hyperemia associated with ROCK inhibitors could be effectively managed with a once-daily dosing regimen.

The phase II clinical studies revealed an unexpected finding as well. Aerie's ROCK inhibitor was apparently too selective for Rho kinase. Other clinical stage ROCK inhibitors with activity against other kinases were previously shown to maintain a stable IOP-lowering effect over 28 days of dosing.

Aerie found that its more selective ROCK inhibitor lost efficacy over 28 days and continued to do so out to 3 months. The company now believes that in addition to inhibiting Rho kinase, ROCK inhibitors also need activity against Protein Kinase C (PKC) to maintain IOP-lowering efficacy over time.

Innovation at Aerie had continued even after its ROCK-selective inhibitor advanced to the clinic. These efforts were rewarded with the discovery of a new class of dual-action ROCK/NET inhibitors that ultimately gave rise to its current lead trabecular outflow drug, AR-13324.

The discovery was made when a newly synthesized ROCK inhibitor produced unprecedented drops in IOP that lasted 24 hours after a single dose in pre-clinical models. Scientists

take-home

The advancement of AR-13324 into phase III represents a major step toward the goal of adding an effective and well-tolerated trabecular outflow drug to the glaucoma armamentarium.

Positive results cited in AR-13324 phase I PK study

AERIE PHARMACEUTOCALS this month reported the results from its recently completed phase I pharmacokinetics (PK) study of AR-13324.

The PK study—in which AR-13324 eye drops were administered once-daily to 18 healthy individuals over an 8-day period to assess systemic exposure to the drug—demonstrated very low systemic exposure to the drug, with blood levels at or below the limit of detection of 0.1 ng/ml at all time points.

There also were no drug-related effects on systemic safety parameters, such as blood pressure and heart rate. All study subjects had IOPs in the normotensive range of 12 to 21 mm Hg, with an average diurnal IOP for the group of about 16 mm Hg prior to dosing. After 8 days of dosing, once-daily administration of AR-13324 reduced the average diurnal IOP to about 11 mm Hg, representing a decrease of about 5 mm Hg, or over 30%.

The completion of the PK study is an important step in preparing for two planned phase III registration studies of AR-13324, which are expected to commence by mid-2014. ■

suspected that the compound had activity against another target and screened it against a large panel of kinase and non-kinase proteins.

That first compound, and its subsequent derivatives, had significant activity against the norepinephrine transporter (NET) in addition to ROCK. Inhibition of NET is known to increase adrenergic signaling and appears to be responsible for the decrease in aqueous humor production observed in primates after AR-13324 application.

The "dual action" of AR-13324 refers not only to its biochemical activity against ROCK and NET, but to the two known physiological mechanisms by which it lowers IOP—increasing trabecular outflow and decreasing aqueous inflow.

MAKING PROGRESS

AR-13324 has successfully completed phase II clinical testing and will be advanced into phase III registration trials in 2014.

In a recent 28-day phase IIb study in patients with glaucoma or ocular hypertension, AR-13324 dosed once-daily in the evening was highly effective at lowering IOP, reducing mean IOP by 5.7 to 6.2 mm Hg. AR-13324 maintained stable activity through 28 days of dosing, consistent with its secondary activity against PKC. It was also well tolerated, with no systemic side effects and a 24% incidence of mild-moderate hyperemia on Day 28.

AR-13324's efficacy profile differed significantly from the comparator latanoprost in a prospective analysis of IOP-lowering efficacy versus baseline IOP.

As reported previously for a variety of glaucoma drugs, latanoprost was more effective in patients with baseline IOPs above 26 mm Hg and less effective in patients with moderately elevated IOPs of 22 to 26 mm Hg.

In contrast, AR-13324 produced the same IOP-lowering efficacy regardless of baseline IOP.

As a result, AR-13324 was less effective than latanoprost in high-baseline patients, but equally as effective as latanoprost in patients with moderately elevated IOPs. This may be significant in clinical practice, since epidemiological studies have shown that about 80% of patients with glaucoma have low-to-moderately elevated IOP at the time of diagnosis.

The advancement of AR-13324 into phase III represents a major step toward the goal of adding an effective and well-tolerated trabecular outflow drug to the glaucoma armamentarium. The fact that it took 8 years to reach this milestone is a reminder of just how difficult it is to develop new drugs with novel mechanisms of action.

The next major milestones for AR-13324 are to complete phase III and win FDA clearance.

"If approval can be achieved, there will be an explosion of academic research on AR-13324 aimed at understanding the benefits of directly treating the diseased trabecular outflow pathway," Dr. Epstein said. "My colleagues and I have been waiting a long time for this."

Editor's Note: Drs. Epstein and Kopczynski just published an article entitled "Emerging Trabecular Outflow Drugs," in *The Journal of Ocular Pharmacology and Therapeutics* in December. The article provides an update on progress with three classes of outflow drugs currently being investgated. Go to *http://bit.ly/1eVoK2h*. ■

JANET B. SERLE, MD

E: *janet.serle@mssm.edu*

Dr. Serle is professor of ophthalmology and glaucoma clinical and research fellowships director, Mount Sinai School of Medicine, New York. Dr. Serle receives funding for research from Akorn Pharmaceuticals, Aerie Pharmaceuticals, and Fovea. She is also a consultant for Alcon Laboratories, Altheos, Forest Laboratories, Ono Pharmaceuticals, and Sucampo Pharmaceuticals. Dr. Serle has received funding for speaking from New World Medical.

CASEY C. KOPCZYNSKI, PHD

Dr. Kopczynski is chief scientific officer, Aerie Pharmaceuticals Inc.

Combination anti-glaucoma drugs: Win-win for patients and physicians

Such medications mean fewer instillations, lower costs, better compliance, manageable IOPs

By Lynda Charters; *Reviewed by Fiaz Zaman, MD*

HOUSTON ::

THE AVAILABILITY OF combination anti-glaucoma therapies is a boon for patients and physicians when considering that about 40% of patients with glaucoma require 2 or more drugs to control elevated IOP levels.

The advantages of combination products are obvious. For patients, fewer daily instillations of drops may be needed and the costs of the drugs then become lower because co-payments are eliminated.

For physicians, the combination products increase patient compliance rates and the efficacy of the products reduces the IOP to more manageable levels.

In addition, while most patients are taking a prostaglandin drug with a normal dose of one drop once daily, most combination products require instillation of 1 drop twice daily, but washout is not an issue with the second or third prescribed drugs in contrast to when patients use multiple individual drugs, according to Fiaz Zaman, MD, in private practice, Houston Eye Associates.

take-home

- **Combination anti-glaucoma medications used alone or in conjunction with a prostaglandin have substantial IOP-lowering effects.**

CHOOSING THE COMBINATION DRUG

Deciding which combination therapy to use for individual patients necessitates considering a number of factors.

There are three primary combination anti-glaucoma therapies, he pointed out:

- ***COMBIGAN*** **(brimonidine tartrate/timolol maleate ophthalmic solution, Allergan),**
- ***COSOPT*** **(dorzolamide hydrochloride-timolol maleate ophthalmic solution, Merck),**
- ***SIMBRINZA*** **(brinzolamide/brimonidine tartrate ophthalmic suspension, Alcon Laboratories).**

Dr. Zaman prefers Combigan in his practice because multiple published studies have reported that the drug, when used with a prostaglandin, achieves a very significant decrease in IOP.

"Normally, when using adjunctive therapy, a minimal 15% to 20% IOP decrease is desired," Dr. Zaman explained. "Numerous studies have shown that Combigan prescribed in addition to a prostaglandin decreases IOP by 25% to 35%, which is phenomenal. The lower the IOP the better. In my opinion, there are sufficient data that indicate that the drug does a superb job."

Cosopt also can lower IOP substantially. However, in a head-to-head study, Combigan had superior IOP-lowering ability. A disadvantage with Cosopt is generic formulations of the drug may not be as efficacious as the brand name formulation, which can be hard to find.

"I tend to avoid the generic drugs in glaucoma for that reason," Dr. Zaman said.

Simbrinza, which is relatively new to the market, is advantageous for some patents because it does not contain a beta-blocker, he pointed out, in contrast to the other two combination drugs.

"Simbrinza is a good medication choice for patients with asthma, for whom beta-blockers are contraindicated," he said. "A disadvantage of Simbrinza is that it is FDA-approved only for instillation three times daily, which adds more to the treatment burden and patient compliance may become an issue.

"Another disadvantage is that the drug is in a suspension that requires shaking before instillation," he said. "Failure to do so may result in less of the active ingredients being instilled in the eye."

A final consideration is allergic reactions to the glaucoma drugs.

"With both Combigan and Simbrinza, the allergy rates are unknown. Brimonidine is a component of both drugs," Dr. Zaman added. "When it was first introduced, it was associated with a 20% allergy rate. Once a patient has an allergic reaction to brimonidine, he or she is allergic for life, thus eliminating this class of medication from use."

Combigan is associated with a low allergy rate (5%). The allergy rate for Simbrinza is unknown because it has been commercially available for only 6 months and its track record has yet to be determined.

GLAUCOMA MANAGEMENT

The decisions for how patients with glaucoma are managed is based on three factors—the IOP, optic nerve structure, and visual function, according to Dr. Zaman.

"The only variable factor in the treatment of glaucoma that has been proven is that lowering the IOP prevents some optic nerve changes from occurring, which in turn decreases the risk of visual loss," he said.

Monitoring of optic nerve changes is done by structural assessments using optic nerve photographs and optical coherence tomography, the Heidelberg Retina Tomograph (Heidelberg Engineering), and GDx-VCC scanning laser polarimetry (Carl Zeiss Meditec) to evaluate the nerve fiber layer.

"Structural changes in the nerve fiber layer can indicate that glaucoma is progressing," he added.

Visual field testing is performed to examine the visual function to detect glaucomatous progression.

"In glaucoma, there is progressive loss of the peripheral visual fields that will ultimately enlarge to incorporate the central visual field, which can lead to blindness if untreated," Dr. Zaman noted.

Therapy can be altered or other therapies added when progression of optic nerve damage and visual field loss becomes evident.

"Safety, efficacy, and compliance are all important when choosing an ocular medication. This is especially important because of the chronicity of glaucoma," he said, pointing out that his drug choices are based on evidence-based medicine.

THE FUTURE

Dr. Zaman said he is impressed with currently available drugs for treating glaucoma. However, he looks to the future for improvements.

"The future is bright for alternative therapies," he said. ■

FIAZ ZAMAN, MD

E: *fiazzaman@gmail.com*

Dr. Zaman has no proprietary interest in any aspect of this report.

Glaucoma in pregnancy: Imperative to discuss and management is key

Treatment regimen should include risk assessment for glaucoma medications

By Nancy Groves; *Reviewed by Martha M. Wright, MD*

MINNEAPOLIS ::

GLAUCOMA IS OFTEN thought of as a disease of aging, but it can affect patients who are much younger and more interested in starting a family than planning for retirement. With women in this age group, ophthalmologists should take extra time before reaching for the prescription pad.

Dr. Wright

"Glaucoma medication exposure is of concern to our patients and to us, not only in pregnancy, but during labor and delivery and in nursing patients," said Martha M. Wright, MD, Haven Professor of Glaucoma, Department of Ophthalmology, University of Minnesota, Minneapolis.

"My rule of thumb in treating women of childbearing age is that when you start a medication for glaucoma, you should discuss the risks of these medications with pregnancy even if they are not pregnant or planning to be pregnant at the time," Dr. Wright said. "Revisit the topic periodically. In some cases, we have the advantage of being told in advance that a pregnancy is being planned so that the ophthalmologist, the patient, and the obstetrician can work together to come up with the best possible plan."

MANAGEMENT APPROACH

Choosing the best management approach is complicated by the fact that many questions about glaucoma medication use during pregnancy are unanswered.

"We have limited information to help us," Dr. Wright said, explaining that animal studies do not necessarily translate into risks for humans, and there have been few studies of glaucoma medications in pregnant women since they are unlikely to enroll in drug studies.

What is known is that the dose and timing of medication can be important, with an earlier exposure in pregnancy having a different outcome than later exposure, Dr. Wright said.

However, it is unclear how the customary eye drop-size dose of a medication used in clinical practice relates to the much larger doses used in pregnancy risk studies.

The best available guide to help physicians assess the risk of glaucoma medications is the FDA Use-in-Pregnancy ratings (See table, at right). How should ophthalmologists use these guidelines?

"The 'obvious' answer is to pick only category A drugs for pregnant patients, but unfortunately there aren't any," Dr. Wright said.

The only readily available drug in FDA Category B is brimonidine tartrate 0.1%, 0.15%, or 2% (Alphagan, Allergan), and most of the routinely prescribed glaucoma agents are in Category C. While high doses of brimonidine in animal studies did not cause fetal damage, it is known that this drug, secreted in breast milk, causes apnea in human infants.

"It's recommended that if you have a patient on brimonidine, that it be stopped prior to delivery," Dr. Wright said.

Prostaglandin analogs are a mainstay of glaucoma treatment, but they are Category C drugs in which risks cannot be ruled out. This class of medication is used to induce labor at much higher doses, and the prostaglandins are embryocidal at higher doses in animals; no human studies have been performed.

Beta-blockers have been used systemically for many years to treat hypertension in pregnant women. However, there may be an association with babies who are small for gestational age, preterm births, and increased perinatal mortality in patients taking oral beta-blockers at doses hundreds to thousands of times the human dose by weight. Beta-blockers are Category C medications.

Beta-blockers are also of concern in nursing women, as they are actively secreted and concentrated in breast milk.

"Babies of mothers taking these medications should be monitored for apnea and bradycardia," Dr. Wright said.

Carbonic anhydrase inhibitors are also Category C medications, known to cause fetal malformation in animal studies at high doses. However, a study in which pregnant women were prescribed acetazolomide (Diamox) for treatment of intracranial hypertension did not show any adverse effects on the fetus.

Regardless of the medication prescribed to a pregnant or nursing patient, one of the goals should be to minimize systemic absorption with a punctal occlusion method.

"If either you or your patient [is] not willing to use medication during pregnancy, then laser trabeculoplasty can be used as a temporizing measure," Dr. Wright said. "Or, if you can do it in advance, some surgical options may be best for these patients. But remember, you want to be sure that your patient is not pregnant at the time that you use an antifibrotic because these are Category X." ■

Use-in-Pregnancy Ratings

CATEGORY	GUIDELINE
A	**Controlled studies show *no risk.* Adequate, well-controlled studies in pregnant women.**
B	**Animal findings show risk, but human findings do not *OR* if no human studies, animal findings are negative.**
C	**Human studies are lacking, and animal studies are either positive for fetal risk, or lacking as well. *Potential benefits may justify the potential risk.***
D	***Positive evidence of risk.* Investigational or post-marketing data show risk to the fetus. Nevertheless, potential benefits may outweigh the potential risk.**
X	***Contraindicated in pregnancy.* Studies in animals or humans show fetal risk which clearly outweighs any possible benefit.**

Sources: Martha M. Wright, MD; FDA

MARTHA M. WRIGHT, MD
P: *612/625-4400* E: *wrigh004@umn.edu*

Dr. Wright did not report any financial interests.

Branded or generic: What's in a name?

Generic drugs safe, effective for majority of patients, but mandate increased surveillance

By Cheryl Guttman Krader; *Reviewed by Malik Y. Kahook, MD*

GENERIC MEDICATIONS CAN offer cost savings for patients and conserve limited health-care resources. Potential challenges can also accompany the use of generic ophthalmic drops, however.

The lower cost of generic products has value for patients in terms of increasing access and possibly compliance, but it also has potential societal benefit, said Wiley A. Chambers, MD.

"For the first time, in 2012, there was a drop in the annual expenditure for prescription medications . . . that was due to an increase in the number of generic products dispensed," said Dr. Chambers, clinical professor of ophthalmology, The George Washington University, and deputy director, Division of Transplant and Ophthalmology Products, Center for Drug Evaluation and Research, FDA, Silver Spring, MD.

"Ophthalmic resources are limited," he said. "If we make the best use of our dollars by using generic products when available, we can spend the money on developing innovator products for new indications."

Malik Y. Kahook, MD—presenting the case for branded medications—noted that the majority of his patients use generics and that he believes generics are typically safe and effective. He also said he believes in cutting health-care costs, but not in cutting corners to get there.

"In cases where product approval was obtained without prior clinical data, our duty is to alert the FDA to confusing variables as well as to potential efficacy and safety issues that can be missed with in vitro testing," said Dr. Kahook, The Slater Family Endowed Chair in Ophthalmology and professor of ophthalmology, University of Colorado School of Medicine, Aurora, CO.

take-home

Although generic medications approved by the FDA are identical to the innovator in their active and inactive ingredients, prescribers must be cognizant about sources of problems associated with the use of ophthalmic generic drugs.

DEFINING GENERIC DRUGS

A generic drug—a product approved by the FDA after being submitted as an Abbreviated New Drug Application—is intended to copy the safety and efficacy of the innovator (or a designated generic to the innovator if the innovator is discontinued), Dr. Chambers explained.

A generic is expected to contain the same active and inactive ingredients as the innovator product. Since all of the ingredients in ophthalmic solutions are dissolved, order of ingredient mixing and particle size are moot issues.

Dr. Chambers also clarified that before regulations for generic medications existed, multiple companies made their own versions of a product containing the same active ingredient (e.g., prednisolone acetate 1% or diclofenac 0.1%). These individual products are each considered an innovator as they have unique formulations and were approved based on data from clinical trials, not in vitro testing. However, there may be generic versions of each "innovator."

As pointed out by Dr. Chambers, "generics" manufactured outside of the United States are not regulated by the FDA. They may differ in their inactive ingredients compared with the innovator product, and those differences can account for differences in efficacy and stability relative to the innovator.

As shown by Dr. Kahook, foreign generic products have also been found to be affected by problems with contamination.

These foreign medications make their way into the hands of U.S. consumers via mail-order purchases. In addition, Dr. Kahook noted some U.S. companies are distributing generic medications manufactured outside of the country.

"Regulatory standards for generics can be different in different parts of the world," Dr. Chambers said. "We have tried in the United States to keep our products . . . true generics when they are ophthalmic solutions, but the lesson for physicians and patients is to be careful about all mail-order products, generic or otherwise."

Container differences between generic and innovator products also create the potential for problems with generics. Dr. Chambers acknowledged that regulations on generic medications were developed for solid oral formulations, not ophthalmic drops. As pointed out by Dr. Kahook, differences in bottle material and dropper configuration with ophthalmic drops can affect the ease of use and volume of drug dispensed. Differences in container appearance, including cap color and dropper configuration, can be a source of confusion for patients.

"Saying that generics are equivalent to the branded medication based on their having the same active and inactive ingredients is not true and does not cover the whole story as there can be issues with bottle type, bottle color, and also labeling issues," Dr. Kahook said.

Dr. Kahook

Though generics are supposed to have the same label as the innovator, he noted, the FDA recently proposed a rule that would permit generic drug makers to update their label if they received information about potential safety problems.

REMAINING VIGILANT

To minimize problems with generics, Dr. Kahook said that all patients seen at the University of Colorado are asked to bring all of their medications to every visit. Any changes in medication and manufacturer are documented, and patients who changed from a branded product to a generic are asked to return for earlier follow-up.

It is important to know about any changes in medications patients are using and to monitor patients for any changes in efficacy or safety. However, a switch to a generic may not be the only culprit as problems can arise for a variety of other reasons, Dr. Chambers noted.

Dr. Chambers encouraged physicians to be attentive to medication container-specific problems with generic ophthalmic medications and to bring them to the attention of the FDA. ■

WILEY A. CHAMBERS, MD

E: *wiley.chambers@fda.hhs.gov*

Dr. Chambers has no relevant financial interests to report. His presentation reflects his personal views and not necessarily those of the FDA.

MALIK Y. KAHOOK, MD

E: *malik.kahook@ucdenver.edu*

Dr. Kahook is a consultant to the FDA and to several manufacturers that make branded and generic ophthalmic medications.

Dr. Chambers and Dr. Kahook spoke as opponents in a point-counterpoint session on branded and generic medications at Glaucoma Subspecialty Day during the 2013 meeting of the American Academy of Ophthalmology.

Ultrasound-based therapy effective for refractory glaucoma patients

Cyclocoagulation results in IOP lowering ≥20% in about 70% of eyes after 1 year

By Cheryl Guttman Krader; *Reviewed by Shlomo Melamed, MD*

ULTRASOUND CIRCULAR CYCLOCOAGULATION (UC³, EyeTechCare)—a fast, simple, non-invasive treatment that safely and effectively lowers IOP in eyes with refractory glaucoma—involves the precise delivery of high-intensity-focused ultrasound to the ciliary body and ciliary processes.

The treatment is performed using a proprietary system (EyeOP1, EyeTechCare) with a control module and a sterile, disposable probe. The probe features six miniaturized 21-MHz ultrasound transducers, a positioning cone, and a suction ring. After the probe is fixated in place, the procedure is initiated via foot pedal control.

Without the need for any additional maneuvers, a series of precisely positioned and evenly distributed coagulative lesions are created in the ciliary body and ciliary processes. Lesioning of these tissues is presumed to lead to IOP reduction secondary to decreased aqueous humor production and increased outflow through a widened uveoscleral pathway.

Safety studies in animals, which included histologic evaluations, confirm the specificity of the treatment as there were no adverse effects on the iris, crystalline lens, sclera, or conjunctiva.

take-home

- **Ultrasound circular cyclocoagulation is a non-invasive treatment for refractory glaucoma that is approved in Europe.**

CLINICAL EXPERIENCE

Data from hundreds of patients treated for advanced refractory glaucoma show the procedure results in a ≥20% reduction in IOP in about 70% of eyes with primary open-angle glaucoma and that the benefit is maintained for at least 1 year.

Clinical experience also demonstrates that the treatment is well tolerated under local (retrobulbar or peribulbar) anesthesia and associated with minimal post-treatment morbidity and no serious complications. Patients may develop some minor conjunctival irritation and mild anterior chamber inflammation, but post-treatment discomfort is minor at worst. There have been no cases of severe permanent hypotony or high IOP spikes after treatment.

"Transscleral cyclophotocoagulation with diode laser has been the cyclodestructive technique of reference for more than 15 years, and it has a very positive impact on patients suffering with refractory glaucoma," said Fabrice Romano, DVM, chief executive officer, EyeTechCare, Rillieux-la-Pape, France. "However, laser energy delivery with transscleral cyclophotocoagulation has low selectivity for the ciliary body and processes, and so the procedure is associated with collateral tissue damage, post-treatment pain, chronic inflammation, and visual acuity loss."

In contrast, the new ultrasound-based procedure is associated with excellent tolerability while producing significant IOP lowering in eyes with refractory glaucoma, Dr. Romano noted.

PROCEDURE DETAILS

The treatment probe comes in three sizes that enable optimal fitting, positioning, and treatment regardless of ocular anatomy. After the positioning cone is properly centered, suction is activated, allowing the suction ring to grip the conjunctiva gently and hold the treatment probe in place without distorting the eye.

Surgeons select the treatment parameters (exposure time per shot) using the control module's intuitive touchscreen display. The total treatment time is about 2 minutes per eye.

The treatment is approved in Europe and is being performed in 10 western European countries, including in France where glaucoma specialists at 10 centers are using it as a routine treatment for patients with refractory glaucoma.

It is being investigated in a prospective, interventional study at the Goldschleger Eye Institute, Sheba Medical Center, Tel Aviv University, Ramat Gan, Israel, that enrolled 20 patients with an IOP ≥30 mm Hg on maximally tolerated medication and who had failed at least one filtering surgery.

Mean pre-treatment IOP was 36.4 mm Hg and was reduced to 18.6 mm Hg at 1 week. At 1 year of follow-up, 4 patients had been re-treated, mean IOP for the 20 eyes was 22.5 mm Hg, and the procedure was considered a success (>20% reduction in IOP) in 65% of eyes.

"Our center often treats glaucoma patients in whom other procedures have failed," said Shlomo Melamed, MD, professor of ophthalmology, Tel Aviv University. "Our experience with [this ultrasound-based procedure] indicates it is an effective and well-tolerated therapeutic modality for that population. However, we believe it has definite potential for earlier use in glaucoma care."

Data from 1 year of follow-up are also available for 52 eyes with refractory glaucoma enrolled in a multicenter study in France. Eligible eyes had IOP >21 mm Hg after one or more filtering surgeries. The study eyes were divided into two groups that varied by treatment exposure time (4 or 6 seconds per shot). IOP in the two groups averaged 30.3 and 29 mm Hg, respectively, at baseline and was reduced by an average of 10 mm Hg at 12 months in both groups, with success rates of 63% and 44%, respectively. ■

ULTRASOUND TECHNIQUE

VIDEO For a video on the ultrasound circular cyclocoagulation technique, go to **http://bit.ly/1as7i2p**. *(Video courtesy of EyeTechCare)*

SHLOMO MELAMED, MD

E: *melamed.shlomo@gmail.com*

Dr. Melamed receives research grants from Allergan, Ellex, EyeTechCare, IOPtima, and SOLX.

FABRICE ROMANO, DVM

E: *fromano@eyetechcare.com*

Dr. Romano is chief executive officer, EyeTechCare, Rillieux-la-Pape, France.

Why utilizing TSCPC is surgeon's choice for advanced glaucoma

Transscleral cyclophotocoagulation is preferred option to traditional filtering surgeries

By Emery Jaffe, MD, *Special to* Ophthalmology Times

DELRAY BEACH, FL ::

AS A COMPREHENSIVE ophthalmologist, I prefer to stay away from traditional glaucoma filtering surgeries—such as trabeculectomy and tube shunts—that bring with them a host of complications and time-consuming, follow-up care.

In South Florida, I discovered a sizable percentage of patients who have moderate-severe glaucoma, and who require treatment. This is complicated by the fact that many glaucoma specialists in this area are close to or already at maximum patient loads, and many patients are unwilling to commit to surgical treatment of glaucoma.

These realities have led to the search for a less invasive treatment to achieve significant IOP reduction in patients. These days, after exhausting conventional office methods of lowering IOP—such as topical medications or selective laser trabeculoplasty (SLT)—I often apply transscleral cyclophotocoagulation (TSCPC) with a glaucoma device (G-Probe, Iridex).

For more than a decade, research has shown TSCPC to be an effective and safe method for the treatment of advanced glaucoma. I have also followed the recent literature on newer techniques that have improved the safety profile.

Douglas E. Gaasterland, MD, introduced a protocol known as the slow coagulation technique, which calls for lower power settings accompanied by longer exposure times. This method helps avoid tissue vaporization, reducing the postoperative inflammatory response.

Steven Vold, MD, has advocated transillumination of the sclera, which highlights the ciliary body for targeting.

I have adopted both of these techniques, as well as made some additional modifications, and have arrived at what I feel is a very safe and effective treatment. (See video, at right)

REDEFINED PROTOCOL

My goal is to have an effective therapy with no complications, so I have a fairly conservative approach toward TSCPC.

I start by using transillumination to visualize the ciliary body and only treat over this region. Transillumination easily highlights the target for treatment. I try to maintain that position posterior to the limbus for the entire treatment.

When I first began performing TSCPC with the slow coagulation treatment aimed closer to the limbus, I experienced numerous pops and a couple of cases resulted in peaked pupils, especially superiorly. These treatments likely killed too many epithelial stem cells and produced severe dry eye that was resistant to treatment.

I am convinced that the combination of the slow coagulation technique with placement of the laser spots farther from the limbus was the modification necessary to eliminate the pain and inflammation that resulted in my earlier treatments.

I currently apply 20 spots with the OcuLight SL Infrared 810-nm laser (Iridex) for my initial treatment. I avoid treating 2 clock hours centered on the nasal and temporal limbus. I apply 10 spots superiorly and 10 spots inferiorly, centered on 12 and 6 o'clock. Each treatment generally begins at 2 watts for 2 seconds, although I adjust for each patient.

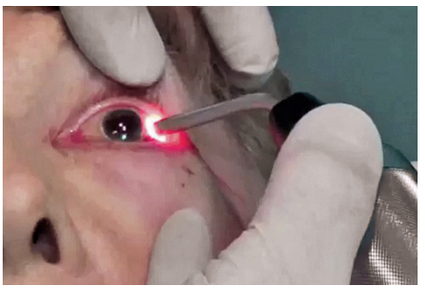
More advanced disease gets treated with higher powers and I reduce the energy level if I hear any pops. I believe that treating directly over the ciliary body and further from the iris root allows for the usage of a higher power with less or no audible pops from cellular disruption. I am seeing an average of 40% reduction in IOP with this method.

I also use difluprednate ophthalmic emulsion (Durezol, Alcon Laboratories) before and after the treatment along with a NSAID and one drop of atropine after treatment to address inflammation aggressively. Patients have much less pain and fewer complications, while still achieving a significant drop in IOP.

take-home

- **One ophthalmologist explains how the search for a less invasive treatment to achieve significant IOP reduction led him to apply transscleral cyclophotocoagulation with a glaucoma device.**

TRANSILLUMINATION TECHNIQUE



VIDEO To watch the transillumination technique, go to **http://bit.ly/1eTaw1T**
(Video courtesy of Emery Jaffe, MD)

SUMMARY

As the population continues to age, the need for effective glaucoma treatments is going to balloon. Though there are a number of minimally invasive glaucoma treatments in various stages of development, most have not shown

Continues on page 19 : ***TSCPC***

OT OphthalmologyTimes.com *ONLINE EXCLUSIVE*

TSCPC CASE STUDY BY DR. JAFFE

AN 86-YEAR-OLD Hispanic male presented for a follow-up exam in March 2012. A general medical history included high blood pressure and adult-onset diabetes mellitus. For more on Dr. Jaffe's case study, go to http://bit.ly/1fCla0y

Fixed combination found to be safe and well-tolerated in phase III trial

Brinzolamide-brimonidine addresses unmet need for significant patient segment

By Cheryl Guttman Krader; *Reviewed by Ivan Goldberg, MD*

SYDNEY, AUSTRALIA ::

PHASE III STUDY results support the conclusion that the carbonic anhydrase inhibitor-alpha agonist fixed combination of brinzolamide 1% and brimonidine 0.2% (Simbrinza Suspension, Alcon Laboratories) is a safe, well-tolerated, and effective treatment for lowering IOP in patients with glaucoma or ocular hypertension that is uncontrolled by monotherapy.

The randomized, multinational, double-masked trial was conducted at 63 centers in the Asia-Pacific region, Europe, United States, Latin America, and Caribbean nations. It included 560 patients who had insufficient IOP control on monotherapy or who were already using more than 1 medication.

Dr. Goldberg

Ivan Goldberg MD, clinical associate professor, Discipline of Ophthalmology, University of Sydney and head, Glaucoma Unit Sydney Eye Hospital, Sydney, Australia, was an investigator in the study.

"The new brinzolamide-brimonidine product is the first fixed-dose combination product that does NOT contain a beta-blocker, and its availability is excellent news for the sizeable group of patients with ocular hypertension or open-angle glaucoma who have relative or absolute contraindications for beta-blocker treatment," Dr. Goldberg said.

"Fixed-dose combinations have become the fastest growing segment of the anti-glaucoma medication market because they decrease exposure to preservatives and provide increased convenience," he added. "With the latter benefit, fixed-dose combinations are a positive contribution for addressing ongoing non-adherence, which is known to increase as the number of medications prescribed increases."

ABOUT THE STUDY

Eligible patients were randomly assigned equally into three groups to receive twice-daily treatment with the brinzolamide-brimonidine fixed combination (BBFC), brimonidine alone, or brinzolamide alone. IOP was measured at 9 and 11 a.m. and 4 p.m. at baseline and week 2, week 6, month 3, and month 6 after randomization.

Baseline diurnal IOP, calculated as the average of the three measurements averaged 25.9 or 26 mm Hg in all three groups.

Mean diurnal IOP change from baseline to 3 months was analyzed as the primary efficacy endpoint, and the results showed the reduction achieved was significantly greater among patients using BBFC compared with the controls treated with brinzolamide alone or brimonidine alone (–7.9 versus –6.5 and –6.4 mm Hg). A significant difference favoring BBFC over the monotherapy treatments was also achieved at all other follow-up intervals.

Safety data showed there were no serious adverse events or study withdrawals that were judged related to study medication nor any clinically meaningful changes in pulse rate, blood pressure, or BCVA in any of the study groups. Overall, adverse event data showed that BBFC was associated with a safety profile consistent with its individual components.

Baseline data in the phase III study showed the three treatment groups were well matched in their demographic and disease characteristics. The patients in the study had an average age of about 65 years, about 70% were white, and about 75% had open-angle glaucoma.

Treatment-related adverse events occurred in 26.5% of patients in the BBFC group, among 11.5% of patients treated with brinzolamide alone, and in 22.9% of brimonidine-treated patients. The only adverse events occurring at a rate >5% were ocular hyperemia, eye pain, and dysgeusia, each of which occurred among 5.7% of patients receiving BBFC. Ocular hyperemia occurred at a rate of 4.6% among patients treated with brimonidine alone.

"There were no safety surprises in the study," Dr. Goldberg said.

Side effects with the fixed-dose combination were as expected given its active ingredients.

"This was the hope in undertaking the study, and it was confirmed by the data," he said. ■

IVAN GOLDBERG, MD

E: *eyegoldberg@gmail.com*

Dr. Goldberg has served as a consultant and advisory board member for Alcon Laboratories, Allergan, Forsight, Merck, and Pfizer, has participate on speakers bureaus for Alcon and received travel support from Alcon and Pfizer.

TSCPC

(Continued from page 18)

to provide sufficient IOP lowering for the majority of advanced glaucoma patients.

TSCPC has been very effective, and quite safe with the parameters I use.

If the patient does not demonstrate sufficient reduction of IOP, or if the effect wears off, I will re-treat with similar powers. Most patients return after 10 to 14 days and their eyes are "quiet" and they are comfortable. I continue to believe that this treatment is convenient and comparatively safe.

I cannot say the same for trabeculectomy and tube shunt procedures. ■

References

1. Schlote T, Derse M, Rassmann K, Nicaeus T, Dietz K, Thiel HJ. Efficacy and safety of contact transscleral diode laser cyclophotocoagulation for advanced glaucoma. *J Glaucoma.* 2001;10:294-301.
2. Gaasterland DE. Diode laser cyclophotocoagulation. Technique and results. *Glaucoma Today.* 2009;7:35-38.

EMERY JAFFE, MD

E: *edj33160@gmail.com*

Dr. Jaffe is in private practice at Jaffe Eye Institute, Delray Beach, FL. He has received honoraria but is not a paid consultant for Iridex.

Warming up to the 'ICE' procedure

Combining microinvasive surgeries may be future of glaucoma treatment to improve results

By Steven R. Sarkisian Jr., MD, *Special to* Ophthalmology Times

OKLAHOMA CITY ::

COMBINING IMPLANTATION of trabecular micro-bypass stents (iStent, Glaukos), cataract surgery, and endoscopic cyclophotocoagulation (ECP) (Endo Optiks)—also referred to as the "ICE" procedure—offers a dual-mechanism glaucoma treatment. This therapy enables surgeons to treat two sides of the glaucoma equation by simultaneously restricting inflow and enabling outflow.

Although medications can achieve a similar effect—such as aqueous suppressants to reduce aqueous production and prostaglandins to increase aqueous outflow—ICE is a surgical option that addresses the patient's cataract and glaucoma in one procedure.

Perhaps the greatest benefit of ICE is that performing ECP and the iStent together can lead to the reduction or elimination of more medications than either procedure alone.

IDEAL PATIENTS, SURGICAL PROCEDURE

Patients ideally suited for ICE are those who are taking multiple medications and suffering from early onset open-angle glaucoma.

I typically start ICE with the "C" component, namely, temporal clear corneal cataract surgery. Once the lens has been implanted, I begin the ECP by first removing the viscoelastic from the capsular bag. I then place Healon GV (Abbott Medical Optics) into the ciliary sulcus in order to optimize visualization of the entire ciliary process.

Next, I perform 360º of ECP followed by removing the viscoelastic from the ciliary sulcus. I place Miochol-E (Bausch + Lomb) in the eye to bring down the pupil, which allows me to visualize the angle for implantation of the iStent. I place more Healon in the anterior chamber so that I can see the entire nasal angle and turn the patient's head away from me about 45º and tilt the microscope as well.

I use a surgical gonioprism, after placing some Healon on the cornea, to visualize the angle. I then implant the iStent through the cataract wound. Once I have made sure the wounds are sealed nicely and there are no leaks, I remove the speculum and the procedure is complete.

After the ICE, I prescribe a fluoroquinolone and difluprednate ophthalmic emulsion 0.05% (Durezol, Alcon Laboratories) for inflammation, to be administered quite aggressively every 2 hours, while awake, the day of the surgery.

I taper the use of the steroid drop rapidly after the first few days, and I monitor the eye for IOP spikes as a result of the steroids. If I find that the patient is having a steroid-response IOP spike, I may switch the prescription to a nonsteroidal anti-inflammatory drug or loteprednol etabonate ophthalmic gel 0.5% (Lotemax 0.5% Gel Drop, Bausch + Lomb).

PEARLS FOR ICE

Placement of the iStent can also be assisted by the use of an endoscope (Endo Optiks) as opposed to a gonioprism. Using the endoscope to visualize the angle eliminates the need for repositioning the patient's head and microscope during the procedure.

The endoscope can also work as a stabilizer. I have often had patients with rapid movement of the eye, which can make implantation of the iStent somewhat difficult. Utilizing the endoscope through a second port in the eye can stabilize the eye for easier and safer iStent implantation.

When I use it, I typically have to open up the paracentesis, and I make sure the monitor is close enough to allow me to visualize the angle properly.

take-home

- ***The combination of microinvasive glaucoma surgeries with cataract surgery may address a patient's cataract and glaucoma in one procedure.***

WHY IT WORKS

Because ECP and the iStent are microinvasive glaucoma surgeries (MIGS), they can be combined easily with cataract surgery. ECP can be done through the same wound as a cataract extraction, which, in my case, is a sub-2-mm procedure. ECP is appealing to patients, because it does not require sutures and therefore won't lead to scarring and astigmatism.

Furthermore, there is no foreign body sensation or issues with having an extraocular reservoir. The recovery for ECP and other MIGS procedures is essentially the same as cataract surgery, which is a substantial benefit to the patient and changes both the surgeon's and patient's attitude about glaucoma surgery from one of "surgery is the last line of defense against glaucoma," to bringing surgery on par with medical management and laser trabeculoplasty in the treatment algorithm.

Combining MIGS procedures is the future of glaucoma surgery. I predict we will see fewer trabeculectomies performed in the United States. Furthermore, mostly fellowship-trained glaucoma specialists, not general ophthalmologists, will do the few that are performed.

As more MIGS become FDA approved, more procedures will be combined in order to improve results and streamline the patient's surgical experience. Any physician familiar with cataract, ECP, and iStent implantation as individual procedures will have little to no learning curve when combining them for ICE. ■

OphthalmologyTimes.com
Online Exclusive

TREATING GLAUCOMA A TOTAL GLOBAL EFFORT

WITH THE 4TH ANNIVERSARY of the devastating earthquake in Haiti, Mildred Olivier, MD, of Rosalind Franklin University and Midwestern University, said it is important to remember the toll glaucoma takes on developing nations. The disease is an unaddressed concern for millions of people in the world. Dr. Olivier said that of all eye diseases, glaucoma needs to be addressed more diligently. Ophthalmologists cannot continue to neglect glaucoma internationally, considering the number of individuals becoming blind, she urged. Go to http://bit.ly/KICr0C.

STEVEN R. SARKISIAN JR., MD
P: *405/271-1093* E: *steven-sarkisian@dmei.org*
Dr. Sarkisian is glaucoma fellowship director, Dean McGee Eye Institute, and clinical associate professor, University of Oklahoma College of Medicine, Oklahoma City. Dr. Sarkisian is an investigator in the MIGS study group and the iStent inject study sponsored by Glaukos Corp. and is on the advisory board for Endo Optiks.

Incorporating New Knowledge Into Daily Glaucoma Management To Improve Overall Outcomes

Watch on demand NOW!

Featuring Steven T. Simmons, MD

- Better understand recent study results and how they require changing routine glaucoma care
- Better utilize target pressures in your patients and incorporate IOP fluctuation into the setting of these targets
- Better utilize present glaucoma therapies, both medical and surgical, to improve the overall glaucoma outcomes in your practice

Watch On Demand

Visit: https://engage.vevent.com/rt/advanstar_events?code=print

Ophthalmology Times®
CUTTING-EDGE ADVANCEMENTS

Sponsored by
ALLERGAN

APC26CS13

RETAIN presented mixed results for BRVO/CRVO with ranibizumab

BRVO achieves good outcomes with as-needed injections; CRVO needs sustained treatment

By Lynda Charters; *Reviewed by Peter A. Campochiaro, MD*

TAKE-HOME

- ***The RETAIN Study of the effect of retinal vein occlusion (RVO) treated with ranibizumab injections found good visual acuity results in patients with branch RVO.***

BALTIMORE ::

The RETAIN Study demonstrated very good long-term outcomes in patients with retinal vein occlusion (RVO) treated with ranibizumab (Lucentis, Genentech). Average visual gains obtained in the first 6 months are maintained for at least 4 years.

However, 50% of patients with branch RVO (BRVO) and 56% of patients with central RVO (CRVO) were still requiring injections of ranibizumab 4 years after initiating treatment to control edema. In most patients, RVO is a chronic disease that requires prolonged follow-up and management, said Peter A. Campochiaro, MD, on behalf of the RETAIN Study group.

Dr. Campochiaro

Following the BRAVO and CRUISE studies and the subsequent HORIZON studies of RVO—which showed substantial short-term benefits from treatment with ranibizumab—researchers were left with unanswered questions regarding long-term outcomes:

- **Is there a time when injections would no longer be needed or is lifetime treatment necessary?**
- **Will vision be maintained or lost over time?**
- **Could adjunctive treatments contribute to the maintenance of treatment benefits and reduce the need for injections?**

Dr. Campochiaro, the George S. and Dolores Dore Professor of Ophthalmology and Neuroscience, Johns Hopkins University School of Medicine, Baltimore, organized the RETAIN trial. Results were published Oct. 7, 2013 in *Ophthalmology* to address these questions.

In the RETAIN Study, 34 patients with BRVO and 32 patients with CRVO who completed the HORIZON study and were followed for another 2 years.

During year 1, patients were evaluated monthly and in year 2 at least every 3 months. When intraretinal fluid was seen on spectral domain-optical coherence tomography (SD-OCT), patients were treated with 0.5 mg of ranibizumab. Scatter photocoagulation was applied in patients who required injections in 2 consecutive months. If injections were still needed 3 months after laser, supplemental scatter photocoagulation combined with grid laser photocoagulation was given.

BRVO PATIENTS

In the RETAIN Study, patients with BRVO had substantial increases in the mean best-corrected visual acuity (BCVA) at 6 months after BRAVO baseline that were well maintained at every time point over the subsequent 4 years, Dr. Campochiaro noted.

"The final mean BCVA in Snellen equivalent was 20/32," he said.

During year 4, the patients were treated with an average of 2 ranibizumab injections. Half of the 34 patients with BRVO achieved resolution of macular edema for a minimum of 6 months after the last ranibizumab injection; 77% of these patients who had resolution of edema received their last injection of ranibizumab within 2 years of their first injection.

Patients who were still requiring injections 2 years after initiating treatment were unlikely to achieve resolution of edema within 4 years, Dr. Campochiaro explained. Patients with unresolved edema required a mean of 3 injections in year 4.

Interestingly, the mean BCVA was 20/32, both in patients with resolved macular edema and those without resolution, indicating that patients with BRVO maintain visual potential even when they have chronic, recurrent edema that requires injections for 4 years.

CRVO PATIENTS

Patients with CRVO in RETAIN also maintained the improved mean BCVA that was obtained at the month 6 endpoint of CRUISE, according to Dr. Campochiaro.

Mean foveal thickness was less stable than that seen in patients with BRVO and the final mean BCVA was 20/50. The percentage of patients with CRVO with resolved macular edema was 44%, and 71% of them achieved resolution during the first 2 years after the start of treatment.

"Unlike patients with BRVO, those with CRVO with resolved macular edema had significantly better BCVA (mean, 20/32) compared with those with unresolved edema (mean, 20/80)," he said.

Those with unresolved edema had substantially greater mean foveal thickness and required a mean of 6 injections during year 4. These patients tended to be older than those with resolved macular edema and more likely to be hypertensive, Dr. Campochiaro noted.

RETAIN Study showed patients with BRVO had better increases in mean BCVA at 6 months

The loss of BCVA in these patients was due to photoreceptor damage, probably from recurrent macular edema and/or ischemic damage to the macula.

This subgroup may benefit from more sustained suppression of vascular endothelial growth factor. ■

PETER A. CAMPOCHIARO, MD

E: *pcampo@jhmi.edu*

Dr. Campochiaro is a consultant for Advanced Cell Technology, Aerpio, Gene Signal, Elan, Genentech, Genzyme, GlaxoSmithKline, Oxford BioMedica, and Regeneron.

For Products & Services advertising information, contact: **Karen Gerome** at 800-225-4569, ext 2670 • Fax 440-756-5271 • Email: kgerome@advanstar.com

For Recruitment advertising information, contact: **Joanna Shippoli** at 800-225-4569, ext 2615 • Fax 440-756-5271 • Email: jshippoli@advanstar.com

PRODUCTS & SERVICES

BILLING SERVICES

PM Medical Billing & Consulting

Exclusive Ophthalmology Billers
Expert Ophthalmology Billers
Excellent Ophthalmology Billers
Triple E = Everything gets Paid

Concentrating on one Specialty makes the difference.

We are a Nationwide Ophthalmology Billing Service. We have been in business over twenty years. Our staff consists of billers who are certified Ophthalmic Techs, Ophthalmic assistants, and fundus photographers who are dual certified ophthalmic coders and billers. This combination of clinical backgrounds in ophthalmology with the certified coding degree is the ideal combination of expertise that you need to dramatically increase your revenue. We will get you paid on every procedure every single time. No more bundling, downcoding or denials…

Primary, Secondary, Tertiary and Patient Billing
Relentless and meticulous follow up.

- Experts in Forensic Billing .Specializing in old AR cleanup
- Credentialing and Re credentialing our Specialty. We have a separate Credentialing Department who has cultivated years of contacts to expedite the process as well as getting providers on plans that are technically closed.
- We can offer you our own Practice Management software at no cost to you or we can VPN into your system if that is what you prefer.
- Totally Hippa compliant. We are certified Hippa and have invested in the most secure Hippa connection that Google and Cisco use.
- Monthly custom reports provided.

We presently work on all of the following Practice Management systems :

NextGen, MD Office, Centricity, Medisoft, Office Mate, MD Intellus, Medware, Medcomp, Management Plus, ADS, Revolution EHR, EyeMd EMR, Next Tec, Open Practice Solutions , Cerner Works and more….

All of our clients were paid the PQRI and E-prescribe bonuses and we are ready for the ICD-10 change

Our staff has years of Attendance at AAO and ASCRS and attends all ongoing Ophthalmology billing and Practice Management continuing education classes. We are always knowledgeable and prepared for all government and commercial changes.

On staff MBA consultants

Call today to schedule a free on site consultation.

We will travel to you anytime to evaluate your AR and show you how we can dramatically increase your Revenue.

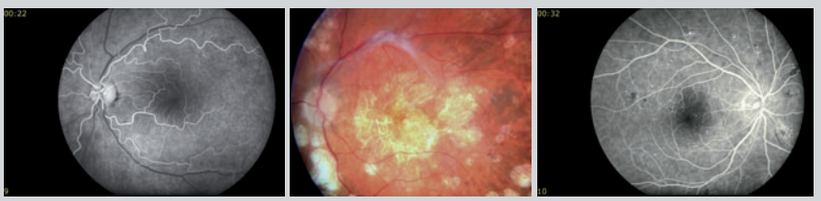
Call toll free at 1-888-PM-BILLING (1-888-762-4554)
Email: pmmedbill@aol.com
Web: www.pmophthalmologybilling.com
24 hours: 516-830-1500

Our Prestigious National Ophthalmology Clients reference list will be provided at your request

PM (Practice Management) Billing will keep an EYE on your Billing so you can keep an EYE on your patients.

DIGITAL IMAGING

DOES YOUR DIGITAL IMAGING SYSTEM CAPTURE IMPRESSIVE 21MP IMAGES?



FUNDUS PHOTO DOES!

Learn more at www.itsthisgood.com 314.533.6000

EQUIPMENT

The Leading Reseller of Premium Preowned Diagnostic Equipment in the U.S.

EYE CARE ALLIANCE®

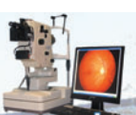
800-328-2020

www.eyecarealliance.com

Repair Services Available!

We also buy used equipment
Call 1-800-328-2020 for a quote today!

VSI Vision Systems Inc



New and Pre-owned
Digital Imaging Systems
Patternless Edgers
OCTs
Mydriatic Fundus Cameras
Complete Lane Packages
866.934.1030
Patternless.com

Buying and Selling Pre-owned Ophthalmic Instrumentation.
Contact Jody Myers at (800) 336-0410 or visit www.floridaeye.com

FLORIDA EYE EQUIPMENT
Since 1989

RECRUITMENT

CALIFORNIA

WANTED

PEDIATRIC OPHTHALMOLOGY/ ADULT STRABISMUS Fellowship Trained BC/BE physician desired for a prestigious 16 provider multisubspecialty Eye Group on California's Gold Coast, 55 miles NW of L.A. Candidate will be busy at inception in a multidisciplinary clinical and surgical setting. Generous initial salary, benefits, with equity partnership opportunity.

Apply with CV to:
miramareye@aol.com

TEXAS

Shah Eye Center is seeking highly motivated individuals to join our physician team. Ideal candidates will be General Ophthalmologists with Glaucoma Fellowship training preferred, Board Eligible/Board Certified Fellowship-Trained Retina Specialists, and Board Eligible/Board Certified Fellowship-Trained Pediatric Ophthalmologists committed to personalized patient care, customer service and outstanding patient outcomes. We are looking for a long term associate who is interested in growing the practice and serving this community. We offer a competitive salary and benefits package.

Shah Eye Center, located in the Rio Grande Valley in South Texas, a "health manpower shortage area", specializes in the treatment and surgery of medical eye conditions including: cataract surgery, retinal diseases, macular degeneration, diabetes eye care, Lasik eye procedures and impaired vision. For more information on this exciting position,

Contact **Karla Puente** at **(956) 205-6510** or at **kpuente@shaheyecenter.com**

Shah Eye Center
FOUNDED ON A VISION OF EXCELLENCE™

New IOL may reduce opacification

Novel accommodating lens with oversized haptics could cut occurrence of ACO/PCO

By Fred Gebhart; *Reviewed by Anne M. Floyd, MD, MS*

TAKE-HOME

- ***The design of a new accommodating IOL shows promise in reducing the capsular bag opacification that can occur following cataract surgery.***

SALT LAKE CITY ::

A new accommodating IOL design shows promise in reducing the capsular bag opacification that can occur following cataract surgery.

A large, fluid-filled lens with oversized haptics that almost completely fills the capsular bag showed little to no opacification in a rabbit model 6 weeks after surgery.

Dr. Floyd

"One of the ultimate goals of IOL development is to design a lens that you can implant and does not require any further interventions," said Anne M. Floyd, MD, MS, former ocular pathology and research fellow, John A. Moran Eye Center, University of Utah, Salt Lake City. "These early animal results are very promising in that regard."

Dr. Floyd, now a resident at Banner Good Samaritan Medical Center, Phoenix, is lead author on one of the first studies to be published on the FluidVision Lens, developed by PowerVision.

"One of the most common postoperative complications of cataract surgery is the development of anterior capsule opacification (ACO) or poster capsule opacification (PCO)," Dr. Floyd said. "Yes, you can use a YAG laser to perform a capsulotomy on the capsule bag to remove overgrowth and open up the window again, but that is one more procedure the patient has to undergo. And it opens up the posterior capsule, something you try to avoid doing because that is one of the barriers between the anterior and posterior segments. If you can avoid opacification in the first place, you don't have to worry about compromising the integrity of that posterior capsule."

The FluidVision Lens is a hydrophobic acrylic accommodating IOL with oversized haptics. The hollow optic is filled with index-matched silicone oil. Oil flows back and forth between the haptics and the optic, changing the curvature of the optic and the power of the correction. The entire device is about a quarter larger than the typical accommodating IOL. The theory is that a larger device that more completely fills and expands the capsular bag is less likely to develop ACO/PCO compared with current devices.

Researchers at Moran implanted the FluidVision lens in 1 eye of 6 New Zealand rabbits. The contralateral eye received a single-piece hydrophobic acrylic PCIOL (AcrySof SA60AT, Alcon Laboratories) that is commercially available.

The primary outcome was a comparison of ACO/PCO development between the two types of lenses. All 12 eyes were examined weekly by slit lamp from postoperative day 1 through week 6. At 6 weeks, the globes were enucleated and examined. Capsular bag opacification was also evaluated and scored from the posterior aspect using the Miyake-Apple view and the eyes were processed for complete histopathologic evaluation.

RESULTS SUPPORT DESIGN

At the 6-week slit lamp exam, the control eyes showed a posterior capsule opacification mean score of 3.0 compared with 0.5 for the FluidVision eyes ($p = 0.001$).

The Miyake-Apple view showed visible opacification on the control eyes but not on the FluidVision eyes.

The control eyes had a mean central PCO score of 3.0 compared with 0.0 for the FluidVision eyes ($p = 0.001$), a peripheral PCO score of 3.5 compared with 0.7 for FluidVision eyes ($p = 0.0006$) and Soemmering's Ring score of 7.0 compared with 2.3 for FluidVision eyes ($p = 0.01$).

"This design was born out of studies suggesting a more open or more expanded capsular bag may lead to prevention of PCO," Dr. Floyd said. "In regard to ACO formation, previous reports described ACO and fibrosis occurring in areas where the anterior capsule comes into contact with the IOL optic. If you prevent that contact, the thinking goes, you might prevent or reduce the ACO."

The results of this study tend to support the new design, Dr. Floyd said.

The anterior capsule remained remarkably clear throughout the study in the FluidVision eyes. The anterior capsule at and around the capsulorhexis edge was held at a distance from the anterior surface of the IOL by the oversized haptics and was almost completely devoid of fibrosis. These results are all the more important since the absence of a capsular reaction support the idea that the lens, which is sensitive to the capsular geometry, will remain stable and that the accommodative function of the lens will not be affected.

LEADING THEORY

"This appears to be an expansive effect," Dr. Floyd said. "The leading theory is that PCO prevention works by mechanical compression of the bag, which inhibits epithelial cells from migrating or infiltrating around the posterior portion of the capsule."

Stretching of the bag at the equatorial region may help to maintain the overall contour of the bag and physically limit the extension of the lens epithelial cells toward the central region of the posterior capsule.

"We need to see further research on the mechanical compression and stretching provided by this device to more fully understand the mechanisms by which it seems to prevent or inhibit PCO," she said. ■

ANNE M. FLOYD, MD, MS

E: *Anne.Floyd@hsc.utah.edu*

Dr. Floyd had no financial disclosures related to the device.

OT OphthalmologyTimes.com
Online Exclusive

A LOOK TO THE FUTURE OF SUBRETINAL IMPLANT

THE DEVELOPMENT OF A subretinal implant may be a significant advancement in terms of restoring useful vision. The wireless, microelectronic neuroprosthetic device (Alpha-IMS, Retina Implant AG) is designed to take the place of the function of photoreceptors in patients with retinal degenerations, such as retinitis pigmentosa. Investigators published their clinical results in the *Proceedings of the Royal Society, Biological Sciences*.

VIDEO Go to **http://bit.ly/1ar6u0B.**

Sunwear lines making spring debut

By Rose Schneider, *Content Specialist,* Ophthalmology Times

IT MAY BE winter, but optical dispensaries are stocking their inventories with the latest sunwear lines designed to help protect patients' eyes from damaging UV rays.

Marc By Marc Jacobs is offering a line of special edition sunglasses just in time for Valentine's Day, which feature a black, acetate squared shape inspired by the 1980s. The collection also includes red hearts printed all over the frame and have a red metal core wire on the temples.

(Image courtesy of götti Switzerland)

The latest sunwear collection from götti Switzerland features eight new pairs with distinctive colors and shapes with mirrored lenses: Pepe includes an integrated acetate ring, while Xandro's style is more sleek with ultrathin metal. Kojak, Kosima, Kitty, and Kashan have intricate details and are more of a feminine shape, while Spin and Stow include a 360° rotation at the temple, allowing the outer edge to rotate inward and better fit in a thin eyeglass case.

MOSCOT also has a new line called MOSCOT Originals–Titanium Collection, which includes the Lemtosh-T, the Miltzen-T, The Nebb-T, and the Zolman-T. The four frames—which are some of the company's most popular—have been refashioned in titanium.

(Image courtesy of Marc By Marc Jacobs)

"We are very excited about our new (collection) because it gives fans the best of both worlds," said Harvey Moscot, co-president of MOSCOT. "If you love your Lemtosh, for example, but want to wear a metal frame, now you can."

Made from strong, hypoallergenic, pliant material that can be easily adjusted for the perfect fit, the four new frames are available with coordinated mirrored sun lenses and in three new color combinations: charcoal/wine, navy/beige, and tortoise/pine. ■

Advertiser Index

This index is provided as an additional service. The publisher does not assume any liability for errors or omissions.

OPHTHALMOLOGY TIMES (Print ISSN 0193-032X, Digital ISSN 2150-7333) is published semi-monthly (24 issues yearly) by Advanstar Communications Inc., 131 W First Street, Duluth, MN 55802-2065. Subscription rates: $200 for one year in the United States & Possessions, Canada and Mexico; all other countries $263 for one year. Pricing includes air-expedited service. Single copies (prepaid only): $13 in the United States & Possessions, Canada and Mexico; $20 all other countries. Back issues, if available are $25 in the U.S. $ Possessions; $30 in Canada and Mexico; $35 in all other countries. Include $6.50 per order plus $2 per additional copy for U.S. postage and handling. If shipping outside the U.S., include an additional $10 per order plus $5 per additional copy. **Periodicals postage paid** at Duluth, MN 55806 and additional mailing offices. **POSTMASTER:** Please send address changes to OPHTHALMOLOGY TIMES, P.O. Box 6009, Duluth, MN 55806-6009. Canadian G.S.T. number: R-124213133RT001, Publications Mail Agreement Number 40612608. Return undeliverable Canadian addresses to: IMEX Global Solutions, PO Box 25542 London, ON N6C 6B2 CANADA. Printed in the U.S.A.

Ophthalmology Times
CUTTING-EDGE ADVANCEMENTS

Cutting-edge advancements for today's ophthalmologist, now available in an app

Introducing the *Ophthalmology Times* app for

iPad and iTunes

Download it for free today at
www.OphthalmologyTimes.com/OTapp

WELCOME TO THE ERA OF CENTURION®

Optimize every moment of your cataract removal procedure with the NEW CENTURION® Vision System.

Active Fluidics™

Automatically optimizes chamber stability by allowing surgeons to customize and control IOP throughout the procedure.

Balanced Energy™

Enhances cataract emulsification efficiency using OZil® Intelligent Phaco and the new INTREPID® Balanced Tip design.

Applied Integration™

Designed to work seamlessly with other Alcon technologies for an integrated cataract procedure experience.

Learn more about the new era of cataract procedures. Visit MyAlcon.com.

Alcon®
a Novartis company

CENTURION®
VISION SYSTEM

For important safety information, please see adjacent page.