GLASSES EYED AS TREATMENT IN CHILDREN

Jury still out on whether spectacles or observation is best path forward for hyperopia

By Lynda Charters;
Reviewed by Donny Won Suh, MD

RESULTS FROM THE Hyperopia Treatment Study 1 (HTS1) have proven to be inconclusive after three years of follow-up in young children with moderate hyperopia treated with glasses compared with observation. A small-to-moderate benefit or no benefit of immediate glasses was seen compared with observation.

The study rationale was that 4% to 14% of children have moderate to high levels of hyperopia, a scenario that carries a significantly increased risk for development of strabismus and amblyopia. Based on previous studies, it is controversial whether glasses should be prescribed immediately for children with moderate myopia to prevent amblyopia and strabismus from developing.

The alternative is observation until signs of decompensation become apparent followed by prescribing of glasses, according to Donny Won Suh, MD, chief of pediatric ophthalmology, University of Nebraska Ophthalmology, Children’s Hospital and Medical Center, Omaha.

Dr. Suh and Marjean Kulp, MD, were protocol chairpersons of the HTS1 that sought to determine the visual acuity (VA) and alignment benefits, if any, of immediate eyeglass

31% vs 4%

“The results mean that if the study was repeated in a similar population, the difference can be up to 31% and in favor of eyeglasses,” he said.

“However, the other extreme was also possible, with 4% in favor of observation.

TECHNOLOGY MAKES PHYSICIANS MORE EFFICIENT

OPHTHALMOLOGISTS, like many physicians in the field of medicine, are finding it increasingly challenging to maintain the pace that operating a practice in today’s business climate requires. Seeing patients is one piece of the puzzle. Physicians have to manage their practices, and this includes inventory management and providing value-based care.

Advancements in technology can help physicians by combating burnout, handling the burden of drug inventory management, and offering value-based care with tools at their fingertips.

Story on page 11

TIPS FOR CONTROLLING DRUG COSTS

FOR OPHTHALMOLOGY PRACTICES, drug prices continue to be an issue for patients, and step-therapy and pre-authorization are responses to increasing drug costs, which exceed any other component of healthcare. Why is this a growing problem for ophthalmologists? Some experts contend that drug prices keep increasing because pharmaceutical companies are running out of new agents that can command premium prices. One reason for this widening gap could be the U.S. patent system.

Story on page 11

Therapeutics

IMAGING Migraines and retinal perfusion
Can migraines cause POAG? Debate lingers

SURGERY Monofocal toric IOLs
Lens is offering improved refractive, visual outcomes

GENE THERAPY Reducing geographic atrophy
FILLY study shows evidence of efficacy for APL-2
maximize efficacy

minimize concerns

In micro-invasive surgery, seek the micro-invasive option...

- 500,000+ Glaukos trabecular micro-bypass stents implanted and 100+ peer-reviewed publications
- Lowest reported post-op mean IOP of any trabecular bypass stent
- Lowest reported rates of significant endothelial cell loss (ECL)†
- Lowest reported rates of peripheral anterior synechiae (PAS)†
- Stents are made of titanium, no nitinol (nickel) allergic responses

TransformMIGS.com | 800.GLAUKOS (452.8567)

* In any trabecular bypass MIGS pivotal trial.
† Significant ECL defined as 30% ECL.

INDICATION FOR USE. The iStent inject Trabecular Micro-Bypass System Model G2-M-IS is indicated for use in conjunction with cataract surgery for the reduction of intraocular pressure (IOP) in adult patients with mild to moderate primary open-angle glaucoma.

CONTRAINDICATIONS. The iStent inject is contraindicated in eyes with angle-closure glaucoma, traumatic, malignant, uveitic, or neovascular glaucoma, discernible congenital anomalies of the anterior chamber (AC) angle, retinoblastoma, thyroid eye disease, or Sturge-Weber Syndrome or any other type of condition that may cause elevated episcleral venous pressure. Warnings. Gonioscopy should be performed prior to surgery to exclude congenital anomalies of the angle, PAS, ruberosis, or conditions that would prohibit adequate visualization of the angle that could lead to improper placement of the stent and pose a hazard.

MRI INFORMATION. The iStent inject is MR-Conditional, i.e., the device is safe for use in a specified MR environment under specified conditions; please see Directions for Use (DFU) label for details.

PRECAUTIONS. The surgeon should monitor the patient postoperatively for proper maintenance of IOP. The safety and effectiveness of the iStent inject have not been established as an alternative to the primary treatment of glaucoma with medications, in children, in eyes with significant prior trauma, abnormal anterior segment, chronic inflammation, prior glaucoma surgery (except SLT performed > 90 days preoperative), glaucoma associated with vascular disorders, pseudoxfoliation, pigmentary or other secondary open-angle glaucomas, pseudophakic eyes, phakic eyes without concomitant cataract surgery or with complicated cataract surgery, eyes with medicated IOP > 24 mmHg or unmedicated IOP < 21 mmHg or > 36 mmHg, or for implantation of more or less than two stents.

ADVERSE EVENTS. Common postoperative adverse events reported in the randomized pivotal trial included stent obstruction (6.2%), intraocular inflammation (5.7% for iStent inject vs. 4.2% for cataract surgery only); secondary surgical intervention (5.4% vs. 5.0%) and BCVA loss ≥ 2 lines ≥ 3 months (2.6% vs. 4.2%).

18

46

39

56

Surgery

20 CONSIDERING NOVEL REGIMEN BEFORE, AFTER CATARACT CASE
Preliminary results show prophylactic treatment may be option with higher patient preference

Gene Therapy

34 DECIPHERING PHASE III DATA FOR LHON
Primary endpoint not met, but secondary measures indicate strong efficacy

Imaging

43 ADVANCES MAY BRING OCT ANALYSIS GAME-CHANGER
Imaging may allow for unique characterization of disease phenotypes, treatment response

What’s Trending

See what the ophthalmic community is reading on OphthalmologyTimes.com

1 7 pediatric eye myths parents should stop believing
OphthalmologyTimes.com/7PedEyeMyths

2 Breaking down the dorzolamide shortage
OphthalmologyTimes.com/Blogs/Dorzolamide

3 Ophthalmology grabs Wall Street’s attention
OphthalmologyTimes.com/Blogs/WallStreet

4 LHON gene therapy: Considering latest data
OphthalmologyTimes.com/LHONPhaseIII

Digital App

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

Video

W. Lloyd Clark, MD, discusses the PANORAMA study results at the 2019 annual meeting of the American Society of Retina Specialists. ModernRetina.com/ASRS19Clark

eNewsletter


Facebook

Like Ophthalmology Times at Facebook.com/OphthalmologyTimes
Ophthalmology Times is a physician-driven media brand that presents cutting-edge advancements and analysis from around the world in surgery, clinical diagnosis, therapeutics, device technology, imaging, and gene therapy 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.
INDICATION
DEXTENZA is a corticosteroid indicated for the treatment of ocular inflammation and pain following ophthalmic surgery.

IMPORTANT SAFETY INFORMATION
CONTRAINDICATIONS
DEXTENZA is contraindicated in patients with active corneal, conjunctival or canalicular infections, including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella; mycobacterial infections; fungal diseases of the eye, and dacryocystitis.

WARNINGS AND PRECAUTIONS
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. Intraocular pressure should be monitored during treatment.

Corticosteroids may suppress the host response and thus increase the hazard for secondary ocular infections. In acute purulent conditions, steroids may mask infection and enhance existing infection.

Use of ocular steroids may prolong the course and may exacerbate the severity of many viral infections of the eye (including herpes simplex).

Fungus invasion must be considered in any persistent corneal ulceration where a steroid has been used or is in use. Fungal culture should be taken when appropriate.

Use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation.

ADVERSE REACTIONS
The most common ocular adverse reactions that occurred in patients treated with DEXTENZA were: anterior chamber inflammation including iritis and iridocyclitis (10%); intraocular pressure increased (6%); visual acuity reduced (6%); cystoid macular edema (6%); corneal edema (6%); eye pain (6%) and conjunctival hyperemia (6%).

The most common non-ocular adverse reaction that occurred in patients treated with DEXTENZA was headache (1%).

Please see brief summary of full Prescribing Information on adjacent page.

*73.6% of physicians in Study 1, 76.4% in Study 2, and 79.6% in Study 3 rated DEXTENZA as easy to insert.
From the Hill: Regulatory update
Drug costs in cross-hairs of D.C. lawmakers

By David Hutton; Reviewed by Cathy Grealy Cohen, CAE, MHSA

Ophthalmologists can face pressures from myriad sources, including lawmakers in Washington, D.C. Keeping tabs on activities on Capitol Hill that could impact ophthalmologists is one of the jobs of Cathy Grealy Cohen, CAE, MHS, vice president for government affairs at the American Academy of Ophthalmology. Speaking at the American Glaucoma Society annual meeting, Cohen noted both Congress and the Trump administration are targeting drug costs as a priority.

“Yeah, you do have a matched agenda here. You are going to see some legislation passing where there is consensus to stop the gaming that the brand companies are playing, their pay for delay,” she said.

CREATE ACT ON HILL
Another item is the Creating and Restoring Equal Access to Equivalent Samples (CREATE) Act, which would enable generic manufacturers to get access to the samples so that they can make generic versions of drugs.

In February, lawmakers reintroduced the CREATE Act. Legislators on Capitol Hill contend the bill would combat tactics they claim brand-name drug companies use to allegedly impede generic and biosimilar competition. It is projected to save nearly 4 billion for the federal government by enabling generic and bio-similar developers to secure the required samples of a reference drug or biologic to demonstrate interchangeability, bioequivalence or biosimilarity.

The House has now advanced the CREATE Act, and three other pieces of bipartisan legislation designed to promote competition and lower drug prices. The Senate committees have included key provisions in legislation moving forward in that body and a floor vote on their drug cost legislation could take place as early as September.

The bills are not expected to have a dramatic impact on prescription drug medications in the short term, but they reportedly could level the playing field for generic drug companies.

In addition to the CREATE ACT (HR 965), other measures under consideration include HR 2375, the Preserve Access to Affordable Generics and Biosimilars Act, which would halt anticompetitive agreements between generic and brand name manufacturers; HR 2374, the Stop STALL-ING Act, which would seek to stop the submissions of sham citizen petitions to the FDA; and HR 2376, the Prescription Pricing for People Act of 2019, which was advanced by a voice vote and would enlist the Federal Trade Commission to study and report on pharmacy benefit managers and whether they steer patients to certain pharmacies for anticompetitive purposes.

OF INTEREST TO OPHTHALMOLOGISTS
There are also other issues that could find their way to the Hill that may pique the interest of ophthalmologists.

“There is a growing consensus that we need to separate the payment to the physician from the price of the drug,” Cohen said. “This includes the ASP Plus 6 or the ASP Plus 4.3. While we were open to that, it is of high risk, for ophthalmology in particular because of our high costs of dealing with complex biologics.”

Cohen said the FDA is proposing some new lighter manufacturing standards...
so that it would be easier for some traditional compounders to become the outsourcing facilities.

“We have some hope that this will give us a lot more options,” she said.

Drug shortages also remain a challenge and Cohen said discussions are ongoing.

“The FDA will tell you that they cannot make a manufacturer make the drug,” she said. “We are talking to other manufacturers trying to get others to make drugs that are in shortage.”

Cohen also cited continuing efforts for Evaluation and Management Code changes that would reduce the burdens on physicians to simplify documentation.

CMS set in motion, according to Cohen, a collapse of the current system of five levels of codes to just two codes. They also included a $12 add-on for certain specialties that supposedly see more complex patients, but they initially excluded ophthalmology from that list.

“We had to fight to get that changed,” she noted. “The good news is that they have decided to put off any collapse for a few years and are open to a different approach. They did give us the immediate documentation reduction.”

Cohen also discussed ongoing discussions to move Medicare to a value-based physician payment system.

“This is on all your fee for service payments,” she noted.

The process has been streamlined, making it easier to pass during the first two years.

“There is not a lot of bonus money for the transition years, but that means that hopefully no ophthalmologists fail,” she said. Ophthalmologists that are participating in the academy’s IRIS Registry are seeing Medicare bonus pay.

The move toward value-based payment models could prove to be a win for physicians and patients alike. Driving support for value-based reimbursement could be the spark for change.

CATHY GREELY COHEN, CAE, MHSA
P: 415/561.8500 E: cgcohen@aaao.org
This article was adapted from Ms. Cohen’s presentation at the American Glaucoma Society annual meeting. She has no financial interests to disclose.

In Brief
FROM STAFF REPORTS

Surgery

ALCON GETS FDA NOD FOR PANOPTIX TRIFOCAL IOL

With FDA approval in hand, Alcon has kicked off the initial commercial launch of the AcrySof IQ PanOptix Trifocal IOL, the first and only trifocal lens for U.S. patients undergoing cataract surgery.

The novel IOL has been clinically demonstrated to offer patients a combination of near, intermediate, and distance vision while significantly reducing the need for glasses after surgery, according to a prepared statement.

Available in more than 70 countries, PanOptix has been shown to deliver a combination of near, intermediate and distance vision while significantly reducing the need for glasses after surgery, said the statement.

In a clinical study at 12 U.S. sites, more than 99% of PanOptix patients said they would choose the lens again. Available in spherical and toric designs, PanOptix is built on Alcon’s proven AcrySof IQ IOL platform that has been implanted in more than 120 million eyes globally, said the company.

“We are proud to bring this new class of IOLs to the largest eye care market in the world,” said David J. Endicott, CEO of Alcon. “We are leveraging Alcon’s years of experience with PanOptix in other countries to provide the best possible training and support for U.S. surgeons. Our goal is to ensure optimal outcomes for cataract patients looking to correct their vision at all distances, with the vast majority of them never needing to wear glasses post-surgery.”

Kerry Solomon, MD, Carolina Eyecare Physicians, PanOptix clinical trial investigator, said the ophthalmology community has been awaiting FDA approval of PanOptix.

“If participating in the clinical trial, I saw first-hand the impact of this lens on my patients,” Dr. Solomon said. “We know patients undergoing cataract surgery today want a replacement lens that delivers the vision they need to live full, active lives without always being dependent on glasses.”

According to Alcon, it plans to begin training ophthalmologists in the United States and making the PanOptix and PanOptix toric IOLs available throughout the rest of the year and into early 2020.

It will also launch a dedicated PanOptix website and multimedia awareness campaign.
The ‘age’ game
Does a patient’s date of birth ever really matter?

THE TERM “AGEISM” was coined in 1969 by Robert Neil Butler to describe prejudicial attitudes toward older people, old age, and the aging process.

Many years ago, an ophthalmologist in the neighboring city of Pasadena referred a patient to see me in Los Angeles. He noted that she was in need of a corneal transplant for a scarred right cornea.

CENTENARIAN PATIENT
The patient, Helen, was a very proper well-spoken and intelligent lady with dense amblyopia in her left eye, to the point that she had been functionally one-eyed her entire life. A glance at her birthdate revealed that life to have been 100 years long!

I explained to Helen that a corneal transplant required a lot of postoperative medications and visits. Was it really going to be worth it to her to go through all that at her age?

ACTIVE PORTFOLIO
“What is the main thing that bothers you about your vision now?” I asked her.

“It’s difficult to make out stock prices in the newspaper,” Helen replied. “I have trouble telling if the price of a stock is 11 and 3/8ths, 11 and 5/8ths or 11 and 7/8ths.”

I laughed because I assumed she was kidding with me.

However, Helen was completely serious, and she didn’t laugh.

“Do you buy and sell a lot of stocks?” I asked with a smile.

“Yes. Every day,” Helen replied, once again with a straight face.

MAKING A DECISION
I was not sure whether it would be a wise move to put a 100-year-old woman through such a surgery, even though she appeared to be completely healthy.

Thinking for a moment, I asked her to return with her son so that we could discuss the procedure and recovery in greater detail.

It turned out that her son was 75 years old, though he looked to be about 45, and, I learned, was the busiest orthopedic surgeon in the hospital where he worked. It was clear to me that the genes in this family were something special.

“Your mother is 100,” I said. “Are you comfortable with her having a corneal transplant?”

“Oh, of course. Why not!” he replied.

The surgery went well and Helen had very little postoperative astigmatism. She had no trouble using her eye drops and coming in for postoperative visits as instructed. Within a few weeks, her vision had improved to 20/40 and she and her son were happy.

BACK TO STOCKS
And here’s the thing that really impressed me: on every single visit for years after her surgery when I would walk into the examination room, Helen would be hard at work with her newspaper open carefully circling the prices of her stocks and managing her portfolio.

To this day, I think of Helen whenever someone tells me that a patient should or should not have something done because of his or her age.
XIIDRA MAY INTERRUPT THE CYCLE OF INFLAMMATION CENTRAL TO DRY EYE DISEASE¹,²

The exact mechanism of action of Xiidra in Dry Eye Disease is not known.¹

Xiidra blocks the interaction of ICAM-1 and LFA-1, which is a key mediator of the inflammation central to Dry Eye Disease. In vitro studies have shown that Xiidra may inhibit the recruitment of previously activated T cells, the activation of newly recruited T cells, and the release of pro-inflammatory cytokines.¹

---

**Indication**

Xiidra® (lifitegrast ophthalmic solution) 5% is indicated for the treatment of signs and symptoms of dry eye disease (DED).

**Important Safety Information**

Xiidra is contraindicated in patients with known hypersensitivity to lifitegrast or to any of the other ingredients.

In clinical trials, the most common adverse reactions reported in 5-25% of patients were instillation site irritation, dysgeusia and reduced visual acuity. Other adverse reactions reported in 1% to 5% of the patients were blurred vision, conjunctival hyperemia, eye irritation, headache, increased lacrimation, eye discharge, eye discomfort, eye pruritus and sinusitis.

To avoid the potential for eye injury or contamination of the solution, patients should not touch the tip of the single-use container to their eye or to any surface.

Contact lenses should be removed prior to the administration of Xiidra and may be reinserted 15 minutes following administration.

Safety and efficacy in pediatric patients below the age of 17 years have not been established.

---

**Check out Xiidra-ECP.com**

---

For additional safety information, see accompanying Brief Summary of Safety Information on the adjacent page and Full Prescribing Information on Xiidra-ECP.com.

**References:**


©2018 Shire US Inc., Lexington, MA 02421. 1-800-828-2038. All rights reserved. SHIRE and the Shire Logo are trademarks or registered trademarks of Shire Pharmaceutical Holdings Ireland Limited or its affiliates. Marks designated “®” and “™” are owned by Shire or an affiliated company.
**BRIEF SUMMARY:**
Consult the Full Prescribing Information for complete product information.

**INDICATIONS AND USAGE**
Xiidra® (lifitegrast ophthalmic solution) 5% is indicated for the treatment of the signs and symptoms of dry eye disease (DED).

**DOSAGE AND ADMINISTRATION**
Instill one drop of Xiidra twice daily (approximately 12 hours apart) into each eye using a single-use container. Discard the single-use container immediately after using in each eye. Contact lenses should be removed prior to the administration of Xiidra and may be reinserted 15 minutes following administration.

**CONTRAINDICATIONS**
Xiidra is contraindicated in patients with known hypersensitivity to lifitegrast or to any of the other ingredients in the formulation.

**ADVERSE REACTIONS**

**Clinical Trials Experience**
Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in clinical studies of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. In five clinical studies of dry eye disease conducted with lifitegrast ophthalmic solution, 1401 patients received at least 1 dose of lifitegrast (1287 of which received lifitegrast 5%). The majority of patients (84%) had ≤3 months of treatment exposure. 170 patients were exposed to lifitegrast for approximately 12 months. The majority of the treated patients were female (77%). The most common adverse reactions reported in 5-25% of patients were instillation site irritation, dysgeusia and reduced visual acuity. Other adverse reactions reported in 1% to 5% of the patients were blurred vision, conjunctival hyperemia, eye irritation, headache, increased lacrimation, eye discharge, eye discomfort, eye pruritus and sinusitis.

**Postmarketing Experience**
The following adverse reactions have been identified during postapproval use of Xiidra. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Rare cases of hypersensitivity, including anaphylactic reaction, bronchospasm, respiratory distress, pharyngeal edema, swollen tongue, and urticaria have been reported. Eye swelling and rash have been reported.

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**
There are no available data on Xiidra use in pregnant women to inform any drug associated risks. Intravenous (IV) administration of lifitegrast to pregnant rats, from pre-mating through gestation day 17, did not produce teratogenicity at clinically relevant systemic exposures. Intravenous administration of lifitegrast to pregnant rabbits during organogenesis produced an increased incidence of omphalocoele at the lowest dose tested, 3 mg/kg/day (400-fold the human plasma exposure at the recommended human ophthalmic dose [RHOD], based on the area under the curve [AUC] level). Since human systemic exposure to lifitegrast following ocular administration of Xiidra at the RHOD is low, the applicability of animal findings to the risk of Xiidra use in humans during pregnancy is unclear.

**Animal Data**
Lifitegrast administered daily by intravenous (IV) injection to rats, from pre-mating through gestation day 17, caused an increase in mean preimplantation loss and an increased incidence of several minor skeletal anomalies at 30 mg/kg /day, representing 5,400-fold the human plasma exposure at the RHOD of Xiidra, based on AUC. No teratogenicity was observed in the rat at 10 mg/kg /day (460-fold the human plasma exposure at the RHOD, based on AUC ). In the rabbit, an increased incidence of omphalocoele was observed at the lowest dose tested, 3 mg /kg /day (400-fold the human plasma exposure at the RHOD, based on AUC), when administered by IV injection daily from gestation days 7 through 19. A fetal No Observed Adverse Effect Level (NOAEL) was not identified in the rabbit.

**Lactation**
There are no data on the presence of lifitegrast in human milk, the effects on the breastfed infant, or the effects on milk production. However, systemic exposure to lifitegrast from ocular administration is low. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for Xiidra and any potential adverse effects on the breastfed child from Xiidra.

**Pediatric Use**
Safety and efficacy in pediatric patients below the age of 17 years have not been established.

**Geriatric Use**
No overall differences in safety or effectiveness have been observed between elderly and younger adult patients.

**NONCLINICAL TOXICOLOGY**

**Carcinogenesis, Mutagenesis, Impairment of Fertility**
Carcinogenesis: Animal studies have not been conducted to determine the carcinogenic potential of lifitegrast. Mutagenesis: Lifitegrast was not mutagenic in the in vitro Ames assay. Lifitegrast was not clastogenic in the in vivo mouse micronucleus assay. In an in vitro chromosomal aberration assay using mammalian cells (Chinese hamster ovary cells), lifitegrast was positive at the highest concentration tested, without metabolic activation. Impairment of fertility: Lifitegrast administered at intravenous (IV) doses of up to 30 mg/kg/day (5400-fold the human plasma exposure at the recommended human ophthalmic dose [RHOD] of lifitegrast ophthalmic solution, 5%) had no effect on fertility and reproductive performance in male and female treated rats.
New battles taking shape in fight to control drug costs

Escalating prices continue to be an issue for patients, hamper treatment options

By Conni Bergman Koury; Reviewed by George A. Williams, MD

For ophthalmology practices, drug prices continue to be an issue for patients, and step-therapy and pre-authorization are responses to increasing drug costs, which exceed any other component of healthcare.

While inflation is less than 2% per year, name brand drug price increases reach double digits year after year, according to George A. Williams, MD, president of the American Academy of Ophthalmology.

That leaves industry leaders to wonder why.

The argument has always been that it is expensive to develop drugs, to innovate and invest in necessary research, said Dr. Williams, who also is chairman of ophthalmology at Oakland University.

“Although true, the real relationship between marketing and administrative costs for pharmaceutical companies compared with what they spend on research is approximately two to one,” he said. “Worldwide and during the past decade, there has been a static relationship between research investment and sales, averaging around 15% to 18%.”

RETURN ON INVESTMENT?

The FDA approves about 200 new drugs every year, with only 15 to 50 classified as new molecular entities, or NMEs. The FDA says that NMEs contain active moieties that have not been approved by the FDA previously, either as a single ingredient drug or as part of a combination product.

“Some drugs are characterized as NMEs for administrative purposes, but nonetheless contain active moieties that are closely related to active moieties in products that have previously been approved by FDA,” according to the FDA website.

One reason for this gap could be the U.S. patent system, Dr. Williams said.

Experts have argued that drug prices keep increasing because pharmaceutical companies are running out of new agents that can command premium prices. One detailed analysis reveals that as some higher-end drugs come off-patent, manufacturers have responded by increasing the price of drugs that remain on patent.

“The system is set up to generate profits, not research and innovation,” Dr. Williams said.

The majority of the costs are attributable to a relatively small number of drugs, he explained.

“For Medicare Part B and Part D—where glaucoma patients live—the per capita growth rate for drug cost is 10% per year. Profit margins for the top 25 drug makers are robust, and these companies have consistently doubled the profit margins of all other companies in the Fortune 500,” Dr. Williams said. “There appears to be bipartisan support for addressing this issue.”

PRE-AUTHORIZATION

Pre-authorization, familiar to all physicians and ophthalmology practices, can involve drugs, devices or surgery. It is granted about 90% of the time, but it is still an impediment to patients’ access. This has piqued the interest of Congress, and the AAO has been advocating for standardization with follow-through in the pre-authorization environment.

STEP-THERAPY

“Step-therapy, a potential game-changer in the drug space, comes from the Centers for Medicare and Medicaid Services decision to allow Medicare Advantage (MA) plans the option of implementing step-therapy across all Part B drugs, including off-label compounded treatments,” Dr. Williams said.

Many questions remain, however, such as: What constitutes a trial or treatment failure? How much vision does the patient have to lose (or not gain)? What happens with the fellow eye?

“These questions create access issues for patients,” Dr. Williams said. “The Academy has been involved in step-therapy for years and will continue to speak to policy makers about the need for consistent, patient-centered coverage policies.”

There remains significant variation in coverage, continues on page 12.
Pears to manage surgery patients on antithrombotic drugs

Different steps may be needed during perioperative period to ensure best outcome

By Lynda Charters

Patients who undergo an ophthalmic procedure and are concomitantly taking antithrombotic drugs, i.e., antiplatelets and anticoagulants, during the perioperative period may require different management than patients not taking those drugs.

Investigators at St. Paul’s Eye Unit, Royal Liverpool University Hospital, Liverpool, UK, surveyed ophthalmologists concerning this scenario and reported that most physicians were comfortable with managing patients taking antiplatelets. However, the survey indicated that the situation was not so clear-cut when patients were taking warfarin and direct oral anticoagulants (DOACs). A.K. Makuloluwa, MD, et al. reported in Eye (2019; https://www.nature.com/articles/s41433-019-0382-6) that “there was variability in managing patients on warfarin and DOACs.” A startling finding was that “40% of [ophthalmologists] were unaware of existing guidelines” for managing these patients.

The authors’ concerns regarding this matter are well-founded in that, for example, within the aging population, more patients are taking these drugs to prevent and treat cardiovascular and ischemic cerebral disease.

“Continuing anti-thrombotic agents peri-operatively may increase the risk of potentially sight-threatening haemorrhagic complications, whereas discontinuing these medications may increase the risk of life-threatening thromboembolic events,” investigators noted.

“Therefore, it is important to understand the indications of anti-thrombotic agents and when it may be safe to discontinue them peri-operatively.”

The team said it believed that it was important to stratify the ophthalmic surgeries depending on the risk of development of hemorrhagic complications during the perioperative period.

They conducted a PubMed search from January 2007 to August 2017 to identify articles that provided recommendations on managing antithrombotic agents during the perioperative period of ophthalmic surgeries and reviewed the incidence rates of the associated hemorrhagic complications. They also reviewed all guidelines in the UK from the Royal College of Ophthalmologists and British Society of Haematology.

STUDY FINDINGS

The literature recommendations that all anti-thrombotic agents be continued for routine cataract surgery or stopped and patients could continue taking warfarin if the International Normalized Ratio (INR) was within the therapeutic range.

For glaucoma surgery, the literature recommended that aspirin and clopidogrel be discontinued when the drugs are monotherapy for primary prevention, but they can be continued for secondary prevention of cardiovascular diseases. P2Y12 receptor inhibitors should be discontinued if used as dual antiplatelet therapy. However, the risks and benefits of continuation of antiplatelet agents need special consideration in neovascular glaucoma and high IOP.

“It is also important to consider and recognize that, intraoperative and post-operative haemorrhagic complications in glaucoma, especially if sustained or prolonged, can cause severe visual loss due to high pressure in already compromised optic nerves,” investigators wrote. “Anticoagulants should be discontinued when it may be safe to discontinue them.”

TAKE-HOME

Knowing the guidelines is key because more patients are taking these drugs to prevent and treat cardiovascular and ischemic cerebral disease.

STEP THERAPY

However, and only 16% of drug indications are covered by all plans, Dr. Williams noted.

A comprehensive analysis indicates that less than half of drug indications are covered by 75% or more of commercial carriers. Prescribing protocols are consistent with the FDA label barely half of the time; they are more restrictive a third of the time; and 5% of the time there is no coverage even when FDA approved, according to Dr. Williams.

The AAO has written to the CMS expressing concern about the impact this has on patients’ access to care, Dr Williams noted. Changes to MA, according to a recent Office of the Inspector General report, may incentivize payers to deny access to services and payment in order to increase the profit of these private companies. In fact, 75% of the denials the MA plans implement that are appealed are reversed, but only 1% of the denials were actually appealed.

The OIG concluded that “this is especially burdensome for beneficiaries with urgent health conditions.” This issue is likely to become more significant with the continuing expansion of MA. In 2018, 35% of Medicare beneficiaries were in Medicare Advantage with some states as high as 60%, Dr. Williams said.

PROPOSALS

One possible solution is to have Americans pay what other countries pay.

“In the United States, we pay approximately 80% more for all drugs—in the retina space, it is substantially more,” Dr. Williams said. “With Medicare part D, patients pay the first $415. Medicare pays 75% of the next $800. After that, patients go into the donut hole.”

The ever growing gross-to-net rebate bubble is the difference between the manufacturer’s list price and the net price, after negotiated rebates and discounts decided by pharmacy benefit managers (PBMs). Last year, it was $166 billion.

“This can produce perverse incentives for drug companies to raise prices and increase discounts, because PBMs are paid by insurers based on the amounts they negotiate for each discount,” Dr. Williams concluded. “These discounts are supposed to be shared with either the insurance provider or with the patient—but it turns out they are not, and our patients pay co-pays on the inflated price. This rebate bubble has exploded in recent years, from $59 billion in 2012 to $126 billion currently.”

George Williams, MD

Pr: 248/288-2280 e: George.Williams@beaumont.edu

This article was adapted from Dr. Williams’ presentation at the 2019 American Glaucoma Society annual meeting. Dr. Williams has no other financial disclosures related to this report.
Experiencing zero-energy lens fragmentation.

Keep the zonules intact

The new miLOOP® from ZEISS is a micro-interventional device, developed to deliver zero-energy lens fragmentation and achieve full-thickness lens fragmentation. The dissecting action of ZEISS miLOOP is designed to reduce force on the delicate capsular bag and zonules.

Visit ZEISS Booth 5669 at AAO 2019 to learn more.
A single dose of dexamethasone intraocular suspension 9% (DEXYCU, EyePoint Pharmaceuticals) affects the IOP the same way that short-term prednisolone acetate does in patients who have undergone cataract surgery based on the results of two phase III studies.

“Decreasing the postoperative drop burden and increasing compliance can be accomplished with Dexycu, the only FDA-approved intraocular steroid that has the same IOP safety profile as the time-tested topical prednisolone acetate suspension,” according to Cynthia Matossian, MD, who is in private practice in Mercer County, NJ, and Bucks County, PA.

The drug is contained in a delivery device made of acetyltributyl citrate. This sustained-release product has received FDA approval to treat inflammation and other conditions. The suspension is injected into the aqueous, under the iris, a 2-mm spherical bolus that forms that bio-erodes over time, releasing higher levels of drug initially with a gradual taper over 30 days, she explained.

A total of 575 patients undergoing cataract surgery were included in the two studies. The first study was a prospective, randomly selected, double-masked, multicenter trial in which the 394 patients were randomly assigned to either 5 μL of a 517-μg dexamethasone intraocular suspension (marketed dose) (n = 156) or 5 μL of placebo (vehicle) (n = 80). (The 394 patients were randomly selected; however, the active and placebo arms only add up to 236 patients, because this study focused on the 342-μg marketed dose received by 158 patients and does not include the 342-μg dose arm.)

The primary outcome measure was the clearing of the anterior chamber cells from the eyes on postoperative day eight; the secondary outcome measures were anterior chamber flare and the clearing of the anterior chamber cells plus anterior chamber flare in the study eye.

In the second phase III study, 181 patients were randomly assigned to receive one injection of dexamethasone intraocular suspension 9% (n = 126) or prednisolone acetate 1% drops instilled four times daily (n = 55). The safety outcomes included the incidence and severity of the treatment-emergent adverse events. The study was not powered to detect differences in efficacy, but the clearing of the anterior chamber cells and the anterior chamber flare were graded, Dr. Matossian explained.

The results of the first study showed that on postoperative day eight, 60% of the patients treated with one dose of dexamethasone intraocular suspension 9% had no cells in the anterior chamber compared with 20% of those randomized to placebo, a difference that reached significance (P < 0.001).

The IOP outcomes and the effect of dexamethasone intraocular suspension 9% on IOP compared with placebo (vehicle injection) or topical prednisolone acetate 1% were analyzed in both phase III studies. The effect of the drug on the IOP is important because in a normal population, 4% to 6% of patients can be steroid responders, which, if not detected or treated, may lead to progression.

The authors proposed their pathway for managing patients taking antithrombotic drugs.

“Expert groups on oculoplastic surgery recommend stopping anti-thrombotic agents during blepharoplasty, lacrimal surgery, and deep orbital surgery as these are considered high risk for sight-threatening haemorrhagic complications,” the investigators noted.

For strabismus surgery, the recommendations are similar to those for glaucoma and vitreoretinal surgeries. For corneal surgery, no evidence was found. Hemorrhagic complications were reported in all groups. The authors proposed their pathway for managing patients taking antithrombotic drugs.

For low-risk procedures (sub-Tenon/topical cataract, corneal, chalazion, eyelid cyst/lesion removal, and strabismus surgeries), anticoagulants can be continued. For anticoagulants, the INR should be check on the surgical day and warfarin continued if within the therapeutic range; the DOAC dose is stopped two days preoperatively (depending on renal function) and restarted one to two days postoperatively if adequate hemostasis is achieved.

For high-risk procedures (peri/retrobulbar anesthesia, glaucoma, vitreoretinal pars plana vitrectomy), vitreoretinal procedures (oncology: endoresection, biopsy of intraocular tumors, plaques/markers), oculoplastics [blepharoplasty, post-septal eyelid surgery], and temporal artery biopsy surgeries), anticoagulants are stopped seven days preoperatively but continued in high-risk patients. Prasugrel, a platelet-aggregation inhibitor [Effent in the United States; Efent in the European Union] is stopped seven days preoperatively, and Ticagrelor, a platelet-aggregation inhibitor [Effent in the United States; Efent in the European Union] is stopped seven days preoperatively.

If low risk (e.g., non-valvular atrial fibrillation), the local anticoagulant service should be informed at the time of listing. If low risk, for the anticoagulants (warfarin, the local anticoagulant service should be informed at the time of listing. If low risk, for the anticoagulants (warfarin, the local anticoagulant service should be informed at the time of listing. If low risk, for the anticoagulants (warfarin, the local anticoagulant service should be informed at the time of listing. For the DOACs, the recommended action is the same as for low-risk procedures.
INDICATIONS AND USAGE
OMIDRIA® (phenylephrine and ketorolac intraocular solution) 1% / 0.3% is added to ophthalmic irrigating solution used during cataract surgery or intraocular lens replacement and is indicated for maintaining pupil size by preventing intraoperative miosis and reducing postoperative ocular pain.

IMPORTANT SAFETY INFORMATION
OMIDRIA must be added to irrigating solution prior to intraocular use.
OMIDRIA is contraindicated in patients with a known hypersensitivity to any of its ingredients.
Systemic exposure of phenylephrine may cause elevations in blood pressure.
Use OMIDRIA with caution in individuals who have previously exhibited sensitivities to acetylsalicylic acid, phenylacetic acid derivatives, and other nonsteroidal anti-inflammatory drugs (NSAIDs), or have a past medical history of asthma.
The most commonly reported adverse reactions at ≥2% are eye irritation, posterior capsule opacification, increased intraocular pressure, and anterior chamber inflammation.

Please see the Full Prescribing Information for OMIDRIA at www.omidria.com/prescribinginformation.

You are encouraged to report Suspected Adverse Reactions to the FDA.
Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.


The healthcare professionals portrayed in this advertisement are consultants of Omeros Corporation.

These cataract surgeons use OMIDRIA® (phenylephrine and ketorolac intraocular solution) 1% / 0.3% for less stress, pure success in their O.R. day.

What about you?
OMIDRIA helps your cataract surgery by inhibiting prostaglandin release to block inflammation and maintain iris tone, preventing miosis and reducing postoperative pain for your patients. Experience less stress in your O.R. day with OMIDRIA.

OMEROS®, the OMEROS logo®, OMIDRIA®, and the OMIDRIA logo® are registered trademarks of Omeros Corporation.

© Omeros Corporation 2019, all rights reserved. 2019-022
Nerve blocks found to be useful option for patients dealing with chronic issues

By Lynda Charters; Reviewed by Ann V. Quan, MD

Patients with chronic ocular pain may benefit from the use of nerve blocks generally used to treat peripheral neuropathic pain. Pain disorders can be nociceptive, characterized by pain that arises from actual or threatened damage to non-neural tissue, such as with severe ocular surface disease, band keratopathy, and intraocular inflammation. They can be neuropathic, as with pain resulting from damage to or changes occurring in the nervous system, such as that caused by a previous cataract, LASIK, or RK surgery; neuralgia associated with the herpes virus; and eye drops containing the preservative benzalkonium chloride, according to Ann V. Quan, MD, an ophthalmology resident, Bascom Palmer Eye Institute, University of Miami Hospital and Clinic, Miami. Neuropathic pain is a complex process resulting from various receptors. The corneal nociceptors are comprised of polymodal nociceptors that sense chemical, thermal, and endogenous inflammatory mediators, mechanoreceptors that sense mechanical stimuli, and cold thermoreceptors that sense evaporation. The terminal nerve endings of the corneal nociceptors interact with the external environment and by doing so, they are susceptible to damage during inflammation or repetitive environmental injuries.

The nociceptive causes of ocular pain, including inflammation, tear dysfunction, and anatomic abnormalities, are commonly treated. The pain often persists, suggesting there can be a neuropathic component. Drs. Quan and colleagues retrospectively reviewed the medical records of patients in the Oculofacial Pain Clinic at the University of Miami from Jan. 1, 2017, to Aug. 11, 2018, to determine if use of nerve blocks can effectively treat chronic ocular pain that likely has neuropathic components.

All of the patients had been treated with a nerve block as part of a treatment regimen. Dr. Quan recounted that nerve blocks were administered using a standard injectable solution of 4 ml of bupivacaine 0.5% (Marcaine, Pfizer) and 1 ml of methyprednisolone acetate (Depo-Medrol, Pfizer) 80 mg/ml mixed in a 5-cc syringe and injected using a 25-gauge needle. The terminal branches of the trigeminal nerve were targeted.

Bupivacaine blocks sodium channels, which prevents depolarization, and inhibits N-methyl-D-aspartate receptor-mediated transmission in the spinal cord and trigeminal nucleus. Of 11 patients (7 men, 4 women; mean age, 54 years) who received nerve blocks, four developed pain after ocular surgery and one each following trauma, radiation, zoster ophthalmicus, pituitary adenoma resection, sepsis, and in the setting of neovascularization, optica, and one with no known pain triggers.

Following administration of a nerve block, seven patients reported immediate pain relief lasting for varying amounts of time (the longest period being seven months).

“We found that nerve blocks typically used to treat peripheral neuropathic pain elsewhere in the body may be successful for treating chronic ocular pain from a variety of causes,” Dr. Quan concluded.

Dr. Matossian summarized the salient points of the study.

“In both phase III studies, the proportions of patients in each IOP category were similar in the treatment and control groups at each time point,” she concluded. “The percentages of patients with IOP increases that were 10 mm Hg or higher were comparable in the dexamethasone intra-ocular suspension and topical prednisolone groups on postoperative day 1, 23.9% versus 18.2%, respectively; on postoperative day 8, 4.0% versus 0.0%, respectively; and on postoperative day 30, 0.0% versus 0.0%, respectively. Twelve patients randomly selected to topical prednisolone required IOP-lowering medications, which successfully lowered the IOP by the time of the next measurement. In the placebo-controlled study, the IOP increases requiring medication also resolved in all cases (13 with the dexamethasone intraocular suspension and 5 with placebo) by postoperative day 15.

Dr. Matossian has no financial interest in any aspect of this report.
Flarex®

(fluorometholone acetate ophthalmic suspension) 0.1%

NOW JOINING THE EYEVANCE™ FAMILY of ophthalmic treatment options

Visit EYEVANCE BOOTH 7309 at AAO 2019
The monofocal toric IOL (enVista Toric Model MX60T, Bausch + Lomb) provides better refractive and visual outcomes to cataract patients with mild-to-moderate astigmatism compared with the IOL’s counterpart without a toric component.

This one-piece hydrophobic acrylic toric model is available with seven cylinder powers with the lowest being 1.25 D (under 1 D at the corneal plane). The optic size of the toric IOL is 6 mm and the length is 12.5 mm. The refractive index is 1.54 at 35° C.

Most patients who have undergone a cataract surgery had some preoperative corneal astigmatism that required management to ensure achievement of the optimal postoperative outcomes.

If not addressed, uncorrected astigmatism that is as minor as 0.75 D can cause symptoms such as visual blur, ghosting, and halos, according to clinical investigator Chad L. Betts, MD.

Dr. Betts and the researchers compared the clinical outcomes obtained with the monofocal toric IOL to those achieved with the non-toric IOL in patients with mild-to-moderate corneal astigmatism.

Seventeen patients were randomly selected to receive the toric IOL and 16 patients to the non-toric IOL.

The study also showed that the toric IOL produced better results for the reductions in cylinder, UCDVA, and the MRSE.

“We found a significantly higher reduction in cylinder with the toric IOL compared with the non-toric IOL” — Chad L. Betts, MD

The monofocal toric enVista Toric IOL from Bausch + Lomb provides a higher reduction in astigmatism and better mean uncorrected distance visual acuity compared with a non-toric IOL after cataract surgery in patients with mild-to-moderate astigmatism.

TAKE-HOME:

- The monofocal toric enVista Toric IOL provides a higher reduction in astigmatism and better mean uncorrected distance visual acuity compared with a non-toric IOL after cataract surgery in patients with mild-to-moderate astigmatism.

MORE ABOUT THE STUDY:

Seventeen patients were randomly selected to receive the toric IOL and 16 patients to the non-toric IOL.

The study also showed that the toric IOL produced better results for the reductions in cylinder, UCDVA, and the MRSE.

“We found a significantly higher reduction in cylinder with the toric IOL compared with the non-toric IOL,” Dr. Betts said.

DIVING DEEPER:

The toric IOL also achieved a reduction in astigmatism of 0.58 D compared with -0.05 D for the non-toric IOL, a difference that ultimately reached significance (p = 0.01). The mean UCDVA achieved with the toric IOL also was significantly (p = 0.04) better compared to the non-toric IOL, i.e., 0.10 logMAR of the minimum angle of resolution (logMAR) VA compared with 0.23 logMAR.

The majority of the patients who received the toric IOL (82%) were within 0.5 D of the target MRSE in contrast to 69% of the patients in the...
I didn’t realize STARS were little dots that twinkled

—Misty L, RPE65 gene therapy recipient

WE’RE SEEING AMAZING RESULTS. AND SO ARE THEY.

Foundation Fighting Blindness is shining a light in the darkness of Inherited Retinal Degenerations. We are the world’s leading organization searching for treatments and cures, and with many treatments already found, today’s innovations are illuminating a future of possibilities.

Patients with Inherited Retinal Degenerations are urged to partner with us to accelerate the discovery of treatment and cures.

We have robust disease information, a national network of local chapters and support groups, local educational events, and our My Retina Tracker patient registry helps to keep your patients connected with clinical and research advancements.

Visit ECPs4Cures.org to make a donation to help find more cures.

FightBlindness.org
Prophylactic drops gain acceptance following routine cataract surgery
High patient preference for easier regimen before, after procedure driving change

By Lynda Charters; Reviewed by Helga P. Sandoval, MD, MSCR

A combination therapy (LessDrops, ImprimisRx) that includes prednisolone acetate, gatifloxacin hydrochloride, and bromfenac used as a prophylactic treatment, provided similar results in patients undergoing routine phacoemulsification compared to the standard individual drop regimens of gatifloxacin, bromfenac, and prednisolone acetate when instilled before and after routine phacoemulsification.

Instillation of prophylactic eye drops, i.e., antibiotics, non-steroidal anti-inflammatory drugs, and steroids, before and after cataract surgery is an important step to ensure optimal outcomes. However, the prophylactic regimen is complicated by a number of factors such as patient compliance; patients’ inability to correctly instill the drops; lack of an understanding of the importance of the prophylactic treatment, the proper method of administration, and drop storage; forgetfulness; and dislike of instilling the drops multiple times a day for 2 to 4 weeks leading to non-compliance, Helga Sandoval, MD, explained.

IOL (Continued from page 18)

non-toric group falling in the same range, according to Dr. Betts.

The research team found that in both IOL groups, the BCDVAs were -0.10 logMAR.

According to the research team, no complications or secondary surgical interventions occurred during the study.

KEY POINTS

Dr. Betts also pointed out that several key points emerged from the study, including patients with mild-to-moderate corneal astigmatism who showed improved refractive and visual outcomes when implanted with the monofocal toric IOL compared to subjects implanted with the non-toric control IOL.

Both groups in the study achieved 20/20 or better BCDVA and with no complications.

CONCLUSIONS

“The aberration-free aspheric monofocal toric IOL provides another surgical option for surgeons to deliver optimal results for their patients with cataracts who have astigmatism,” Dr. Betts concluded.

‘The aberration-free aspheric monofocal toric IOL provides another surgical option for surgeons to deliver optimal results for their patients with cataracts who have astigmatism.’ — Chad L. Betts, MD

CHAD L. BETTS, MD
E: bettscl@mcdonaldeye.com
This article is based on Dr. Betts’ presentation at the American Society of Cataract and Refractive Surgery annual meeting. Dr. Betts is a clinical investigator for Bausch + Lomb.
Dr. Sandoval and coauthor Kerry Solomon, MD, both from Carolina Eyecare Physicians, Mt. Pleasant, SC with an affiliated faculty appointment at Storm Eye Institute, Medical University of South Carolina, Charleston, SC, are conducting a prospective, randomly selected, contralateral eye study in which they assess the efficacy of the combination drop therapy compared to the standard prophylactic treatment of gatifloxacin 0.5%, bromfenac 0.07%, and prednisolone acetate 1%. Thirty-five patients undergoing bilateral routine cataract surgery will be included in the study. The first eye to undergo surgery is randomized to one of the two treatments and the fellow eye received the other treatment.

On postoperative days 15 and 30, the patients undergo pachymetry, measurement of intraocular pressure (IOP) and retinal thickness; and were questioned about the presence of a foreign-body sensation, stinging and burning, and pain and discomfort rated on a scale of 0 to 10; and the treatment preference.

RESULTS
At the time of this report, data from 19 patients (11 women, eight men; mean age, 68.9 years) were available. No differences were seen between the two groups in the mean surgical time, phaco time, cumulative dissipated energy, or the amount of fluid used.

The investigators also reported that at the one-month evaluation, the mean macular thicknesses, the mean pachymetric values, and the mean IOPs did not differ significantly between the two groups.

Regarding adverse effects, the postoperative inflammation in both groups was minimal at all time periods. The most common sign was cells on the first postoperative day.

More patients in the control group reported burning and stinging at one month compared with the LessDrops group, i.e., 16% vs. 5%.

When questioned about their treatment preferences, the vast majority of patients reported that they were satisfied or very satisfied with the treatment in 94.7% of cases (18/19), with no statistically significant difference between the two groups. All subjects preferred the LessDrops regimen to the standard drops regimen.

“These preliminary results indicated that LessDrops is a prophylactic treatment alternative with higher patient preference,” Dr. Sandoval concluded. “We did not observe any differences in the parameters analyzed between the two study groups and no unanticipated adverse events occurred.”
Safety key for intracameraly injected mydriatic agents in cataract surgery

Lower systemic exposure, fewer cardiovascular events compared to eye drop regimen

By Lynda Charters

The side effect that may go along with a drug is always a concern, regardless of the age or general health of a patient. However, those concerns are amplified in older populations, particularly those who are at increased risk of cardiovascular events.

“Cataract is associated with old age and, as the population age, the demand for cataract surgery is increasing and will likely continue to increase,” according to the investigators of a study in which the systemic exposure to the combination of tropicamide/phenylephrine after intracameral or topical administration before performing cataract surgery was evaluated. “Additionally, elderlies are at an increased risk of developing multiple pathologies and are consequently polymedicated.”

According to investigators, this drug combination is considered the gold standard to establish stable mydriasis during cataract surgery with lens implantation.

However, Jose Guell, MD, and colleagues pointed out that these drugs usually must be instilled multiple times intraoperatively, which may result in an overdose associated with increased risk of cardiovascular events and ocular surface toxicity, the latter of which can lead to keratopathy and decreased intraoperative visualization.

To avoid prolongation of the time to mydriasis preoperatively with administration of drugs in the surgical center or even at home where the patients are unsupervised, an intracameral fixed combination of mydriatic drugs and an anesthetic (ICMA) at the start of cataract surgery has been investigated and is considered safe and effective.

“A particular benefit of intracameral mydriatics/anesthetic is the excellent bioavailability directly in the target tissues and the putative lower systemic absorption compared to [eye drop] formulations,” according to Dr. Guell, et al. “The synergistic effect of the two mydriatic components also permits lower doses of each to be used, further limiting the local toxicity of these drugs.”

Patients also have been reported to be more comfortable intraoperatively, with less preparatory and surgical time compared with use of drops.

THE STUDY

Considering these benefits, the current investigators wanted to determine the systemic exposure experienced by 271 patients receiving the ICMA formulation (tropicamide 0.02%, phenylephrine 0.31%, and lidocaine 1%) in the operated eye compared with 283 patients treated with the standard topical administration (tropicamide 0.5% and phenylephrine 10%), referred to as the safety set. High-performance liquid chromatography was performed before and after administration of the drug regimen to determine the plasma levels in 15 patients in each group.

The investigators reported that 198 patients in the ICMA group received one 200-microliter dose, which exposed them to a calculated level of 0.04 mg of tropicamide and 0.62 mg of phenylephrine; none received an additional mydriatic. In the rest of the ICMA group, 72 patients received another 100-microliter injection for a maximal dose of 0.06 mg of tropicamide and 0.93 mg of phenylephrine; one patient received a third 100-μL injection.

In the safety set group, the respective exposures with three drops were calculated to be 0.45 and 10.2 milligrams, 11.3-fold and 16.5-fold higher of the two mydriatic components also permits lower doses of each to be used, further limiting the local toxicity of these drugs.”

RESULTS OF BLOOD SAMPLING

The mean patient age of the 30 patients who underwent blood sampling was 71.3 years, with a range, 51.3 to 85.5. Most (80%) were older than 65 years. All of these patients received the standard regimen of mydriatics in both groups (except for one patient in the ICMA group who received another 100-μL injection).

In the 15 patients in the ICMA group, tropicamide was not detected at 2, 12, and 30 minutes after injection but was detected in 73.3% of patients in the safety set group at 2 minutes and in all patients at 12 and 30 minutes (maximal plasma concentration, 3.16 nanograms/milliliter at 30 minutes in the safety set group).

Phenylephrine was detected in the ICMA group in two patients (maximal concentrations, 0.140 and 0.587 nanogram/milliliter) and in all 15 patients in the safety set at least one time point (range of maximal concentration between 0.109 and 1.42 nanogram/milliliter); in 38.5% of patients, the maximal phenylephrine concentration was over 0.59 nanogram/milliliter.

When the two groups were compared, the authors reported that more patients in the safety set group had a “meaningful increase” in hypertension and/or tachycardiac events, that is, 11.2% vs. 6.0% in the ICMA group, respectively, a difference that reached significance (p=0.03).

The study results showed that the “ICMA result has lower systemic ocular surface exposure to phenylephrine and tropicamide than the ... topical treatment.”

“The ICMA treatment permits the correct dose of the appropriate agents to be administered consistently at a convenient time (at the start of surgery), in a safe and monitored environment (the operating room) at an appropriate site (anterior chamber) with less [cardiovascular] side effects compared to the usual dilation procedure,” the investigators concluded.

‘A particular benefit of intracameral mydriatics/anesthetic is the excellent bioavailability directly in the target tissues and the putative lower systemic absorption compared to [eye drop] formulations.’ — Jose Guell, MD

Note: The authors reported their findings on behalf of the Intracameral Mydrane and Ethics Group in Clinical Ophthalmology (2019;13:811-819).
DUREZOL® Emulsion, a topical corticosteroid, is indicated for:

• The treatment of inflammation and pain associated with ocular surgery.
• The treatment of endogenous anterior uveitis.

Dosage and Administration

For the treatment of inflammation and pain associated with ocular surgery instill one drop into the conjunctival sac of the affected eye 4 times daily beginning 24 hours after surgery and continuing throughout the first 2 weeks of the postoperative period, followed by 2 times daily for a week and then a taper based on the response.

For the treatment of endogenous anterior uveitis, instill one drop into the conjunctival sac of the affected eye 4 times daily for 14 days followed by tapering as clinically indicated.

Most Common Adverse Reactions

• Bacterial infections – Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions, steroids may mask infection or enhance existing infection. If signs and symptoms fail to improve after 2 days, the patient should be re-evaluated.

• 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.

• Contact lens wear – DUREZOL® Emulsion should not be instilled while wearing contact lenses. Remove contact lenses prior to instillation of DUREZOL® Emulsion. The preservative in DUREZOL® Emulsion may be absorbed by soft contact lenses. Lenses may be reinserted after 10 minutes following administration of DUREZOL® Emulsion.

INDICATIONS AND USAGE

DUREZOL® (difluprednate ophthalmic emulsion) 0.05% is a topical corticosteroid that is indicated for:

• The treatment of inflammation and pain associated with ocular surgery.
• The treatment of endogenous anterior uveitis.

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. 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 – 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 beyond 28 days 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, steroids may mask infection or enhance existing infection. If signs and symptoms fail to improve after 2 days, the patient should be re-evaluated.

• 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.

• Contact lens wear – DUREZOL® Emulsion should not be instilled while wearing contact lenses. Remove contact lenses prior to instillation of DUREZOL® Emulsion. The preservative in DUREZOL® Emulsion may be absorbed by soft contact lenses. Lenses may be reinserted after 10 minutes following administration of DUREZOL® Emulsion.

Most Common Adverse Reactions

• In postoperative ocular inflammation and pain studies, ocular adverse reactions occurring in 5-15% of subjects included corneal edema, ciliary and conjunctival hyperemia, eye pain, photophobia, posterior capsule opacification, anterior chamber cells, anterior chamber flare, posterior capsule opacification, and conjunctival hyperemia, eye pain, photophobia, posterior capsule opacification, anterior chamber cells, anterior chamber flare, conjunctival edema, and blepharitis.

• In the endogenous anterior uveitis studies, the most common adverse reactions occurring in 5-10% of subjects included blurred vision, eye irritation, eye pain, headache, increased IOP, iritis, limbic and conjunctival hyperemia, punctate keratitis, and uveitis.

For additional information about DUREZOL® Emulsion, please see Brief Summary of Prescribing Information on adjacent page.

*Limitations apply. For commercially insured patients. Up to a $155 cap per bottle. Patient will be responsible for any co-pay once limit per bottle is reached. This offer is not valid under Medicare, Medicaid, or any other federal or state program. Not valid for cash-paying patients. Novartis reserves the right to rescind, revoke, or amend this program without notice. Additional terms and conditions apply. Please see co-pay materials for details.

References:
4. T-DZL-1375846

Explore the potency and proven efficacy of DUREZOL® Emulsion at durezolhcp.com.
DUREZOL® (difluprednate ophthalmic emulsion) 0.05%

Initial U.S. Approval: 2008

BRIEF SUMMARY: Please see package insert for full prescribing information.

1 INDICATIONS AND USAGE

1.1 Ocular Surgery
DUREZOL® (difluprednate ophthalmic emulsion) 0.05%, a topical corticosteroid, is indicated for the treatment of inflammation and pain associated with ocular surgery.

1.2 Endogenous Anterior Uveitis
DUREZOL® is also indicated for the treatment of endogenous anterior uveitis.

4 CONTRAINDICATIONS

The use of DUREZOL®, as with other ophthalmic corticosteroids, is contraindicated in most active 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 disease of structural tissues.

5 WARNINGS AND PRECAUTIONS

5.1 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, IOP should be monitored.

5.2 Cataracts
Use of corticosteroids may result in posterior subcapsular cataract formation.

5.3 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 beyond 28 days 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.

5.4 Bacterial Infections
Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions, steroids may mask infection or enhance existing infection. If signs and symptoms fail to improve after 2 days, the patient should be reevaluated.

5.5 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).

5.6 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 culture should be taken when appropriate.

5.7 Topical Ophthalmic Use Only
DUREZOL® is not indicated for intraocular administration.

5.8 Contact Lens Wear
DUREZOL® should not be instilled while wearing contact lenses. Remove contact lenses prior to instillation of DUREZOL®. The preservative in DUREZOL® may be absorbed by soft contact lenses. Lenses may be reinserted after 10 minutes following administration of DUREZOL®.

6 ADVERSE REACTIONS

The following serious reactions are found elsewhere in the labeling:

- Elevated IOP (see Warnings and Precautions (5.1))
- Posterior subcapsular cataract formation (see Warnings and Precautions (5.2))
- Secondary ocular infection (see Warnings and Precautions (5.4))
- Perforation of the globe (see Warnings and Precautions (5.3))

6.1 Ocular Surgery
Ocular adverse reactions occurring in 5% to 15% of subjects in clinical studies with DUREZOL® included conjunctival hyperemia, lid and conjunctival edema, and blepharitis. Other ocular adverse reactions occurring in 1% to 5% of subjects included reduced visual acuity, punctate keratitis, eye inflammation, and iritis. Ocular adverse reactions occurring in less than 1% of subjects included application site discomfort or irritation, corneal pigmentation and striae, episceritis, eye prunus, eyelid irritation and crusting, foreign body sensation, increased lacrimation, macular edema, sclera hyperemia, and uveitis. Most of these reactions may have been the consequence of the surgical procedure.

6.2 Endogenous Anterior Uveitis
A total of 200 subjects participated in the clinical trials for endogenous anterior uveitis, of which 106 were exposed to DUREZOL®. The most common adverse reactions of those exposed to DUREZOL® occurring in 5% to 10% of subjects included blurred vision, eye irritation, eye pain, headache, increased IOP, iritis, limbal and conjunctival hyperemia, punctate keratitis, and uveitis. Adverse reactions occurring in 2% to 5% of subjects included anterior chamber flare, corneal edema, dry eye, iridocyclitis, photophobia, and reduced visual acuity.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy Teratogenic Effects

Pregnancy Category C
Difluprednate has been shown to be embryotoxic (decrease in embryonic body weight and a delay in embryonic ossification) and teratogenic (cleft palate and skeletal anomalies) when administered subcutaneously to rabbits during organogenesis at a dose of 1-10 mcg/kg/day. The no-observed-effect-level (NOEL) for these effects was 1 mcg/kg/day, and 10 mcg/kg/day was considered to be a teratogenic dose that was concurrently found in the toxic dose range for fetuses and pregnant females. Treatment of rats with 10 mcg/kg/day subcutaneously during organogenesis did not result in any reproductive toxicity, nor was it maternally toxic. At 100 mcg/kg/day after subcutaneous administration in rats, there was a decrease in fetal weights and delay in ossification, and effects on weight gain in the pregnant females. It is difficult to extrapolate these doses of difluprednate to maximum daily human doses of DUREZOL® since DUREZOL® is administered topically with minimal systemic absorption, and difluprednate blood levels were not measured in the reproductive animal studies. However, since use of difluprednate during human pregnancy has not been evaluated and cannot rule out the possibility of harm, DUREZOL® should be used during pregnancy only if the potential benefit justifies the potential risk to the embryo or fetus.

8.3 Nursing Mothers

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

8.4 Pediatric Use

DUREZOL® was evaluated in a 3-month, multicenter, double-masked trial in 79 pediatric patients (39 DUREZOL®, 40 prednisolone acetate) 0 to 3 years of age for the treatment of inflammation following cataract surgery. A similar safety profile was observed in pediatric patients comparing DUREZOL® to prednisolone acetate ophthalmic suspension, 1%.

8.5 Geriatric Use

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

U.S. Pat.: www.alconpatients.com
©2013, 2016 Novartis

Distributed by:
Alcon Laboratories
Fort Worth, Texas 76134 USA
T2017-52
April 2017
Home-based screenings are still in the early stages. Time will tell which approaches and tools are most effective and convenient.

De Moraes et al. conducted a study (JAMA Ophthalmology 2018) in 445 patients and found that the contact lens sensor recordings may have a better association with visual field progression than Goldman mean IOP measured multiple times during office hours.

The authors concluded that the CLS may be useful in assessing the risk of functional loss, even when insufficient visual field information is available. Several methods of performing visual field tests at home are available. The most applicable to home use at this time are the Visual Fields easy and the Melbourne Rapid Fields (MRF), which are iPad apps, and Peristat, an online perimeter test.

Visual Fields easy is used for performing supra threshold parametric screening and can be downloaded free from iTunes. The 3.5 minute test covers 30° of the visual field.

According to Dr. Han, it showed good correlation with the Humphrey Visual Field testing, and about 80% repeatability in a 2017 study in the American Journal of Ophthalmology by Johnson et al, who evaluated the app’s performance in Nepal.

The MRF glaucoma app can be used to assess the central and peripheral visual field, using a seven-step process that tests 34 x 25 degrees of field and requires four to six minutes per eye. False positives, false negatives, and fixation loss can be monitored, and the app will send a notification to a designated clinician if a significant change has been detected. A 2016 study in Translational Vision Science and Technology demonstrated good test-retest reliability.

Another option for patients is Peristat, a free web-based perimeter test that can be performed on any computer with a 17-inch or larger screen and an Internet connection via keepyoursight.org. This test maps 24 degrees of visual function and ensures reliability through measurement of fixation losses, false positives, and false negatives.

In a study comparing Peristat online perimetry with the Humphrey perimeter in a clinical setting, Peristat exhibited a reasonable ROC curve as well as significant correlation with the conventional HVF, said Dr. Han, who was the corresponding author of the 2016 study in Translational Vision Science and Technology. In the analysis of Peristat’s ability to distinguish patients with moderate and severe glaucoma from those with normal vision, the area under the curve was 0.87–0.88, sensitivity was 80%, and specificity was 90%.

While the availability of teleglaucoma tools indicates a growing interest in allowing patients to be more involved in managing their care, Dr. Han pointed out several barriers that need to be resolved. First, it’s more challenging for physicians to manage large-scale data points from testing conducted in homes than in an office setting.

“Doctors may have low confidence in their ability to make decisions based on images alone,” Dr. Han said.

Then there are the nonclinical issues that need to be addressed, such as reimbursement and state licensure requirements that currently may limit a physician’s ability to provide care via teleglaucoma. Teleglaucoma, and particularly home-based screening, are still in the early stages, and time will determine which approaches and tools are most effective and convenient, Dr. Han concluded.

Home-based screenings are still in the early stages. Time will tell which approaches and tools are most effective and convenient.
When patients were analyzed by different degrees of hyperopia, a greater difference was seen in the low hyperopia group, with about 30% failing observation and about 10% failing glasses.
The first FDA-approved pharmacologic treatment that targets the root pathogenesis of neurotrophic keratitis

With OXERVATE, up to 72% of patients achieved complete corneal healing at 8 weeks*1

- Cenegermin-bkbj, the active ingredient in OXERVATE, is structurally identical to the human nerve growth factor (NGF) protein made in ocular tissues.4
- NGF is an endogenous protein involved in the differentiation and maintenance of neurons, and acts through specific high-affinity (ie, TrKA) and low-affinity (ie, p75NTR) NGF receptors in the anterior segment of the eye to support corneal innervation and integrity.1 Endogenous NGF is believed to support corneal integrity through 3 primary mechanisms (shown in preclinical models): corneal innervation, reflex tear secretion, and corneal epithelial cell proliferation and differentiation3,5,6

Explore the breakthrough therapy at Oxervate.com/HCP

Indication

OXERVATE is a recombinant human nerve growth factor indicated for the treatment of neurotrophic keratitis.

Important Safety Information

WARNINGS AND PRECAUTIONS

Patients should remove contact lenses before applying OXERVATE and wait 15 minutes after instillation of the dose before reinsertion.

ADVERSE REACTIONS

The most common adverse reaction in clinical trials that occurred more frequently with OXERVATE was eye pain (16% of patients). Other adverse reactions included corneal deposits, foreign body sensation, ocular hyperemia, ocular inflammation, and increase in tears (1%-10% of patients).

For additional safety information, see accompanying Brief Summary of Safety Information on the adjacent page and full Prescribing Information on Oxervate.com/HCP.


© 2019 Dompé U.S. Inc. All rights reserved.

US-OXE-1900050 08/19
Brief Summary of Safety
Consult the full Prescribing Information for complete product information.

INDICATIONS AND USAGE
OXERVATE™ (cenegermin-bkbj) ophthalmic solution 0.002% is indicated for the treatment of neurotrophic keratitis.

Dosage and Administration
Contact lenses should be removed before applying OXERVATE and may be reinserted 15 minutes after administration.
If a dose is missed, treatment should be continued as normal, at the next scheduled administration.
If more than one topical ophthalmic product is being used, administer the eye drops at least 15 minutes apart to avoid diluting products. Administer OXERVATE 15 minutes prior to using any eye ointment, gel or other viscous eye drops.

Recommended Dosage and Dose Administration
Instill one drop of OXERVATE in the affected eye(s), 6 times a day at 2-hour intervals for eight weeks.

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 two clinical trials of patients with neurotrophic keratitis, a total of 101 patients received cenegermin-bkbj eye drops at 20 mcg/mL at a frequency of 6 times daily in the affected eye(s) for a duration of 8 weeks. The mean age of the population was 61 to 65 years of age (18 to 95). The majority of the treated patients were female (61%). The most common adverse reaction was eye pain following instillation which was reported in approximately 16% of patients. Other adverse reactions occurring in 1-10% of OXERVATE patients and more frequently than in the vehicle-treated patients included corneal deposits, foreign body sensation, ocular hyperemia, ocular inflammation and tearing.

USE IN SPECIFIC POPULATIONS
Pregnancy
Risk Summary There are no data from the use of OXERVATE in pregnant women to inform any drug associated risks. Administration of cenegermin-bkbj to pregnant rats or rabbits during the period of organogenesis did not produce adverse fetal effects at clinically relevant doses. In a pre- and postnatal development study, administration of cenegermin-bkbj to pregnant rats throughout gestation and lactation did not produce adverse effects at clinically relevant doses.
Animal Data
In embryofetal development studies, daily subcutaneous administration of cenegermin-bkbj to pregnant rats and rabbits throughout the period of organogenesis produced a slight increase in post-implantation loss at doses greater than or equal to 42 mcg/kg/day (267 times the MRHOD). A no observed adverse effect level (NOAEL) was not established for post-implantation loss in either species. In rats, hydrocephaly and ureter anomalies were each observed in one fetus at 267 mcg/kg/day (1709 times the MRHOD). In rabbits, cardiovascular malformations, including ventricular and atrial septal defects, enlarged heart and aortic arch dilation were each observed in one fetus at 83 mcg/kg/day (534 times the MRHOD). No fetal malformations were observed in rats and rabbits at doses of 133 mcg/kg/day and 42 mcg/kg/day, respectively. In a pre- and postnatal development study, daily subcutaneous administration of cenegermin-bkbj to pregnant rats during the period of organogenesis and lactation did not affect parturition and was not associated with adverse toxicity in offspring at doses up to 267 mcg/kg/day. In parental rats and rabbits, an immunogenic response to cenegermin-bkbj was observed. Given that cenegermin-bkbj is a heterologous protein in animals, this response may not be relevant to humans.

Lactation
There are no data on the presence of OXERVATE in human milk, the effects on breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered, along with the mother’s clinical need for OXERVATE, and any potential adverse effects on the breastfed infant from OXERVATE.

Pediatric Use
The safety and effectiveness of OXERVATE have been established in the pediatric population. Use of OXERVATE in this population is supported by evidence from adequate and well-controlled trials of OXERVATE in adults with additional safety data in pediatric patients from 2 years of age and older [see Clinical Studies (14)].

Geriatric Use
Of the total number of subjects in clinical studies of OXERVATE, 43.5% were 65 years old and over. No overall differences in safety or effectiveness were observed between elderly and younger adult patients.

NONCLINICAL TOXICOLOGY
Carcinogenesis and Mutagenesis Animal studies have not been conducted to determine the carcinogenic and mutagenic potential of cenegermin-bkbj.
Impairment of Fertility Daily subcutaneous administration of cenegermin-bkbj to male and female rats for at least 14 days prior to mating, and at least 18 days post-coitum had no effect on fertility parameters in male or female rats at doses up to 267 mcg/kg/day (1709 times the MRHOD). In general toxicology studies, subcutaneous and ocular administration of cenegermin-bkbj in females was associated with ovarian findings including persistent estrus, ovarian follicular cysts, atrophy/reduction of corpora lutea, and changes in ovarian weight at doses greater than or equal to 19 mcg/kg/day (119 times the MRHOD).

© 2019 Dompé U.S. Inc. All rights reserved. US-OXE-1900010 06/19
Despite advances in treatment strategies, retinopathy of prematurity (ROP) continues to be a leading cause of childhood blindness due to inadequate screening, and barriers to inadequate screening are numerous and include shortage of ophthalmologists trained and willing to screen for ROP and lack of patient access to trained ophthalmologists in resource-poor communities.

Telemedicine has great potential to improve screening for treatment-warranted ROP. SUNDROP and eROP studies have clearly demonstrated the accuracy of telemedicine as a screening tool.

**PURPOSE**
The study focuses on a handheld, portable, easy-to-use, child-friendly device for wide-field fundus photography in children.

To evaluate the feasibility and accuracy of screening for clinically significant posterior pole vascular dilation and tortuosity in premature infants (plus disease) using RetinaScope.

**METHODS**
The study was approved by the University of Michigan Institutional Review Board, Sparrow Clinical Research Institute, and registered on ClinicalTrials.gov Identifier NCT03076697. It included 27 premature infants, including 14 males and 13 females, with a mean gestational age of 27.7 weeks. Two had clinically diagnosed plus disease.

For all patients, the mean postmenstrual age at the time of examination was 41.2 weeks.

In the study, each patient underwent a dilated fundus examination with scleral depression by an ophthalmologist. Photographs of the retina were acquired with RetinaScope from standard 5 fields of view.

All of the images were graded by two independent masked retina specialists who assessed photograph quality and the presence or absence of plus disease.

**RESULTS**
No infant with clinically determined plus disease was missed by the masked graders evaluating smartphone-based retinal photography. Agreement between the two graders for the presence or absence of plus disease was \( k = 0.83, 95\% CI = 0.80-0.86. \)

Three patients had intraretinal hemorrhages in zone 2 and one patient had a ridge in zone 2. Both graders accurately noted these pathologies on photographs.

Two patients had a ridge in zone 3, which was not well photographed and not noted by the graders but was noted on the clinical examination.

**CONCLUSION**
The study found that smartphone-based retinal photography holds promise in ophthalmic care of children.

Our work adds to the growing body of literature on the feasibility and utility of portable non-contact fundus photography devices for ROP screening particularly for plus disease and Zone 1 and 2 disease.

Clinical diagnosis of plus disease is highly variable; fundus photography and automated analysis may provide advice at the point of care.

Our sample size was small and the performance metrics may not be generalizable, and future work will explore wide-field optical elements for imaging zone 3.

**ACKNOWLEDGEMENTS**

Yannis Paulus, MD, FACS (PI)
Tyson Kim, MD, PhD (co-PI)
Philip Lieu, MD
Vaidehi Dedania, MD
Cynthia Qian, MD
Cagri Besirli, MD, PhD
Todd Margolis, MD, PhD
Daniel Fletcher, PhD

**VIDEO**
See Dr. Patel’s presentation online at OphthalmologyTimes.com/video/dr-tapan-patel-presentation

**EDITOR’S NOTE**

*Ophthalmology Times is pleased to recognize Tapan P. Patel, MD, PhD, resident, Kellogg Eye Center, University of Michigan, Ann Arbor, MI, as the fifth-place honoree of the second Ophthalmology Times Research Scholar Honoree Program. Dr. Patel’s abstract is featured here.*

The Ophthalmology Times Research Scholar Honoree Program is dedicated to the education of retina fellows and residents by providing a unique opportunity for fellows/residents to share notable research and challenging cases with their peers and mentors. The program is supported by unrestricted grants from Regeneron Pharmaceuticals and Carl Zeiss Meditec Inc.
Superior efficacy.
Optimal simplicity.1,2

Once-daily Rocklatan® significantly lowers IOP in patients with open-angle glaucoma or ocular hypertension—superior to latanoprost and netarsudil at every measured timepoint in phase 3 clinical trials.1,2

The first and only once-daily fixed-dose combination of prostaglandin + ROCK inhibitor

Nearly 60% of Rocklatan® patients achieved a target pressure of 16 mmHg or less2

The majority of ocular adverse events were mild and tolerable, with minimal systemic adverse events1,3

Once-daily dosing relieves treatment burden and may improve adherence and treatment outcomes1,4

IMPORTANT SAFETY INFORMATION

Contraindications
None.

Warnings and Precautions
- Pigmentation changes
- Eyelash changes
- Intracorneal inflammation
- Macular edema

Adverse reactions
Rocklatan®: The most common ocular adverse reaction is conjunctival hyperemia (59%). Five percent of patients discontinued therapy due to conjunctival hyperemia. Other common ocular adverse reactions were: instillation site pain (20%), corneal verticillata (15%), and conjunctival hemorrhage (11%). Eye pruritus, visual acuity reduced, increased lacrimation, instillation site discomfort, and blurred vision were reported in 5-8% of patients.

Netarsudil 0.02%: Instillation site erythema, corneal staining, increased lacrimation and erythema of eyelid.

Latanoprost 0.005%: Foreign body sensation, punctate keratitis, burning and stinging, itching, increased pigmentation of the iris, excessive tearing, eyelid discomfort, dry eye, eye pain, eyelid margin crusting, erythema of the eyelid, upper respiratory tract infection/ nasopharyngitis/influenza, photophobia, eyelid edema, myalgia/arthritis/back pain, and rash/allergic reaction.

Please see brief summary on the adjacent page.

For full Prescribing Information, please visit Rocklatan.com.
You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

INDICATIONS AND USAGE
Rocklatan® (netarsudil and latanoprost ophthalmic solution) 0.02%/0.005% is approved for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

DOSAGE AND ADMINISTRATION
The recommended dosage is one drop in the affected eye(s) once daily in the evening. If one dose is missed, treatment should continue with the next dose in the evening. The dosage of Rocklatan® should not exceed once daily. Rocklatan® may be used concomitantly with other topical ophthalmic drug products to lower IOP. If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes apart.

References:
Rocklatan® (netarsudil and latanoprost ophthalmic solution) 0.02%/0.005% Rx Only

BRIEF SUMMARY
Consult the Full Prescribing Information for complete product information.

INDICATIONS AND USAGE
Rocklatan® (netarsudil and latanoprost ophthalmic solution) 0.02%/0.005% is indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

DOSAGE AND ADMINISTRATION
The recommended dosage is one drop in the affected eye(s) once daily in the evening.

If one dose is missed, treatment should continue with the next dose in the evening. The dosage of Rocklatan® should not exceed once daily. Rocklatan® may be used concomitantly with other topical ocular hypotensive drug products to lower IOP. If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes apart.

CONTRAINDICATIONS
None.

WARNINGS AND PRECAUTIONS
Pigmentation
Rocklatan® contains latanoprost which has been reported to cause changes to pigmented tissues. These changes include increased length, thickness, pigmentation, the number of lashes or hairs, and misdirected growth of eyelashes. Eyelash changes are usually reversible upon discontinuation of treatment.

Macular Edema
Macular edema, including cystoid macular edema, has been reported during treatment with latanoprost. Rocklatan® 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.

Herpetic Keratitis
Reactivation of Herpes Simplex keratitis has been reported during treatment with latanoprost. Rocklatan® should be used with caution in patients with a history of herpetic keratitis. Rocklatan® should be avoided in cases of active herpes simplex keratitis because it may exacerbate inflammation.

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 the administration of Rocklatan® and may be reinserted 15 minutes after administration.

ADVERSE REACTIONS
Clinical Trials 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 trials of another drug. 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 trials of another drug. Rocklatan® contains netarsudil and latanoprost, which should be used with caution in patients with a history of allergy to any component of the formulation.

Drug Interactions
Although specific drug interaction studies have not been conducted with Rocklatan®, in vitro studies have shown that precipitation occurs when eye drops containing thimerosal are mixed with latanoprost opthalmic solution (0.005%). If such drugs are used, they should be administered at least five (5) minutes apart.

The combined use of two or more prostaglandins or prostaglandin analogs including latanoprost ophthalmic solution is not recommended. It has been shown that administration of these prostaglandin drug products more than once daily may decrease the IOP lowering effect or cause paradoxical elevations in IOP.

Use in Specific Populations
Pregnancy
There are no available data on netarsudil opthalmic solution use in pregnant women to inform any drug associated risk; however, systemic exposure to netarsudil from ocular administration is low. Intravenous administration of netarsudil to pregnant rats and rabbits during organogenesis did not produce adverse embryofetal effects at clinically relevant systemic exposures.

Animal Data
Netarsudil administered daily by intravenous injection to rats during organogenesis caused abortions and embryofetal lethality at doses ≥0.3 mg/kg/day (126-fold the plasma exposure at the RHOD, based on C_{max}). The no-observed-adverse-effect level (NOAEL) for embryofetal development toxicity was 0.1 mg/kg/day (40-fold the plasma exposure at the RHOD, based on C_{max}).

Netarsudil administered daily by intravenous injection to rabbits during organogenesis caused embryofetal lethality and decreased fetal weight at 5 mg/kg/day (1480-fold the plasma exposure at the RHOD, based on C_{max}). Malformations were observed at ≥ 0.3 mg/kg/day (1330-fold the plasma exposure at the RHOD, based on C_{max}), including thoracogastroschisis, umbilical hernia and absent intermediate lung lobe. The NOAEL for embryofetal development toxicity was 0.5 mg/kg/day (214-fold the plasma exposure at the RHOD, based on C_{max}).

For latanoprost, in 4 of 16 pregnant rabbits, no viable fetuses were present at a dose that was approximately 80 times higher than the RHOD. Latanoprost did not produce embryofetal lethality in rabbits at a dose approximately 15 times higher than the RHOD.

Lactation
There are no data on the presence of netarsudil or latanoprost in human milk, the effects on the breastfed infant, or the effects on milk production. However, systemic exposure to netarsudil following topical ocular administration is low, and it is not known whether measurable levels of netarsudil would be present in maternal milk following topical ocular administration. It is also not known whether latanoprost or its metabolites are excreted in milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Rocklatan® and any potential adverse effects on the breastfed child from netarsudil and latanoprost.

Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

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

NONCLINICAL TOXICOLOGY
Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term studies in animals have not been performed to evaluate the carcinogenic potential of netarsudil. Netarsudil was not mutagenic in the Ames test, in the mouse lymphoma test, or in the in vivo rat micronucleus test. Studies to evaluate the effects of netarsudil on male or female fertility in animals have not been performed.

Latanoprost was not carcinogenic in either mice or rats when administered by oral gavage at doses of up to 170 mcg/kg/day (approximately 2800 times the recommended maximum human dose) for up to 20 and 24 months, respectively. Latanoprost was not mutagenic in bacteria, in mouse lymphoma, or in mouse micronucleus tests. Chromosome aberrations were observed in vitro with human lymphocytes. Additional in vitro and in vivo studies on unscheduled DNA synthesis in rats were negative. Latanoprost has not been found to have any effect on male or female fertility in animal studies.

For additional information, refer to the full prescribing information at www.Rocklatan.com.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit MedWatch or call 1-800-FDA-1088.

Manufactured for: Aerie Pharmaceuticals, Inc., Irvine, CA 92614, U.S.A.

Rocklatan® is a registered trademark of Aerie Pharmaceuticals, Inc.

U.S. Patent Nos.: 8,450,344; 8,394,826; 9,096,569; 9,415,043; 9,931,336; 9,993,470
The phase 2 FILLY study met its primary endpoint of statistically significant reduction in geographic atrophy (GA) lesion growth in eyes treated with the investigational complement factor 3 inhibitor, APL-2 (Apellis Pharmaceuticals), compared to sham.

Additional findings from a post-hoc analysis showed that over the 12-month study, the treatment benefit of APL-2 injections given monthly or every other month was maintained irrespective of the presence of select risk factors for GA progression, according to Eleonora Lad, MD, PhD, associate professor of ophthalmology, Duke University, Durham, NC.

Dr. Lad, a principal investigator for the phase II FILLY Study at the Duke Eye Center, and is the lead investigator of the phase III Apellis OAKS study, pointed out that APL-2 administration resulted in significant decrease in GA progression regardless of gender, age subgroups, and baseline lesion sizes.

**ABOUT THE STUDY**
The FILLY study randomly selected 246 patients 2:2:1:1 to undergo single-masked intravitreal treatment for 12 months, with APL-2 every month or every other month or sham every month or every other month.

Patients were eligible for participation if they had BCVA ≥20/320 and a diagnosis of GA of the macular secondary to AMD with total GA area ≥2.5 mm² if the GA was multifocal.

The analyses presented by Dr. Lad evaluated the impact of select baseline characteristics on progression of GA at month 12 in the FILLY study. Variables examined as potential predictors of GA progression included clinical and functional features that have been well-described as prognostic factors in the literature—lesion size, multifocality, location, low luminance deficit, and presence of reticular pseudodrusen—as well as patient demographics.

**BENEFITS ACROSS AGE GROUPS**
The data showed that, in general, benefit of APL-2 over sham was observed regardless of patient age, gender, baseline GA characteristics, baseline BCVA, and baseline low-luminance deficit.

Multivariable analyses identified two key risk factors for GA progression: 1) baseline GA lesion location and 2) baseline low-luminance deficit. Treatment effect with APL-2 remained statistically significant when the population was controlled for these two key risk factors.

“These results are in agreement with the prior literature on risk factors for GA progression,” said Dr. Lad, who also is director of grading, Duke Reading Center. “This is an important finding, as it conclusively demonstrates that the FILLY study population was a typical GA population.”

In addition, the fact that APL-2 was beneficial in reducing GA growth, after controlling for the key risk factors for GA progression in the multivariable analysis, further reinforces the positive results from the FILLY study.

“Note that baseline BCVA dropped out as a prognostic variable, which illustrates the power of doing a multivariable analysis,” Dr. Lad explained.

Dr. Lad also commented on the strengths and limitations of the research she presented.

“The strengths are that the data come from a relatively large, prospective phase II study, in which GA progression was evaluated by an independent reading center in a masked fashion and in which visual acuity was measured by masked examiners,” she said. “Its limitations include the fact that it is a post-hoc analysis and there were small sample sizes in the subgroups.”

**CONCLUSION**
Dr. Lad noted that because of the positive results in FILLY, two phase III studies are now under way evaluating APL-2 as a treatment for GA associated with age-related macular degeneration.

---

**Risk factors for GA progression**
- Baseline GA lesion location
- Baseline low-luminance deficit

**TAKE-HOME**
- The results of the phase II FILLY study are in agreement with the prior literature on risk factors for GA progression.

---

**ELEONORA LAD, MD, PHD**

This article was adapted from Dr. Lad’s presentation at the at the 37th annual scientific meeting of the American Society of Retina Specialists. Dr. Lad is a scientific advisor to and receives research funding from Apellis and other companies that are developing treatments for dry age-related macular degeneration.
FOR ROTATIONAL STABILITY, THERE’S NO COMPARISON$^{1,2}$


Please see Important Product Information on the adjacent page.
Gene therapy for LHON: Deciphering phase III data

Primary endpoint not met, but secondary measures indicate strong efficacy

By Cheryl Gutman Krader; Reviewed by Robert C. Sergott, MD

RESCUE, THE PHASE III study investigating GS010 (GenSight Biologics) for Leber Hereditary Optic Neuropathy (LHON) due to the G11778A ND4 mitochondrial mutation in patients with up to six months of vision loss, did not meet its primary endpoint.

Data from secondary outcome measures and from a longer follow-up in RESCUE and in a completed phase III trial that enrolled patients with a longer history of vision loss (REVERSE), however, provide strong signals of efficacy, including a potential benefit in untreated fellow eyes.

ABOUT LHON

LHON is an inherited form of vision loss. Although this condition usually begins in a person’s teens or twenties, rare cases may appear in early childhood or later in adulthood. Over time, vision in both eyes worsens with a severe loss of sharpness (visual acuity) and color vision.

In most cases, symptoms begin with one eye first, followed a few weeks later by visual failure in the other eye. Extremely rarely there may be neurologic abnormalities, such as peripheral neuropathy, postural tremor, nonspecific myopathy, and movement disorders.

ACRYSOFT® IQ TORIC IOL IMPORTANT PRODUCT INFORMATION

CAUTION: Federal (USA) law restricts this device to the use by or on the order of a physician.

INDICATIONS: The AcrySof® IQ Tonic posterior chamber intraocular lenses are intended for primary implantation in the capsular bag of the eye for visual correction of aphakia and pre-existing corneal posterior sides of the lens; residual viscoelastics may allow the lens to rotate. Optical theory suggests that high astigmatic patients (i.e. > 2.5 D) may experience spatial distortions. Possible toxic IOL related factors may include residual cylindrical error or axis misalignments. Prior to surgery, physicians should provide prospective patients with a copy of the Patient Information Brochure available from Alcon for this product informing them of possible risks and benefits associated with the AcrySof® IQ Tonic Cylinder Power IOLs. Studies have shown that color vision discrimination is not adversely affected in individuals with the AcrySof® Natural IOL and normal color vision. The effect on vision of the AcrySof® Natural IOL in subjects with hereditary color vision defects and acquired color vision defects secondary to ocular disease (e.g., glaucoma, diabetic retinopathy, chronic uveitis, and other retinal or optic nerve diseases) has not been studied. Do not resterilize; do not store over 45° C; use only sterile irrigating solutions such as BSS® or BSS PLUS® Sterile Intracocular Irrigating Solutions.

ATTENTION: Reference the Directions for Use labeling for a complete listing of indications, warnings and precautions.

ACCEP TABLE SAFETY

The collective clinical trial experience also shows that the gene therapy is well-tolerated by patients and has an acceptable safety profile.

“The GS010 phase III trials are rigorously designed and conducted studies, and any well-done clinical trial often generates unexpected findings.” – Robert C. Sergott, MD

‘The GS010 phase III trials are rigorously designed and conducted studies, and any well-done clinical trial often generates unexpected findings.’

The primary outcome measure in RESCUE looked at ETDRS best corrected visual acuity (BCVA) at week 48 post-injection. To meet the primary endpoint, the results had to show a +15-letter difference in BCVA favoring the GS010-treated eyes compared to sham.

PRIMARY ENDPOINT ANALYSIS

The primary endpoint analysis showed, however, that there was essentially no difference between groups. Eyes treated with GS010 had a mean BCVA loss of 19 ETDRS letters compared with baseline while on average, sham-treated eyes had a loss of 20 ETDRS letters.

As expected and consistent with the natural history of LHON, mean BCVA in both groups declined after study entry and reached a nadir, according to the study. The GS010-treated eyes achieved a mean BCVA improvement of 13 ETDRS letters relative to the nadir while sham-treated eyes improved by a mean of 11 letters.

Gene therapy

The GS010 treated eyes showed a +15-letter improvement in visual acuity compared to the sham group at week 48.

LHON is a genetic condition affecting the optic nerve and can lead to visual loss. The GS010 gene therapy aims to improve vision in these patients.

Alcon

© 2018 Novartis    7/18    US-FOR-18-E-1605
Data from RESCUE that supports the efficacy of GS010 included the finding that GS010-treated eyes were threefold more likely than sham-treated eyes to have 20/200 or better BCVA at week 48 (p = 0.0247).

In addition, an analysis comparing outcomes between fellow eyes in individual patients showed that the change from baseline of high-contrast visual acuity was at least 0.3 LogMAR (15 ETDRS letters) better in the treated eye than in the sham-treated eye in 24% of subjects.

Researchers found that similar result was obtained in an analysis comparing improvements in low-contrast visual acuity, which is an even more sensitive measure of visual function than high-contrast visual acuity, said Dr. Sergott.

**Seeing Improvement**

At week 72, which is the second scheduled read-out of the RESCUE data, GS010-treated eyes improved by 21 ETDRS letters from nadir. According to the research team, sham-treated eyes closely tracked GS010-treated eyes, improving 21.7 ETDRS letters equivalent from nadir.

In both study groups, 40% of eyes improved by a clinically meaningful difference (+15 ETDRS letters), from nadir.

Further evidence to support the idea that a treatment benefit may be identified over time comes from the REVERSE trial that investigated GS010 in patients who had vision loss for six to 12 months before receiving treatment.

In this cohort of patients who were more likely to have entered a chronic phase of disease characterized by less rapid vision loss, BCVA improved by a mean of 11 ETDRS letters from baseline to week 48. The results were seen both in GS010-treated eyes and the sham-treated contralateral control eyes.

By week 96, BCVA in the GS010-treated eyes had improved by a mean of 15.4 ETDRS letters compared with baseline, representing a gain of 28.1 ETDRS letters relative to the worst vision.

**Interpreting the Data**

There are various factors that may explain why the RESCUE trial did not meet its primary efficacy endpoint. Premature timing of the evaluation is one possibility.

RESCUE entered patients who were early in the course of their disease when there is typically rapid neuronal degeneration and loss of vision. Because it takes time after GS010 injection for the gene to be incorporated into cells and for the cells to begin to express functioning proteins, it takes time after GS010 injection for the gene to be incorporated into cells and for the cells to begin to express functioning proteins, which is consistent with what is known about the natural history of the disease. After reaching a nadir, BCVA remained more stable in the sham-treated eyes but was on an improving trend in the GS010-treated group at the week 48 visit.

“Additional analyses of outcomes in RESCUE after 72 weeks show that the eyes are tracking together in terms of showing continuing recovery of BCVA,” Dr. Sergott said.

**Some Surprises**

While discovering BCVA improvement in sham-treated eyes in the GS010 trials was somewhat of a surprise to the research team, access of GS010 into the control eye is a more plausible explanation than spontaneous recovery, said Dr. Sergott.

“Cases of spontaneous vision improvement in patients with LHON are infrequent, and OCT imaging has shown us that from the time of onset of vision loss, there is not spontaneous structural recovery in the retina or optic nerve,” he explained.

“Defying that natural history, data from 96 weeks of follow-up in REVERSE show that the thickness of the retinal ganglion cell layer and retinal nerve fiber layer increased by 30% to 100% in some eyes treated with GS010, and the improvements are occurring bilaterally in some cases.”

**Conclusion**

Dr. Sergott also pointed out that studies of anti-VEGF therapy for retinal vascular diseases document systemic exposure to the medication after intravitreal injection and show a possible therapeutic effect in untreated fellow eyes.

“Based on neutralizing antibody measurements in the peripheral blood and transient increases in liver function tests, we know that GS010 injected into the vitreous enters the systemic circulation, indicating the possibility of its access to the contralateral eye,” he concluded.
AMD risk phenotypes targeted in direct-to-consumer genetic database

Identification of patients at high risk could aid in quicker diagnosis, better treatment

By Cheryl Guttman Krader

GENETIC TESTING CAN identify patients with high-risk genotypes for age-related macular degeneration (AMD), said Theodore Leng, MD, MS.

Dr. Leng presented the results of a national cross-sectional study that assessed the frequency of the two most common genetic variants associated with an increased risk of developing AMD—CFH Y402H and ARMS2 A69S—in a cohort of approximately 3.5 million adults who had used DTC genetic testing (23andMe) between 2013 and 2019.

Dr. Leng is assistant professor of ophthalmology and director of Clinical and Translational Research, Stanford Byers Eye Institute, Stanford University, Palo Alto, CA.

“Identification of patients with high-risk genotypes for AMD may aid in improved disease identification and monitoring for disease progression, which can facilitate earlier treatment of advanced AMD and optimize visual outcomes,” he said.

Approximately 80% of individuals genotyped during the study period gave their consent. The study population had an average age of 47.3 years and included 56% females and 44% males. Almost three-fourths of the cohort were of European descent.

The study found overall frequencies of 35.2% for the Y402H allele and 23.0% for A69S. Analyses looking at allele frequencies across genetic ancestries showed that the Y402H variant was common (~30%) across all ancestries except among East Asians, where the frequency was just 5.6%. East Asians had the highest frequency (41.6%) of the A69S allele.

“The distribution of genotypes found in our study correlates almost exactly with what would be predicted by the Hardy-Weinberg Equilibrium,” said Dr. Leng.

Connecting the dots: Genetics and impact on diabetic retinopathy

Sixty-five genes identified by researchers, with several belonging to signaling pathways

By Lynda Charters

DIABETIC RETINOPATHY (DR) is a major retinal microvascular complication of diabetes and while much is known about DR, the mechanisms underlying its etiology remain a mystery.

With this part of the puzzle still unsolved, the treatments that presently are available for DR are inadequate because they cannot reverse or prevent the ocular complications of diabetes.

Investigators from the Medical College of Georgia, Augusta University, led by Ashok Sharma, PhD, of the Center for Biotechnology and Genomic Medicine and the Department of Population Health Sciences, took the next step in the evaluation of 65 genes that had been identified in association with DR.

The genes were identified by linkage analysis, candidate gene association, and genome-wide association studies. Most of these genes that are associated with DR had been identified through candidate gene-based association studies, according to investigators.

Dr. Sharma and associates hoped that mapping them to biologic processes and pathways, they could add to the understanding of the functional role of these genes in the pathogenesis of DR.

The genetic analysis performed in the current study found that most of these genes belong to various biologic pathways that make a significant contribution to the pathogenesis of DR.

These include insulin signaling, angiogenesis (hypoxia-inducible factor-1 signaling, regulation of blood vessel size, vascular endothelial growth factor signaling), inflammation (interleukin-6 signaling, leukocyte adhesion, transforming growth factor-B, and tumor necrosis factor signaling), lipid metabolic process, neurogenesis (neural cell differentiation, neurotrophin signaling), and protein kinase signaling.

The authors added that DR is a microvascular disease of the retina and the leading cause of visual disability in patients with diabetes.
**INDICATIONS AND USAGE**

ILEVRO® (nepafenac ophthalmic suspension) 0.3% is a nonsteroidal, anti-inflammatory prodrug indicated for the treatment of pain and inflammation associated with cataract surgery.

**Dosage and Administration**

One drop of ILEVRO® 0.3% should be applied to the affected eye one-time-daily beginning 1 day prior to cataract surgery, continued on the day of surgery and through the first 2 weeks of the postoperative period. An additional drop should be administered 30 to 120 minutes prior to surgery.

**IMPORTANT SAFETY INFORMATION**

**Contraindications**

ILEVRO® 0.3% is contraindicated in patients with previously demonstrated hypersensitivity to any of the ingredients in the formula or to other nonsteroidal anti-inflammatory drugs (NSAIDs).

**Warnings and Precautions**

- **Increased Bleeding Time** – With some NSAIDs, including ILEVRO® 0.3%, there exists the potential for increased bleeding time. Ocuarly applied NSAIDs may cause increased bleeding of ocular tissues (including hyphema) in conjunction with ocular surgery.
- **Delayed Healing** – Topical NSAIDs, including ILEVRO® 0.3%, may slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.

**Adverse Reactions**

The most frequently reported ocular adverse reactions following cataract surgery occurring in approximately 5% to 10% of patients were capsular opacity, decreased visual acuity, foreign body sensation, increased intraocular pressure, and sticky sensation.

For additional information about ILEVRO® 0.3%, please refer to the Brief Summary of Prescribing Information on the adjacent page.

**ACTIVATE SAVINGS FOR ILEVRO® SUSPENSION**

For as little as $15, eligible patients can access proven efficacy for post–cataract-surgery pain and inflammation.2-4

- Ocular pain completely resolved in 84% to 86% of patients at day 14.1,3,5
- Inflammation completely cleared in 61% to 65% of patients at day 14.1,3,5

ILEVRO® Suspension is the only prodrug NSAID formulated for once-daily post-op use.2-4-6

- ILEVRO® Suspension should be applied to the affected eye one-time-daily beginning 1 day prior to cataract surgery, continued on the day of surgery and through the first 2 weeks of the postoperative period. An additional drop should be administered 30 to 120 minutes prior to surgery.2
- Use of ILEVRO® Suspension more than 1 day prior to surgery or use beyond 14 days post surgery may increase patient risk and severity of corneal adverse events.2

**Terms and Conditions:** Limitations apply. Eligible, commercially insured patients may pay as little as $15 in out-of-pocket expenses for each 3-mL or 1.7-mL bottle of ILEVRO® 0.3%, with a maximum benefit per bottle of $285. This offer is not valid under Medicare, Medicaid, or any other federal or state program. See additional terms and conditions at www.copay.novartispharma.com.

**Study Design:** Results from 2 randomized, multicenter, controlled, double-masked trials of adult patients undergoing cataract extraction. In Study 1, patients were randomized to receive either ILEVRO® Suspension (n=851), NEVANAC® Suspension (n=845), ILEVRO® Suspension vehicle (n=211), or NEVANAC® Suspension vehicle (n=213). In Study 2, patients were randomized to receive either ILEVRO® Suspension (n=540) or ILEVRO® Suspension vehicle (n=286).1,3

161% to 65% with ILEVRO® Suspension versus 24% to 32% with vehicle; P<0.05.
184% to 86% with ILEVRO® Suspension versus 38% to 46% with vehicle; P<0.05.

**References:**

ILEVRO* (nepafenac ophthalmic suspension) 0.3%, topical ophthalmic

Initial U.S. Approval: 2005

BRIEF SUMMARY: Please see package insert for full prescribing information.

1 INDICATIONS AND USAGE
ILEVRO* 0.3% is indicated for the treatment of pain and inflammation associated with cataract surgery.

2 CONTRAINDICATIONS
ILEVRO* 0.3% is contraindicated in patients with previously demonstrated hypersensitivity to any of the ingredients in the formula or to other nonsteroidal anti-inflammatory drugs (NSAIDs).

3 WARNINGS AND PRECAUTIONS
5.1 Increased Bleeding Time
With some NSAIDs including ILEVRO* 0.3%, there is the potential for increased bleeding time due to interference with thromboxane aggregation. There have been reports that orally applied nonsteroidal anti-inflammatory drugs may cause increased bleeding of ocular tissues (including hyphema) in conjunction with oculary surgery. It is recommended that ILEVRO* 0.3% be used with caution in patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time.

5.2 Delayed Healing
Topical NSAIDs including ILEVRO* 0.3%, may slow or delay healing. Topical corticosteroids are also known to slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.

5.3 Corneal Effects
Use of topical NSAIDs may result in keratitis. In some susceptible patients, continued use of topical NSAIDs may result in epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration, or corneal perforation. These events may be sight threatening. Patients with evidence of corneal epithelial breakdown should immediately discontinue use of topical NSAIDs including ILEVRO* 0.3% and should be closely monitored for corneal health.

Postmarketing experience with topical NSAIDs suggests that patients with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface diseases (e.g., dry eye syndrome), rheumatoid arthritis, or repeat ocular surgeries within a short period of time may be at increased risk for corneal adverse events, which may become sight threatening. Topical NSAIDs should be used with caution in these patients.

Postmarketing experience with topical NSAIDs also suggests that use more than 1 day prior to surgery or use beyond 14 days post-surgery may increase patient risk and severity of corneal adverse events.

5.4 Contact Lens Wear
ILEVRO* 0.3% should not be administered while using contact lenses.

6 ADVERSE REACTIONS
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 the rates in the clinical studies of another drug and may not reflect the rates observed in practice.

6.1 Serious and Otherwise Important Adverse Reactions
The following adverse reactions are discussed in greater detail in other sections of labeling:
- Increased Bleeding Time [see Warnings and Precautions (5.1)]
- Delayed Healing [see Warnings and Precautions (5.2)]
- Corneal Effects [see Warnings and Precautions (5.3)]

6.2 Ocular Adverse Reactions
The most frequently reported ocular adverse reactions following cataract surgery were capsular opacity, decreased visual acuity, foreign body sensation, increased intraocular pressure (IOP), and sticky sensation. These reactions occurred in approximately 5% to 10% of patients.

Other ocular adverse reactions occurring at an incidence of approximately 1% to 5% included conjunctival edema, corneal edema, dry eye, lid margin crusting, ocular discomfort, ocular hyperemia, ocular pain, ocular pruritus, photophobia, tearing, and vitreous detachment.

Some of these reactions may be the consequence of the cataract surgical procedure.

6.3 Non-Ocular Adverse Reactions
Non-ocular adverse reactions reported at an incidence of 1% to 4% included headache, hypertension, nausea/vomiting, and sinusitis.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Teratogenic Effects
Pregnancy Category C: Reproduction studies performed with nepafenac in rabbits and rats at oral doses up to 10 mg/kg/day have revealed no evidence of teratogenicity due to nepafenac, despite the induction of maternal toxicity. At this dose, the animal plasma exposure to nepafenac and amfenac was approximately 70 and 630 times human plasma exposure at the recommended human topical ophthalmic dose for rats and 20 and 180 times human plasma exposure for rabbits, respectively. In rats, maternally toxic doses greater than or equal to 10 mg/kg were associated with dystocia, increased postimplantation loss, reduced fetal weights and growth, and reduced fetal survival.

Nepafenac has been shown to cross the placental barrier in rats. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, ILEVRO* 0.3% should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Non-teratogenic Effects
Because of the known effects of prostaglandin biosynthesis inhibiting drugs on the fetal cardiovascular system (closure of the ductus arteriosus), the use of ILEVRO* 0.3% during late pregnancy should be avoided.

8.3 Nursing Mothers
Nepafenac is excreted in the milk of lactating rats. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ILEVRO* 0.3% is administered to a nursing woman.

8.4 Pediatric Use
The safety and effectiveness of ILEVRO* 0.3% in pediatric patients below the age of 18 years have not been established.

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

ACUPRIDE®
a Novartis Company

Distributed by:
Alcon Laboratories, Inc.
Fort Worth, Texas 76134 USA
©2014, 2019 Novartis
*trademark of Novartis
T2019-21
Migraine affects 12% of the population, and is the third most prevalent illness in the world. It has been associated with stroke and myocardial infarction, as well as retinal vessel occlusion, ischemic optic neuropathy and normal tension glaucoma, according to Alexander Barash, MD, New York Medical Care.

Dr. Barash pointed out that these associations are stronger for those patients who have migraine with aura than without aura.

Whether or not migraine can significantly increase the risk of developing primary open-angle glaucoma remains controversial.

Aura (which includes visual disturbances and/or other neurologic symptoms) occurs in about 25% of patients who experience migraine, and it is often a primary cause for referral to an ophthalmologist.

“During aura, there are changes in the cerebral blood flow,” he said, noting that people who have migraine also have brains that are more easily damaged, and they need a higher blood flow to survive focal ischemia.

The pattern of migraine aura cannot be fully explained by changes in cerebral blood flow, and the areas of decreased blood flow do not directly correspond to the cortical areas responsible for the aura.

“Aura may indicate more severe ischemia that predisposes to complications,” Dr. Barash said.

Using optical coherence tomography angiography (OCT-A), Dr. Barash and colleagues aimed to identify changes to macular and peripapillary retinal perfusion during migraine with aura.

“We wanted to know what happens to retinal perfusion during migraine,” he said.

For the study, Dr. Barash recruited three male patients who had migraine with aura. Patients underwent 3 x 3 mm and 6x6 mm macular and 4.5 x 4.5 mm optic nerve head OCT-A scans in both eyes during a baseline day without migraine, and during five episodes of aura and immediate post-aural migraine.

The analysis included angiographic densities of macular superficial and deep capillary layers, and the radial peripapillary capillary layer.

Patients who experienced migraine without aura were not included in the study, according to Dr. Barash.

“During aura, there are changes in the cerebral blood flow,”

— Alexander Barash, MD

Images demonstrate overall macular perfusion density at baseline, during aura, and a migraine. The overall density decreases during post-aural migraine. Researchers are trying to determine whether migraine can increase the risk for developing primary open-angle glaucoma, an idea that remains controversial.

(0.01996).

The overall perfusion density was significantly decreased during post-aural migraine as compared to that of aura in both the superficial and deep macula on 6x6 mm scans (p=0.00689, respectively), and the deep macula on 3x3 mm (p=0.01996).

We wanted to know what happens to retinal perfusion during migraine,” he said.

For the study, Dr. Barash recruited three male patients who had migraine with aura. Patients underwent 3 x 3 mm and 6x6 mm macular and 4.5 x 4.5 mm optic nerve head OCT-A scans in both eyes during a baseline day without migraine, and during five episodes of aura and immediate post-aural migraine.

The analysis included angiographic densities of macular superficial and deep capillary layers, and the radial peripapillary capillary layer.

Patients who experienced migraine without aura were not included in the study, according to Dr. Barash.

“We wanted to know what happens to retinal perfusion during migraine,” he said.

For the study, Dr. Barash recruited three male patients who had migraine with aura. Patients underwent 3 x 3 mm and 6x6 mm macular and 4.5 x 4.5 mm optic nerve head OCT-A scans in both eyes during a baseline day without migraine, and during five episodes of aura and immediate post-aural migraine.

The analysis included angiographic densities of macular superficial and deep capillary layers, and the radial peripapillary capillary layer.

Patients who experienced migraine without aura were not included in the study, according to Dr. Barash.

“We wanted to know what happens to retinal perfusion during migraine,” he said.

For the study, Dr. Barash recruited three male patients who had migraine with aura. Patients underwent 3 x 3 mm and 6x6 mm macular and 4.5 x 4.5 mm optic nerve head OCT-A scans in both eyes during a baseline day without migraine, and during five episodes of aura and immediate post-aural migraine.

The analysis included angiographic densities of macular superficial and deep capillary layers, and the radial peripapillary capillary layer.

Patients who experienced migraine without aura were not included in the study, according to Dr. Barash.

“We wanted to know what happens to retinal perfusion during migraine,” he said.

For the study, Dr. Barash recruited three male patients who had migraine with aura. Patients underwent 3 x 3 mm and 6x6 mm macular and 4.5 x 4.5 mm optic nerve head OCT-A scans in both eyes during a baseline day without migraine, and during five episodes of aura and immediate post-aural migraine.

The analysis included angiographic densities of macular superficial and deep capillary layers, and the radial peripapillary capillary layer.

Patients who experienced migraine without aura were not included in the study, according to Dr. Barash.

“We wanted to know what happens to retinal perfusion during migraine,” he said.

For the study, Dr. Barash recruited three male patients who had migraine with aura. Patients underwent 3 x 3 mm and 6x6 mm macular and 4.5 x 4.5 mm optic nerve head OCT-A scans in both eyes during a baseline day without migraine, and during five episodes of aura and immediate post-aural migraine.

The analysis included angiographic densities of macular superficial and deep capillary layers, and the radial peripapillary capillary layer.

Patients who experienced migraine without aura were not included in the study, according to Dr. Barash.

“We wanted to know what happens to retinal perfusion during migraine,” he said.

For the study, Dr. Barash recruited three male patients who had migraine with aura. Patients underwent 3 x 3 mm and 6x6 mm macular and 4.5 x 4.5 mm optic nerve head OCT-A scans in both eyes during a baseline day without migraine, and during five episodes of aura and immediate post-aural migraine.

The analysis included angiographic densities of macular superficial and deep capillary layers, and the radial peripapillary capillary layer.

Patients who experienced migraine without aura were not included in the study, according to Dr. Barash.
In PANORAMA, EYLEA significantly improved DR severity scores at week 52

Proportion of patients achieving a ≥2-step improvement in ETDRS-DRSS* score from baseline (primary endpoint)†‡

- **EYLEA 2 mg every 8 weeks† (n=134)**: 80%‡ of patients
- **EYLEA 2 mg every 16 weeks‡ (n=135)**: 65%‡ of patients
- **sham (n=133)**: 15%‡ of patients

The percentage of patients with a ≥2-step improvement on the ETDRS-DRSS from baseline at 100 weeks was 38%, 38%, and 16% in VISTA and 32%, 28%, and 7% in VIVID with EYLEA 2 mg every 8 weeks after 5 initial monthly doses, EYLEA 2 mg every 4 weeks, and control, respectively (secondary endpoint).†

PANORAMA study design: Multicenter, double-masked, controlled study in which patients with moderately severe to severe NPDR (ETDRS-DRSS: 47 or 53) without central-involved DME (CI-DME) (N=402; age range: 25-85 years, with a mean of 56 years) were randomized to receive 1) 3 initial monthly EYLEA 2 mg injections, followed by 1 injection after 8 weeks and then 1 injection every 16 weeks; 2) 5 initial monthly EYLEA 2 mg injections, followed by 1 injection every 8 weeks; or 3) sham treatment. Protocol-specified visits occurred every 28±7 days for the first 5 visits, then every 8 weeks. The primary efficacy endpoint was the proportion of patients who improved by ≥2 steps on the ETDRS-DRSS from baseline to week 24 in the combined EYLEA groups vs sham and at week 52 in the EYLEA 2 mg every-16-week and EYLEA 2 mg every-8-week groups individually vs sham. A secondary endpoint was the proportion of patients developing the composite endpoint of proliferative DR (PDR) or anterior segment neovascularization.

VISTA and VIVID study designs: Two randomized, multicenter, double-masked, controlled studies in which patients with DME (N=862; age range: 23-87 years, with a mean of 63 years) were randomized and received 1) EYLEA 2 mg administered every 8 weeks following 5 initial monthly doses; 2) EYLEA 2 mg administered every 4 weeks; or 3) macular laser photocoagulation (control), at baseline and then as needed. Protocol-specified visits occurred every 28±7 days. In both studies, efficacy endpoints included the mean change from baseline in best-corrected visual acuity (BCVA), as measured by ETDRS letters, at 52 weeks (primary endpoint) and 100 weeks (secondary endpoint).

INDICATIONS AND IMPORTANT SAFETY INFORMATION

**INDICATIONS**

EYLEA is indicated for the treatment of patients with Neovascular (Wet) Age-related Macular Degeneration (AMD), Macular Edema following Retinal Vein Occlusion (RVO), Diabetic Macular Edema (DME), and Diabetic Retinopathy (DR).

**CONTRAINDICATIONS**

- EYLEA is contraindicated in patients with ocular or periocular infections, active intraocular inflammation, or known hypersensitivity to aflibercept or to any of the excipients in EYLEA.

*Early Treatment Diabetic Retinopathy Study–Diabetic Retinopathy Severity Scale: An established grading scale for measuring the severity of DR.
†Full analysis set.
‡3 initial monthly injections, followed by 1 injection after 8 weeks and then 1 injection every 16 weeks.
§5 initial monthly injections, followed by 1 injection every 8 weeks.

EYLEA is a registered trademark of Regeneron Pharmaceuticals, Inc.

**REGENERON**

© 2019, Regeneron Pharmaceuticals, Inc. All rights reserved.
777 Old Saw Mill River Road, Tarrytown, NY 10591
EYLEA can help prevent DR vision-threatening complications that can lead to blindness¹

Significantly fewer patients developed PDR or ASNV with EYLEA at week 52²

Composite endpoint of patients who developed PDR or ASNV at week 52 (event rates) (secondary endpoint)³⁺

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Event Rate (%)</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>EYLEA 2 mg every 8 weeks⁴</td>
<td>2.4%‡</td>
<td>0.12</td>
</tr>
<tr>
<td>EYLEA 2 mg every 16 weeks⁵</td>
<td>4.0%‡</td>
<td>0.15</td>
</tr>
<tr>
<td>sham (n=133)</td>
<td>20.1%</td>
<td></td>
</tr>
</tbody>
</table>

*P<0.01 vs sham.

All patients were treatment-naïve to focal or grid laser photocoagulation, panretinal photocoagulation, and any anti–vascular endothelial growth factor (anti-VEGF) treatment.² Composite endpoint of developing PDR or anterior segment neovascularization (ASNV) was diagnosed by either the reading center or investigator through week 52. Event rate was estimated using the Kaplan-Meier method.³

WARNINGS AND PRECAUTIONS

- Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately. Intraocular inflammation has been reported with the use of EYLEA.
- Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with VEGF inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately.
- There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA compared with 1.5% (9 out of 595) in patients treated with ranibizumab; through 96 weeks, the incidence was 3.3% (60 out of 1824) in the EYLEA group compared with 3.2% (19 out of 595) in the ranibizumab group. The incidence in the DME studies from baseline to week 52 was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

ADVERSE REACTIONS

- Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment.
- The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and intraocular pressure increased.

Please see Brief Summary of Prescribing Information on the following pages.

Table 2: Most Common Adverse Reactions (% in RVO Studies)

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>EYLEA (N=218)</th>
<th>CRVO (N=194)</th>
<th>Control (N=182)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conjunctival hemorrhage</td>
<td>25%</td>
<td>28%</td>
<td>27%</td>
</tr>
<tr>
<td>Injection site pain</td>
<td>2%</td>
<td>4%</td>
<td>6%</td>
</tr>
<tr>
<td>Injection site hemorrhage</td>
<td>3%</td>
<td>2%</td>
<td>4%</td>
</tr>
<tr>
<td>Vitreous detachment</td>
<td>3%</td>
<td>5%</td>
<td>6%</td>
</tr>
<tr>
<td>Retinal pigmentation</td>
<td>3%</td>
<td>1%</td>
<td>3%</td>
</tr>
<tr>
<td>Retinal detachment</td>
<td>4%</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>Local reaction</td>
<td>2%</td>
<td>3%</td>
<td>4%</td>
</tr>
<tr>
<td>Local reaction</td>
<td>3%</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Local reaction</td>
<td>2%</td>
<td>2%</td>
<td>2%</td>
</tr>
</tbody>
</table>

Table 3: Most Common Adverse Reactions (% in DME Studies)

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>Baseline to Week 52</th>
<th>Baseline to Week 100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conjunctival hemorrhage</td>
<td>15%</td>
<td>10%</td>
</tr>
<tr>
<td>Injection site pain</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Injection site hemorrhage</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>Vitreous detachment</td>
<td>3%</td>
<td>5%</td>
</tr>
<tr>
<td>Retinal pigmentation</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Local reaction</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Local reaction</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Local reaction</td>
<td>1%</td>
<td>1%</td>
</tr>
</tbody>
</table>

Less common adverse reactions reported in <1% of the patients treated with EYLEA were hypereosinophilia, retinal edema, and conjunctival hemorrhage.
Budding technology could be an OCT analysis game-changer
Performance of emerging option for physicians promising in initial application

By Cheryl Guttman Krader; Reviewed by Justis P. Ehlers, MD

A CUTTING-EDGE IMAGE analysis platform for higher order OCT analysis successfully extracted novel fluid features and evaluated them for resolution extent and tempo, reported Justis P. Ehlers, MD.

“Current conventional OCT metrics used in most clinical trials are limited to global measures of retina thickness, retinal volume or perhaps manual linear measurements of areas of interest,” said Dr. Ehlers, Norman C. and Donna L. Harbert Endowed Chair of Ophthalmic Research at the Cole Eye Institute, Cleveland Clinic, Cleveland, OH.

“New tools for higher-order OCT assessment enables in-depth evaluation of more specific features of interest, such as targeted retinal layers or fluid compartments, and may allow for unique characterization of disease phenotypes and treatment response,” he noted.

EMERGING TECHNOLOGY
Dr. Ehlers also explained that this is an emerging technology in ophthalmology.

“Further research is currently ongoing, including for subretinal material and sub-RPE feature extraction and layer-based assessment,” he pointed out. “In addition, subvacular feature and radiomics interrogation of these data-rich images may provide unique insights into disease process and prognosis. Ultimately, these approaches may lead to the identification of imaging biomarkers for predicting optimal response to therapeutics, best dosing regimens, and overall prognosis.”

According to Dr. Ehlers, the novel analysis was applied to OCT scans that were collected in OSPREY, a 56-week, phase II study comparing brolucizumab (Novartis) and aflibercept (Eylea, Regeneron) for the treatment of neovascular AMD.

MATCHED TREATMENT
The study began with a matched treatment period during which both anti-VEGF agents were given as three monthly loading doses and then every eight weeks through week 32. For the final brolucizumab dosing cycle, the treatment interval was extended to 12 weeks.

For the novel OCT analysis, macular cube scans were uploaded into the software platform and segmented using an automated expert reader then validated the segmentation accuracy.

The software analyzed volume and area of macular fluid within the intraretinal and subretinal fluid compartments.

REDUCTIONS
The research team noted that analyses of the scans collected during the matched Q8 week treatment phase showed dramatic reductions over the course of the study in both intraretinal fluid volume and subretinal fluid volume with both anti-VEGF agents and a similar effect between brolucizumab Q12 week dosing and aflibercept Q8 week dosing.

“These findings from the preliminary assessments are consistent with the previously published anatomic data from the phase II OSPREY study,” Dr. Barash noted that while he did not account for potential medication use, “it would be interesting to see what the results might be if patients are on vasodilators.”

Dr. Barash also acknowledged that future studies should also include females, as migraine tends to affect more women than men (with studies showing a lifetime prevalence of 43% for women—about 28 million women in the U.S. alone—and only 18% for men).

The small number of patients in this study did not allow for statistical comparison of concordance between the eyes, but Dr. Barash said he hopes larger studies will allow for proper powering.

Panelists J. Fernando Arevalo, MD, PhD, FACS, Johns Hopkins University; and Michael S. Ip, MD, Doheny Eye Institute, said they don’t often see patients with migraine.

However, while the data is interesting, neither panelist said it would alter their current treatments for patients with retinal vein occlusion or glaucoma.

REFERENCES:
1. Migraine Research Foundation. About Migraine. Available at: https://migraineresearchfoundation.org/about-migraine/migraine-facts/

ALEXANDER BARASH, MD
p: 212/243-2300
This article is derived from Dr. Barash’s presentation at the 2019 American Society of Artioa Specialists annual meeting in Chicago. He has no financial disclosures.
Gaining clinical insights via view of retinal epithelial tears

Technology helping physicians can monitor patients for maximum analysis

By Vanessa Caceres; Reviewed by Nicole Eter, MD

CHOROIDAL NEOVASCULARIZATION beneath the retinal pigment epithelium (RPE) can best be detected by indocyanine green angiography, spectral-domain-OCT, and OCT-angiography (OCT-A), according to Nicole Eter, MD, professor and chairperson, Department of Ophthalmology, and vice dean of clinical affairs, medical faculty, University of Muenster, Muenster, Germany.

Dr. Eter shared several clinical insights relevant to retinal pigment epithelial detachment (PED), which occurs with various retinal diseases, including exudative age-related macular degeneration (AMD).

“They’re a very heterogeneous cluster and have been excluded from the majority of randomized clinical trials,” she explained.

Some variants of AMD-associated pigment epithelial detachments include drusenoid PED, serous avascular and serous vascular PED, and fibrovascular PED, the last two of which are considered vascularized PED.

OCT-A has made it easier for clinicians to scan layer by layer for neovascularization. OCT-A has proven the existence of purely serous PED without CNV, and by layer for neovascularization. OCT-A has proven the existence of purely serous PED without CNV, and by layer for neovascularization.

The right imaging helps to determine the extent of CNV under the RPE. OCT-A has proven the existence of purely serous PED without CNV, and by layer for neovascularization.

The RPE tear was opposite of hyperreflective lines and at the margin of the PED detachment in most cases. After more anti-VEGF treatment, fundus autofluorescence had lowered, and SD-OCT showed the absence of the RPE in the area of the RPE tear.

The researchers identified several risk factors for PEDs, including PED lesion height, PED lesion diameter, subretinal clefts, microrips, duration of PED, and a small ratio of CNV size to PED size.

Although persistent subretinal fluids status post-tear appears to lead to subsequent repair with a thickened proliferative tissue at the area of RPE loss, enlargement has been observed in some cases. In a review, follow-up measurements of unilobular PED tears in eight patients showed no change in lesion area size (0.14 ± 0.33 mm), Dr. Eter said. The multilobular PED tears in three patients showed a progression in lesion area size of 1.80 ± 0.74 mm.

“Due to further shrinkage, the tears grew larger,” Dr. Eter said, cautioning that multilobular tears should not be treated further with anti-VEGF due to the potential danger of progression.

The analysis platform also could generate novel parameters, such as “true zero” fluid or “anatomically minimal fluid” (i.e., real-world dry retinas), and retinal fluid index (i.e., percentage of total retinal volume composed of intraretinal fluid).

The analysis platform also could generate novel parameters, such as “true zero” fluid or “anatomically minimal fluid” (i.e., real-world dry retinas), and retinal fluid index (i.e., percentage of total retinal volume composed of intraretinal fluid).

According to Dr. Ehlers, the research opens new horizons for physicians to understand and have access to the latest imaging techniques, ensuring they can provide the best outcomes for their patients going forward.

“These new parameters could provide new insights about the rate and extent of fluid resolution, differential responses between anti-VEGF agents, and prognostic markers,” he concluded. “Targeted computational feature analysis in age-related macular degeneration, diabetic macular edema, and other retinal diseases may enable image-based phenotyping for risk-stratification and precision decision making.”

OCT ANALYSIS

( Continued from page 43)

Ehlers explained. “This exploratory post hoc analysis was not powered to demonstrate statistical significance. Further validation studies are needed using larger datasets.”

POWERFUL POTENTIAL

Dr. Ehlers further explained that analysis platform has the capability of analyzing proportional reduction of volumes.

CONCLUSION

According to Dr. Ehlers, the research opens new horizons for physicians to understand and have access to the latest imaging techniques, ensuring they can provide the best outcomes for their patients going forward.

“These new parameters could provide new insights about the rate and extent of fluid resolution, differential responses between anti-VEGF agents, and prognostic markers,” he concluded. “Targeted computational feature analysis in age-related macular degeneration, diabetic macular edema, and other retinal diseases may enable image-based phenotyping for risk-stratification and precision decision making.”

JUSTIS P. EHLLERS, MD

E: justis.p.ehlers@gmail.com

This article was adapted from Dr. Ehlers’ presentation at the 2019 meeting of the American Academy of Ophthalmology. Dr. Ehlers has no related disclosures.

NICOLE ETER, MD

E: eter@uni-muenster.de

This article is adapted from Dr. Eter’s presentation at the Retina Subspecialty Day at the annual meeting of the American Academy of Ophthalmology. Dr. Eter has no related disclosures.

SEPTEMBER 1, 2019 :: Ophthalmology Times
Let Us Be Your Eyes and Ears

Introducing EyePod: Podcasts from *Ophthalmology Times*

This new audible resource from *Ophthalmology Times* engages with key opinion leaders in interviews about the latest innovations in the areas of surgery, clinical diagnosis, pharmaceutical advancements, research, and technology, plus practice management.

Hear the voices of ophthalmic innovation.

[OphthalmologyTimes.com/EyePod]
In this experimental study, the investigators sought to evaluate and compare the inhibitory effects of topical high-dose, low-dose, and subconjunctival bevacizumab on corneal vascularization in a rat model. The 20 male animals were divided into four groups for this project. The first had controls that were treated with only topical artificial tears. In the second, the subconjunctival injection group was treated with 0.05 ml of bevacizumab on days one, four and seven. In a third, the low-dose topical bevacizumab group, a dose of 4 mg/ml was given twice daily. The fourth group, the high-dose topical bevacizumab group, received 12.5 mg/ml twice daily. (Photos courtesy of Yonca A. Akova, MD, FEBO)

**TEST GROUPS**
The animals were divided into four groups. The first had controls that were treated with only topical artificial tears twice daily. In the second, the subconjunctival injection group was treated with 0.05 ml (1.25 mg) of bevacizumab on days 1, 4, and 7. In the third group, the low-dose topical bevacizumab group that was treated with a dose of 4 mg/ml twice daily.

Researchers sought to evaluate and compare the inhibitory effects of topical high-dose, low-dose and subconjunctival bevacizumab on corneal vascularization in rats and because of that might ultimately be useful for treating corneal neovascularization in humans, according to Yonca A. Akova, MD, FEBO.

**take-home**
- Topical and subconjunctival administration of bevacizumab reduced the sizes of the areas of corneal neovascularization in a rat model.

**‘Clinical use of bevacizumab may have an additional effect in the treatment of neovascularization.’**

— Yonca A. Akova, MD, FEBO

Topical and subconjunctival administration of bevacizumab (Avastin, Genentech Inc.) reduced experimental corneal vascularization in rats and because of that might ultimately be useful for treating corneal neovascularization in humans, according to Yonca A. Akova, MD, FEBO.
The animals were sacrificed and the eyes enucleated 10 days after the procedure, and the corneas were removed and examined histopathologically.

**STUDY RESULTS**
The results of the corneal histologic examination showed that the active treatment groups, i.e., groups two, three, and four, fared significantly better than the control group.

The mean percentages of the neovascularized corneal areas in groups one, two, three and four, respectively, were 63.32%, 30.22%, 26.76%, and 25.52%, differences that reached significance (p < 0.01 for all comparisons), Dr. Akova reported.

“Bevacizumab is able to inhibit corneal angiogenesis, without any differences seen in this effect when the route of administration was changed from topical to subconjunctival and when the topical dosage was increased from 4 mg/ml to 12.5 mg/ml,” Dr. Akova commented.

**RESULTS**

<table>
<thead>
<tr>
<th>Control Group</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean percentage of neovascularized corneal area (%)</td>
<td>63.32 ± 13.10</td>
<td>30.22 ± 15.73</td>
<td>26.76 ± 10.23</td>
</tr>
<tr>
<td>p value</td>
<td>&lt; 0.01</td>
<td>&lt; 0.01</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

The study results led to several conclusions. ‘Clinical use of bevacizumab may have an additional effect in the treatment of corneal neovascularization.’

— Yonca A. Akova, MD, FEBO

Researchers noted. “Clinical use of bevacizumab may have an additional effect in the treatment of corneal neovascularization.”

Both topical and subconjunctival application of bevacizumab reduces experimental corneal vascularization significantly compared to the control group. Clinical use of bevacizumab may have an additional effect in the treatment for corneal neovascularization.

(Photos courtesy of Yonca A. Akova, MD, FEBO)
Novel ocular bandage gel for topical use on pathway to regulatory approval

Hyaluronic acid-based drops show promise for promoting corneal epithelial wound repair

By Cheryl Guttman Krader

A NOVEL DEVICE being developed as a treatment for punctate epitheliopathies (PE) and corneal wounds continues to progress along the clinical trial pathway leading to regulatory approval. Known as the ocular bandage gel (OBG, EyeGate Pharma), the product is a novel cross-linked thiolated carboxymethyl hyaluronic acid (CMHA-S) liquid gel.

“Hyaluronic acid is known to have lubricant, wound healing, and hydrating properties, and it is familiar to ophthalmologists as an ophthalmic viscosurgical device, an inactive ingredient in artificial tears sold in the United States, and a standard of care treatment for dry eye disease and corneal repair in countries outside the United States,” said Stephen From, chief executive officer, EyeGate Pharma, Waltham, MA.

“Our aim is to bring into the U.S. market the first pure preservative-free HA product for topical ophthalmic use, the first topical ophthalmic product with an indication for treating PE, and the first topical ophthalmic product indicated for healing corneal wounds,” he said.

DESIRABLE CHARACTERISTICS. The proprietary covalent crosslinking process confers the HA-based product with unique physico-chemical properties that offer advantages associated with enhanced performance. The crosslinking creates a stable hydrogel that resists degradation and interacts with mucins and ions on the ocular surface leading to a prolonged non-blurring residence time.

From noted. “The covalent crosslinking limits HA degradation, and because our product is not metabolized to chemically active byproducts, is non-immunogenic, and does not achieve its intended purposes through chemical actions, it can be developed as a device rather than as a pharmaceutical product.”

Another desirable attribute, the cross-linked HA has a high shear thinning rate. Consequently, the viscous OBG is easily dispensed as a liquid when the drop is squeezed out of the bottle tip, and it spreads quickly and evenly over the ocular surface without causing blur when subjected to the force of the blinking lid.

“As a natural lubricant and because of its high shear thinning rate, OBG is very comfortable and soothing on the eye and will fulfill a significant clinical unmet need in ophthalmology in the United States,” said Barbara Wirostko, MD, chief medical officer of EyeGate Pharma and adjunct professor of ophthalmology, University of Utah.

CLINICAL USES. The potential to use OBG to promote corneal wound repair and manage corneal epithelial defects is based on its ability to coat the ocular surface and provide a protective hydrating mechanical barrier that facilitates and accelerates reepithelialization. To date, two pilot trials have been from both studies were the basis for an ongoing pivotal trial that will be used to support FDA approval for a wound repair indication. The pivotal trial intends to enroll 270 patients.

From pointed out that the PRK population is being investigated as a model for the wound healing indication. PRK involves controlled mechanical removal of corneal epithelium with subsequent excimer laser photobleaching of the underlying Bowman’s layer and anterior stroma, including the subepithelial nerve plexus.

Corneal wounds created while performing PRK are an excellent model for other epithelial defects, as these patients undergo the creation of large 8 to 9 mm epithelial defects following a standardized protocol to perform refractive laser surgery.

“The PRK procedure creates a large standardized wound at baseline and thus enables one to follow these defects in a methodical manner over days,” he explained. “Furthermore, time to closure is a very objective observation and can be recorded with images. We believe, however, that OBG would have benefits for promoting reepithelialization of other sizes and types of corneal wounds.”

A PILOT STUDY. A first pilot study investigating OBG for accelerating reepithelialization after PRK enrolled patients undergoing bilateral surgery.

A total of 39 patients were randomly placed into three groups: The first group received a BCL and used OBG four times a day; the second group used OBG four times a day; and the third group received a BCL and used artificial tears four times daily.

Patients were followed from the time of corneal reepithelialization. By day three post PRK, 54.5% of eyes in Group 1, 80% of eyes in Group 2, and 45.5% of eyes in Group 3 had achieved reepithelialization.

Analyses of epithelial defect measurements obtained on day one after surgery further demonstrated the benefit of OBG to accelerate healing as early as day one. On postop day one, horizontal and vertical defect lengths were 37% and
29% smaller, respectively, in Group 2 eyes that were treated only with the OBG drops compared with the controls in Group 3 that were managed with a BCL and artificial tears.

Patients in the study assigned to use OBG continued treatment for 14 days.

During the study, the investigational product was well-tolerated and was not associated with any safety concerns.

Adverse events associated with redundant epithelium and recurrent corneal erosions were not observed in the eyes treated with the OBG alone but occurred in eyes in both groups that received a BCL.

Enrollment in a second pilot study investigating OBG for treatment of PE was expected to begin at the end of August.

The first pilot study evaluated both sign and symptom endpoints. Patients were evaluated after seven, 14, and 28 days, and statistically significant differences favoring OBG for greater symptom improvement measured with the SPEED questionnaire were observed on days seven and 28.

No statistically significant differences between groups were found in changes in total corneal staining, but there was a large numeric difference favoring OBG in the analysis of central corneal staining.

"Improvement in staining of the central cornea is especially important because of the impact of central epitheliopathy on vision," From said. "Considering that epithelial nerve density is highest in the central cornea, the numeric treatment-related difference in reduction in staining observed in the study is also consistent with the statistically significant difference recorded in symptoms."

**FUTURE PLANS**

EyeGate is also working on the development of combination products that incorporate OBG with a fluoroquinolone or an anti-inflammatory agent.

The idea behind the combination fluoroquinolone product is that antibiotic treatment is standard of care for managing corneal wounds. The anti-inflammatory combination would be intended for use in the management of more severe dry eye disease for which treatment with anti-inflammatory medications is generally recommended.

Crosslinked CMHA-S is sold globally as a product for veterinary use [Remend Corneal Repair Gel (Bayer Animal Health) and Aptus (Orion Pharmaceuticals)] in the management of superficial corneal ulcers.

---

**Cutting corners before cutting corneas?**

If you haven’t been testing for MMP-9 you might be.

If elevated MMP-9, a key inflammatory biomarker for dry eye, is tested for and detected prior to surgery, you have an opportunity to customize your treatment plan which may improve post-surgical outcomes and reduce complications.

InflammaDry, the one-and-only rapid point-of-care test that detects MMP-9

- CLIA waived
- Results in minutes
- 4 simple steps
- Minimally invasive
- Requires no special equipment

Stop cutting corners and start testing with InflammaDry today. Contact your Quidel Account Manager at 800.874.1517.

---

**STEVEN FROM**

E: sfrom@eyegatepharma.com

From is CEO of EyeGate.
DALK procedure moves to forefront as innovations overcome hurdles

Intraoperative OCT, femtosecond laser may make it more consistently predictable

By Cheryl Guttman Krader; Reviewed by Marjan Farid, MD

DEEP ANTERIOR LAMELLAR keratoplasty (DALK) has well-recognized advantages compared with penetrating keratoplasty when transplantation is needed in eyes with anterior corneal disease.

However, the difficulty of bar- ing Descemet’s membrane without perforating it using the big-bubble technique has limited DALK uptake by corneal surgeons.

Intraoperative OCT combined with the use of the femtosecond laser can enable successful completion of the big-bubble dissec- tion by improving visualization and predictability of the depth of the stromal layers. In the future, the femtosecond laser may also be used to precisely make a smooth deep lamellar dissection, thereby obviating the need for the big-bubble, said Marjan Farid, MD.

“Further exploration and advocacy is needed to bring these innovations in technology into the hands of every corneal surgeon,” said Dr. Farid, professor of ophthalmology, and director of cor- nea, cataract and refractive surgery, Gavin Herbert Eye Institute, University of California, Irvine, CA.

Dr. Farid noted that application of the femto- second laser to keratoplasty was pioneered at the University of California, Irvine, by Roger Stein- ert, MD. For DALK, the technique involves use of the laser to create a zig-zag incision in both the host and donor tissue. In the host, the laser is programmed to perform a ring lamellar cut at a depth of 300 μm and with an inner diameter of 3 mm. The technique allows precise removal of 300 μm of the ante- rior stroma and enables visualization of the posterior cornea layers, thereby allowing more accurate needle inser- tion and air injection.

The zig-zag cut also allows for bet- ter alignment of the graft and recipi- ent tissues, and its use is associated with less astigmatism and higher order aberra- tions, more rapid and stronger wound healing, and faster visual recovery Dr. Farid said.

Intraoperative OCT guidance offers another ap- proach for enabling accurate needle placement when creating the big-bubble. Dr. Farid demonstrated its application with a video provided by Namrata Sharma, MD, DNB, MNAMS, Delhi, India.

“With intraoperative OCT, the surgeon is able to visualize Descemet’s membrane through the entire process, which decreases the risk of per- foration, and also help with placement of visco-elastic and positioning of the scissors for the final cut,” she said.

MARJAN FARID, MD
E: mfarid@uci.edu
Dr. Farid is a consultant/advisor to Johnson & Johnson Vision.

take-home

Intraoperative OCT and the femtosecond laser may make deep anterior lamellar keratoplasty more consistently predictable.

Although the femtosecond laser can cut to a precise depth, the quality of the cut achieved using the laser for deep lamel- lar dissection has limited its application in DALK.

Dr. Farid explained that the organization of the collagen fibers differs in the posterior and anterior cornea, and ini- tial efforts to use a femtosecond laser to create a smooth deeper cut resulted in a surface with ridges and irregularities that would degrade optical quality.

Dr. Farid and Audrey Talley-Rostov, MD, Se- attle, have teamed up to work on overcoming this problem by adjusting the laser energy, spot size, and spot separation on newer generation la- sers. Dr. Farid presented evidence showing that a smooth cut was created using the technique in a human cadaver eye.

Femto deep cuts are done with low energy, as seen in images at right. The femto laser settings can be adjusted to make a smooth, deep layer pass to create the cut. No big bubble or manual dissection is required, offering more precision and predictability. Photos courtesy of Marjan Farid, MD.
Boston type 1 keratoprosthesis versus Auro-keratoprosthesis

As cost limits use of device in developing countries, physicians look for options

By Nancy Groves; Reviewed by Juan Carlos Serna Ojeda, MD, MSc

SEVERAL LONG-TERM STUDIES have demonstrated the effectiveness of the Boston type 1 keratoprosthesis (Boston Kpro) artificial cornea device.

Amid its promise, the cost of this device may limit its use in developing countries, despite subsidies corresponding to the gross domestic product of each country, according to Juan Carlos Serna Ojeda, MD, MSc, a cornea, ocular surface, and refractive surgeon in Mexico City, Mexico.

Dr. Serna reported the outcomes of a retrospective comparative study of the artificial cornea device and a similar, but less expensive, keratoprosthesis developed by Indian manufacturer Aurolab.

In a previous small case series reported in 2016, the auroKpro was found to be effective in restoring vision in patients with end-stage corneal diseases.

C O M P A R A T I V E S T U D Y

The comparative study, led by Sayan Basu, MBBS, MS, at the Tej Kohli Cornea Institute, L V Prasad Eye Institute, in Hyderabad, India, included a large cohort of patients with severe bilateral corneal blindness who had surgery between August 2009 and October 2016.

Starting in 2011, when the auroKpro became available, both devices were offered to patients, who chose based on the price and the waiting time, Dr. Serna said.

The final analysis of anatomical retention rates, visual improvement, and complications showed that the auroKpro had shorter long-term anatomical retention and less visual recovery compared to the original device.

“It may have applicability in situations where the affordability or availability of the Boston Kpro is a limiting factor,” Dr. Serna said.

In the study, the anatomical outcome was the duration for which the device remained in the eye without being spontaneously extruded, explanted, exchanged, or being enucleated or eviscerated. The functional outcome was defined as best-corrected visual acuity (BCVA) with failure being considered as worse than 20/200 at any time.

Survival time was calculated in months from one month after the date of surgery to the date of failure or the last follow-up.

The study cohort included 134 eyes of 130 patients. The Boston Kpro was surgically implanted in 78 eyes of 75 patients and the auroKpro in 56 eyes of 55 patients. Both groups were comparable at baseline.

“Surgery was considered successful in 90 (67%) of all cases at the final follow-up,” Dr. Serna said.

Overall anatomical retention rates were similar: Boston Kpro, 55/78, 70.5%; auroKpro, 35/56, 62.5%; (p = 0.23). The Kaplan-Meier analysis showed separation between the two groups starting at about one year, favoring the Boston Kpro (p = 0.345). Dr. Serna also reported that 25 eyes never recovered to BCVA of 20/200 or better due to pre-existing pathologies.

Complications were similar between the two groups. In both, new glaucoma (29% in the Boston Kpro group, 21% in the auroKpro group) or the worsening of pre-existing glaucoma (29% in the Boston Kpro group and 18% in the auroKpro group at baseline) were the most common adverse events. Spontaneous extrusion rates were significantly higher in the auroKpro group vs. the Boston Kpro group, 12.5% versus 2.5%, (p = 0.23).

Reporting functional outcomes, Dr. Serna said that for patients who continued the follow-up schedule and retained the keratoprostheses, more than 85% in both groups maintained a BCVA of 20/200.

“But importantly, the survival probability of maintaining this visual acuity decreased from two years and beyond, mostly in the auroKpro group,” he added.

Dr. Serna concluded that a randomly selected clinical trial of both devices is needed to obtain a better comparison. He also emphasized that design modifications are continuously being made to improve the auroKpro and other lower-cost Kpro devices, and that efforts are under way to make the Boston Kpro more affordable.

C O N C L U S I O N

Researchers found that both the auroKpro and the Boston Kpro are effective treatment options for patients with severe bilateral corneal blindness. The auroKpro can be considered an alternative to the Boston Kpro when affordability or availability of the Boston Kpro may limit its use.


This article is adapted from Dr. Serna’s presentation at the American Academy of Ophthalmology annual meeting. Dr. Serna did not report any relevant financial disclosures.
P.M. Medical Billing Corp

P.M. Medical Billing is the largest, oldest and most experienced 100% onshore medical ophthalmology billing service in the United States. By ensuring our clients receive the maximum reimbursements for claims, we enable you to focus on expanding, buying the best equipment, spending more time with individual patients, and making the money that you deserve. Our ultimate goal has been and always will be to maximize our clients’ revenue.

P.M. Medical Billing Provides:

- Integration Into Your Current Practice Management & EMR
- A Dedicated Account Manager (Not A Call Center)
- Certified Ophthalmic Coders, Billers & Techs
- Experts In Forensic Billing & A/R Clean Up
- A Full In House Credentialing Department
- Low Cost Practice Management Software
- End To End Medical Billing & Follow Up
- Best Collection Rates In The Industry
- Full Service Patient Billing
- 100% HIPAA Compliance
- Fee Schedule Analysis

CALL TODAY
For A Free
No Obligation
Practice, Billing
& A/R Analysis

Email: info@pmbiller.com
Web: www.pmbiller.com
24 hours: 516-830-1500
1-888-PM-BILLING
(1-888-762-4554)

Focused Medical Billing is a full service medical billing firm servicing all specialties of Ophthalmology. With our firm our focus is to maximize our client’s revenue and dramatically decrease denials by utilizing 30 years of Ophthalmology billing/coding experience and expertise. Our firm provides accurate clean claim submissions on first submissions with relentless A/R follow up to obtain a 98% collection rate that so many of our clients enjoy.

Services Include:
- Expert Coders: Billing to Primary, Secondary & Tertiary insurance companies
- A/R Clean Up and analysis
- Patient Billing
- Posting of all Explanation of benefits
- Credentialing & Re-Credentialing
- Eligibility
- Fee Schedule Analysis
- Monthly Reports
- No long term commitment or contract required
- 100% HIPAA Compliant
- Stellar letters of reference

Call us today for your free, no obligation consultation
Ph: 855-EYE-BILL ext. 802
Email: amay@focusedmedicalbilling.com
Web: www.focusedmedicalbilling.com

“You’re focused on your patients, we’re focused on you”
RALEIGH, NORTH CAROLINA

Solo Ophthalmology Practice for Sale
Rexwoodseye@gmail.com

Reach your target audience.
Our audience.

Ophthalmologists and allied eye care professionals. Contact me today to place your ad.

Joanna Shippoli
Account Manager
440-891-2615
jshippoli@mmhgroup.com

Ophthalmology Times

Narrow your candidate search to the best.

Place a recruitment ad in Ophthalmology Times — in print or online.

Joanna Shippoli
Account Manager | 440-891-2615
jshippoli@mmhgroup.com

Ophthalmology Times
CAREERS

INTERNATIONAL

Live & Work in the South Pacific!

- Seeking talented, kind, ethical, comprehensive ophthalmologist for US island of Saipan
- Part-time or Full-time. Locum tenens welcome.
- $350K with low low taxes, exotic travel nearby
- State-of-the-art clinic, excellent support staff

Visit www.MarianasEye.com/Jobs
Page password: eye@9
Or email: davidkhorram@gmail.com

Recruitment Advertising Can Work For You!
Reach highly-targeted, market-specific business professionals, industry experts and prospects by placing your ad here!

VERMONT

The Division of Ophthalmology at the University of Vermont College of Medicine, in alliance with the University of Vermont Medical Center, is seeking an academic neuro-ophthalmologist. This individual must have completed a board approved 3- or 4-year ophthalmology residency or a 3-year neurology residency and a clinical neuro-ophthalmology fellowship, and be board certified or board eligible, and eligible for medical licensure in the State of Vermont. The successful applicant will be appointed at the Assistant/Associate Professor level in the Clinical Scholar Pathway, commensurate with years of experience and accomplishments.

Duties will include providing clinical care to neuro-ophthalmology patients, teaching the principles of ophthalmology to medical students and undergraduate students in Allied Health programs, providing teaching experience for residents in training, developing basic and/or clinical research, and performing additional departmental and/or sectional administrative duties as assigned by the Chair of the Department of Surgery.

This is a full-time, 12 month, salaried, faculty appointment and carries with it attending staff privileges at The University of Vermont Medical Center. Salary is competitive and commensurate with ability and experience.

Located in Burlington, the University of Vermont Medical Center serves as Vermont’s only academic medical center: Burlington is a vibrant community located on the shores of Lake Champlain, between the Adirondack and Green Mountains. With year-round recreational opportunities, safe communities and excellent schools, this progressive community has been frequently cited as one of the most livable cities in the U.S.

The University is especially interested in candidates who can contribute to the diversity and excellence of the academic community through their research, teaching, and/or service. Applicants are requested to include in their cover letter information about how they will further this goal.

Sanford Eye Center is seeking a BC/BE Ophthalmologist to add to its current group of 5 ophthalmologists and 3 optometrists, with one physician focusing on pediatric patients.

- Ideal candidate would be a comprehensive ophthalmologist with fellowship training in glaucoma
- Call is 1:5
- Work 4.5 days per week
- Competitive compensation and comprehensive benefit package
- Excellent retention incentive & relocation allowance

Sioux Falls is one of the fastest growing areas in the Midwest. As the largest city in the state, it balances an excellent quality of life and strong economy with a safe, clean living environment. The cost of living is competitive and South Dakota has no state income tax. Sioux Falls offers amenities of a community twice its size such as fine dining, shopping, arts, sports and nightlife.

For More Information Contact: Deb Salava, Sanford Physician Recruitment at (605) 328-6993 or (866) 312-3907 or email: debra.salava@sanfordhealth.org
Early laser treatment beneficial in central serous chorioretinopathy

Condition is most prevalent among young, middle-age adult male patients

By Alejandro Lavaque, MD; Special to Ophthalmology Times

IN PATIENTS WITH central serous chorioretinopathy (CSR), fluid accumulates under the retina, causing a serous detachment and vision loss. The condition occurs most often in young and middle-aged adults (20 to 50 years of age), with men being affected more often than women. Although vision loss with CSR is usually temporary, it can recur and become chronic anywhere from 30% to 50% of the time.1

PRESENTATION AND BACKGROUND
The most common symptom that patients present with is blurry central vision in one eye. Patients may also complain of micropsia, metamorphopsia, hyperopic shift, central scotoma, and reduced contrast sensitivity.2 Upon examination, the patient will often have some involvement in the other eye. Depending on the location and amount of subretinal fluid, patients may not have any symptoms.

The exact causes of CSR are not fully understood. However, it is known that systemic exposure to corticosteroids is a risk factor.2 An association has also been made between CSC and patients with so-called type A personalities.3 It has been hypothesized that the body’s natural corticosteroids produced when under stress may trigger CSR in prone individuals. This makes the condition a “reactive choroiditis.”

CSR is typically a self-limiting disease, and visual recovery usually occurs spontaneously within two to three months without treatment. Patients should discontinue or limit corticosteroids, and patients with type A personality can be offered lifestyle modifications and stress management.

TREATMENT STRATEGIES
Although observation is the standard initial treatment for CSR, there are instances where treatment is appropriate. For acute, chronic, and recurrent CSR, various treatments have been used including medical therapies, intravitreal antiangiogenic growth factor agents, and surgical management. Photodynamic therapy has been used focally to treat leakage. Several reports and studies have demonstrated that reduced-dose and reduced fluence PDT can be used in chronic CSR patients to decrease subretinal fluid and improve best-corrected visual acuity (BCVA).4-6 Focal laser photocoagulation and subthreshold approaches have been used to speed up resolution of subretinal fluid. Spots are applied to areas of leakage identified on fluorescein angiography and/or optical coherence tomography angiography (OCTA).

In my practice, I have found that early detection of CSR and the use of laser treatment using PASCAL with Endpoint Management (EpM; Topcon) is safe and effective and leads to quick restoration of vision without macular damage in most cases.

SAFETY, EFFICACY
I evaluated the safety and efficacy of PASCAL EpM in 23 eyes of 21 patients with acute of CSR (average follow-up = 26 months). The short-pulse laser treatment was applied to the area of hyperactivity in the choroid seen on optical coherence tomographyangiography. No other topical or systemic treatment was prescribed.

Before treatment, mean BCVA was 20/80, the mean central macular thickness (CMT) was 549 μm, and the mean choroidal thickness (CT) was 289 μm. After laser treatment, mean BCVA improved to 20/30, mean CMT to needing two treatments and one needed three.

REFERENCES

‘Although observation is the standard initial treatment for CSR, there are instances where treatment is appropriate.’

—Alejandro Lavaque, MD

It has been reported that about 50% of CSR patients have at least one relative with findings upon retinal examination, indicating some genetic inheritance is at play.2 Hypertension and heart disease as well as current or recent pregnancy can increase one’s risk for CSR. Other drugs may also trigger CSR such as stimulants, decongestants, erectile dysfunction medications, and some anti-cancer agents.5
Technology makes physicians more efficient, reduces burnout

Inventory management, value-based care also benefit from systems

By David Hutton; Reviewed by Michael B. Rivers, MD

**BURNOUT IS A** problem that is not going away. As retina surgeons become increasingly busy, operating their practices more efficiently is a key to success.

Seeing patients is only a part of the process. Physicians have to manage their practice, and this includes inventory management, and providing value-based care.

With so many balls in the air at the same time, retina specialists become susceptible to burnout. According to Michael B. Rivers, MD, retina surgeons often see 90 to 100 patients a day, making it extremely difficult for them to take time off, or even keep up with other practice needs. This phenomenon is not unique to retina specialists.

Dr. Rivers, director, EMA Ophthalmology, at Modernizing Medicine, noted as retina practices have become larger, an increase in patient volume has become an issue as physicians have seen their practices change.

“Along came the ability to treat wet macular degeneration,” he explained. “That was a huge change for retina practices. These patients that you would normally see once a year and you wouldn’t have any treatment for them, you were suddenly seeing them once a month.”

As a result, the volume of patients began to increase almost overnight.

Dr. Rivers recounted a physician he recently visited who sees more than 120 patients a day. The visits do not require a lot of decision making.

“This contributes to burnout because it is not intellectually challenging,” he said. “They have no control over their lives.”

Some physicians may take more vacation, but when they return from vacation, the patients still need to be seen.

“It is a real change if you have moved to a surgical practice with a few patients to a tremendous number of patients,” Dr. Rivers added.

**GOING ELECTRONIC**

Another change, according to Dr. Rivers, has been the advent of electronic health records (EHR).

“You have this burden of documentation for the federal government with software that isn’t designed to help the physician as a provider,” he said.

Dr. Rivers left his practice to join Modernizing Medicine, which offers physicians solutions to many of the problems connected to the daily operation of a practice.

The company was founded in 2010 by Daniel Cane and Michael Sherling, MD, MBA.

The goal, according to Dr. Rivers, is to make it easy to enter data into the company’s system and also to deliver data back to the clients.

“Everything we do is to make it easier for clinicians,” he said. “We also want to get them more information.”

Physicians can operate more efficiently with software that is easy to use with an app that is graphically oriented. Users can dictate rather than type.

“We also try to provide as much functionality as possible so that the software learns what types of things you do and presents information to you so things are easier,” Dr. Rivers said.

The software allows physicians to focus on diabetic retinopathy and wet macular degeneration. It also allows physicians to communicate with patients.

“Information can be printed out and handed to the patients,” Dr. Rivers said. “We also have a patient portal and additional patient engagement tools such as automated appointment reminders and surveys.”

This will lead to an increase in information for both patients and physicians and improved communications.

**INVENTORY MANAGEMENT**

Drug inventory is key for a retina practice and the drugs used to treat wet macular degeneration and diabetic issues are expensive. The physicians have to purchase medications up front and track it and ensure it is assigned to the right patient and billed correctly.

“Drug inventory software is a very important part of the documentation process with electronic health records,” Dr. Rivers explained.

Optical and ASC inventory also are key for physicians.

Drug inventory management is a large burden for any practice. A retina specialist may buy $500,000 in inventory each year.

“That is a tremendous amount of money,” Dr. Rivers said. “Even a few percent loss can add up to a tremendous amount of money.”

Automation can be key to successful inventory practices, and can ensure efficient flow.

Patients benefit from anything that helps the physician work more effectively. These efficiencies can help physicians operate more efficiently and spend more time with patients.

Through the automated systems, drugs are billed correctly through insurance. Dr. Rivers noted that automation and software design for drug inventory is critical to the retina practice.
VALUE BASED CARE

Over the last decade or so, trends have moved from paying for care because it has been delivered to understanding the quality of care that is provided.

“Value based care as a concept is to say that you want to provide cost-effective care and understand outcomes,” Dr. Rivers said. “Not only am I paying for something, if I am a payer or the federal government, but I also want to understand what value is being provided to patients for every dollar that I put in.”

It can be another level of burden for physicians, who traditionally have billed patients because services were provided. Now insurance companies want documentation about why something is happening and the value of a procedure for patients and whether standard procedures are followed.

If insurance providers tell a physician they have to provide outcome data on their patients with macular degeneration, the automated system allows them to deliver the information from the EHR.

“Our software is easy to get data in but we also have analytics in our package where data analysis is delivered to the client,” Dr. Rivers noted. “If I want to find patients who have been treated with wet macular degeneration with a specific drug and what the outcomes are, I can do that. That is very powerful.”

The software allows physicians to access data on specific diagnoses as well as treatment algorithms and associated costs. This enables them to make financial decisions, and also provide data to payers.

“True value based healthcare is understanding clinical success, outcomes and the financial cost,” Dr. Rivers said. “This allows physicians to understand their costs. The business of medicine is like any other business. The more information you have, the better decisions you can make.”

When practices are successful, they run more efficiently, and can have more physicians and staff. The end result is shorter wait times and a staff that is more engaged.

IN THE FIELD

Ajit Nemi, MD, MBA, Lotus Vision, Atlanta, GA, noted that it took a few weeks to get acquainted with the system, but he, along with his technician, have become more efficient with creating and finishing notes. It helps with efficiency.

“The available plans are detailed and fully customizable and I don’t have to do much data/text entry,” he explained. “I am actually able to leave the office earlier than I was able to before. As a cornea, cataract and refractive surgeon, I appreciate the comprehensive counseling information and treatment protocols for the diagnoses I most commonly encounter.”

Dr. Nemi noted that the system allows him to create operative reports for anterior segment procedures with the touch of a button, eliminating the need to dictate reports over the phone.

“EMA also provides specific charting protocols for post-operative patients that allow the physician to complete notes efficiently while automatically generating the appropriate codes and modifiers for the postop period,” he said.

Erik W. Niemi, DO, Advanced Eyecare, PC, Bennington, VT, noted that the EMA has made the practice’s communications and documentation more efficient than ever.

“The system is intuitive, with a clean layout and user interface that makes information easy to find,” he said. “For routine communications, I can complete and send custom preset letters to a primary care physician before leaving the exam room. We also have much easier on-call access to patient data as our physicians in any office can read each other’s notes instead of relying on the patient’s explanation.”

In the field, Dr. Rivers noted that physicians are finding the software is helping them operate at peak efficiency.

“When a practice is running efficiently, it can provide better care,” Dr. Rivers said. “That is a win for the physician and for the patient. You can have humans talk to patients, and that is what is important.”

MICHAEL B. RIVERS, MD
E: michael.rivers@modmed.com
Dr. Rivers is director, EMA Ophthalmology for Modernizing Medicine. He has no other financial disclosures.
Oh, the hazards of online symptom searches

“Sorry, no discount because you self-diagnosed using Google.”

This index is provided as an additional service. The publisher does not assume any liability for errors or omissions.
WHEN RELIABILITY COUNTS
THE RIGHT PACK MATTERS

Minimize your pack-building time
Expedite your OR experience
Treat more patients

CustomEyes® your pack

Learn about how you can CustomEyes® your surgical pack today!

bvimedical.com
866-906-8080

Visit BVI Booth 6458 at AAO 2019

BVI, BVI Logo and all other trademarks (unless noted otherwise) are property of Beaver-Visitec International, Inc. ("BVI") © 2019 BVI. 1498237-04
For All Your Surgical Needs
From our FDA-Registered Outsourcing Facility

### INJECTABLE FORMULATIONS*

<table>
<thead>
<tr>
<th>Product</th>
<th>Description</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tri-Moxi®</td>
<td>(Triamcinolone acetonide and moxifloxacin)</td>
<td>15mg/1mg/mL</td>
</tr>
<tr>
<td>Dex-Moxi®</td>
<td>(Dexamethasone sodium phosphate and moxifloxacin)</td>
<td>1mg/5mg/mL</td>
</tr>
<tr>
<td>Dex-Moxi-Ketor®</td>
<td>(Dexamethasone sodium phosphate, moxifloxacin, and ketorolac tromethamine)</td>
<td>1mg/0.5mg/0.4mg/mL</td>
</tr>
<tr>
<td>Buffered lidocaine hydrochloride</td>
<td></td>
<td>1%</td>
</tr>
<tr>
<td>Buffered lidocaine hydrochloride</td>
<td></td>
<td>2%</td>
</tr>
<tr>
<td>Mitomycin</td>
<td></td>
<td>0.04%</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td></td>
<td>5mg/mL and 1mg/mL</td>
</tr>
<tr>
<td>Hyaluronidase</td>
<td></td>
<td>175 units/mL</td>
</tr>
<tr>
<td>Lidocaine hydrochloride/Epinephrine in BSS (PF/SF)</td>
<td></td>
<td>(0.75/0.025)%</td>
</tr>
<tr>
<td>Phenylephrine hydrochloride/Lidocaine hydrochloride (PF/SF)</td>
<td></td>
<td>(1.5/1)%</td>
</tr>
</tbody>
</table>

### TOPICAL FORMULATIONS*

<table>
<thead>
<tr>
<th>Product</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mydriatic 2</td>
<td>(Tropicamide and phenylephrine)</td>
</tr>
<tr>
<td>Mydriatic 4</td>
<td>(Tropicamide, proparacaine, phenylephrine and ketorolac)</td>
</tr>
<tr>
<td>Steroid, Antibiotic, NSAID</td>
<td></td>
</tr>
<tr>
<td>Steroid, Antibiotic</td>
<td></td>
</tr>
<tr>
<td>Steroid, NSAID</td>
<td></td>
</tr>
<tr>
<td>Steroid</td>
<td></td>
</tr>
</tbody>
</table>

### ORAL FORMULATIONS*

<table>
<thead>
<tr>
<th>Product</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>MKO Melt®</td>
<td>(Midazolam, ketamine HCl and ondansetron)</td>
</tr>
<tr>
<td>Steroid, Antibiotic, NSAID</td>
<td></td>
</tr>
<tr>
<td>Steroid, Antibiotic</td>
<td></td>
</tr>
<tr>
<td>Steroid, NSAID</td>
<td></td>
</tr>
<tr>
<td>Steroid</td>
<td></td>
</tr>
</tbody>
</table>

Visit us at AAO booth #7601 Moscone West Exhibit Hall

Order at: www.order.imprimisrx.com

*For professional use only. ImprimisRx specializes in customizing medications to meet unique patient and practitioner needs. No compounded medication is reviewed by the FDA for safety or efficacy. ImprimisRx does not compound copies of commercially available products. References available upon request.

ImprimisRx, Tri-Moxi, Dex-Moxi, Dex-Moxi-Ketor, and MKO Melt are registered trademarks of Harrow Health, Inc. ©2019 ImprimisRx. All rights reserved. IMP00390 Rev.5 08/19 As of 08.15.19
Expert Roundtable: Incorporating OXERVATE™ Into the Treatment of Neurotrophic Keratitis

ROUNDTABLE PARTICIPANTS

Edward Holland, MD (Chair)
Cincinnati Eye Institute
and the University of Cincinnati
Cincinnati, OH

Marjan Farid, MD
UCI Health Gavin Herbert Eye Institute
University of California, Irvine

Cynthia Matossian, MD, FACS
Matossian Eye Associates
Pennington, NJ

Jay Pepose, MD, PhD
Pepose Vision Institute
St. Louis, MO
Introduction

The OXERVATE™ (cenegermin-bkbj) ophthalmic solution 0.002% (20 mcg/mL) Neurotrophic Keratitis Roundtable engaged medical experts with experience in the diagnosis and management of neurotrophic keratitis (NK). The goal of the roundtable was to review relevant literature on NK and OXERVATE clinical trial data; identify opportunities to raise NK awareness among clinicians; discuss assessment and therapy of NK; and provide input on the selection of appropriate patients for OXERVATE (cenegermin-bkbj), a therapy recently approved for the treatment of NK. The roundtable participants were Edward Holland, MD (chair); Marjan Farid, MD; Cynthia Matossian, MD, FACS; and Jay Pepose, MD, PhD.

Neurotrophic Keratitis

Neurotrophic keratitis is a rare disease with an estimated prevalence of 1.6 to 4.2 cases per 10,000 persons. The disease is degenerative and characterized by impaired function of the corneal sensitivity and the development of persistent epithelial defects (PED), which can progress to corneal ulcer, melting, and perforation. Neurotrophic keratitis is associated with damage at any level to the fifth cranial nerve, from the trigeminal nucleus to the corneal nerve endings. This damage can arise from a wide variety of ocular and systemic conditions, including herpetic keratitis, dry eye disease (DED), ocular chemical burns, corneal surgery, diabetes, multiple sclerosis, and neurosurgical procedures. Use of contact lenses and chronic topical medications, such as anesthetics, antibiotics, antivirals, beta blockers, glaucoma medications, and nonsteroidal anti-inflammatory drugs, are also associated with NK development. Impairment of the blinking reflex due to lowered corneal sensitivity; reduced tear secretion and tear film instability leading to desiccation of the corneal surface; and loss of trophic support and epithelial breakdown are all thought to play a role in the pathogenesis of NK and the progression of the disease.

One of the important trophic factors involved in maintaining corneal health is nerve growth factor (NGF), which is constitutively released in healthy human corneas. Acting via specific receptors in corneal tissues, NGF plays an important role in the development and survival of peripheral sensory neurons, maintenance of corneal homeostasis, and induces stromal healing and remodeling. NGF has been investigated as a potential target pathway for novel therapeutic agents to treat NK.

The natural history of NK is not completely understood, and, until recently, there have been no FDA-approved treatments for the disease. NK is a rare degenerative disease of the trigeminal nerve that may cause breakdown and scarring of the corneal epithelium, potentially leading to vision loss. If left untreated, NK progresses to severe disease with associated risks of vision loss as a result of corneal perforation and scarring, which can result in anatomic loss of the eye; yet, even when treated with conventional therapies, the disease has the potential to adversely impact visual outcomes. Corneal transplantation can be employed as a treatment of last resort; however, persistent anesthesia associated with NK causes impaired epithelial wound healing, and NK patients are prone to inflammation. These factors significantly increase the risk of recurrence of corneal ulceration in the graft, resulting in a higher risk of failure in patients with NK.

Conventional treatment options for NK have been limited to symptom management rather than addressing the underlying cause of the disease, namely, nerve injury and the loss of corneal sensitivity, which can arise due to herpetic infection, trauma, and other disorders.
Neurotrophic Keratitis Awareness

According to the roundtable participants, there is a need to increase awareness of NK among the medical community, in part because there has been no disease-specific treatment available, and there are significant gaps in education about NK diagnosis and management. They noted that optometrists, as well as general ophthalmologists and primary care physicians, account for most initial referrals of NK patients.

The participants observed that NK often goes undiagnosed, or it is misdiagnosed and treated as DED or herpetic infection. According to Dr. Holland, patients who present with neurotrophic corneal ulcers are often inappropriately prescribed topical antivirals for active herpes simplex virus (HSV) keratitis based on the finding of an abnormal epithelium with a dendritic-shaped corneal lesion. However, the latter finding is not specific for HSV and may be present in patients with resolved herpetic infectious epithelial keratitis or those who have never been infected with the virus. HSV keratitis can generally be ruled out, except perhaps in some instances where the immune system is compromised, if a patient receiving topical antiviral treatment fails to show corneal improvement. In such cases the antiviral treatment should be discontinued, since chronic use can be toxic to the corneal surface.

Physicians should be aware of the various conditions commonly associated with the development of NK, some of the more common being herpetic keratitis and postsurgical nerve damage. According to some estimates, NK develops in an average of 6% of HSV keratitis cases, 12.8% of herpes zoster keratitis cases, and 2.8% of patients undergoing surgical procedures for trigeminal neuralgia. No epidemiological data are available in the literature regarding the incidence of NK associated with other common conditions known to cause the disease, such as chemical burns, diabetes, contact lenses, and acoustic neuroma, as well as less frequent causes, such as space-occupying intracranial masses, multiple sclerosis, leprosy, and various genetic disorders.

Another educational gap identified by the participants was the lack of awareness and underutilization of corneal sensitivity testing when diagnosing NK. Nerve damage leading to loss of corneal sensitivity is the hallmark feature of NK, and testing for corneal sensitivity is critical for confirming the diagnosis of the disease; however, the test is often either not performed routinely or inadequately performed in clinical practice.

Neurotrophic Keratitis Diagnosis

Since NK is a degenerative disorder that can potentially lead to profound vision loss resulting from scarring and corneal perforation, it is critical that the condition be detected and diagnosed as early as possible so that treatment can be initiated promptly. Evaluation for NK should include a detailed evaluation of the patient’s medical history to identify potential risk factors (eg, history of corneal surgery, trauma, abuse of topical anesthetics, chronic treatment with topical medications, chemical burns, or contact lens abuse), followed by corneal sensitivity testing prior to administering any drops and corneal staining.

The decrease or absence of corneal sensitivity is the diagnostic hallmark of NK. For NK patients with PED, potential sources of toxicity should be removed, and then if anesthesia or hypoesthesia remain, this can potentially be NK. Assessment of corneal sensation is fundamental to the diagnosis of NK, although such testing is currently underutilized in clinical practice. Corneal sensitivity testing,
which is critical for confirming a diagnosis in suspected cases of NK, can be performed by using a Cochet-Bonnet aesthesiometer or more conventional methods, such as a wisp of cotton applied to the corneal surface. NK patients typically show reduced blinking and sensation in response to the stimulus; however, if the test shows normal corneal sensation, it is unlikely that the patient has NK.6 The participants noted that corneal sensitivity testing is a commonly missed step, which is a contributing factor to NK underdiagnosis or misdiagnosis.10 Dr Holland routinely uses the cotton swab method to test for corneal sensation and stressed that it should be a routine part of the workup for all patients with ocular surface disease, particularly for new patients and ideally before they have received any eye drops, since topical ocular medications can alter corneal sensation. It can also be useful to compare the response in the affected and unaffected eye in patients with unilateral NK, and to test and compare the central and peripheral areas of the cornea.

Vital staining with fluorescein or lissamine green is routinely used to evaluate ocular surface integrity in NK. Fluorescein staining is preferred for assessing and grading corneal epithelial alterations and the presence of stromal ulceration and thinning, while lissamine green staining, which correlates highly with dry eye syndromes, is used to assess conjunctival epithelial integrity and to identify mucus filaments.11-12

In vivo confocal microscopy (IVCM) has been used to qualitatively and quantitatively detect corneal nerve changes in a variety of conditions, such as keratoconus, bullous keratopathy, diabetic neuropathy, and herpes simplex keratitis.8 A significant reduction of corneal nerve density that was strongly correlated with decreased corneal sensation was demonstrated using IVCM in patients with NK.3,10 In addition, IVCM also showed a higher number of hyperreflective keratocytes and a lower epithelial and endothelial cell density in NK patients.3,10 The participants suggested that, while this imaging technique may be of value for the diagnosis and monitoring NK, it is not available in most practices. Anterior segment optical coherence tomography (OCT) has also been used to demonstrate changes in epithelial thickness and reflectivity as well as stromal thinning in NK eyes.10

One way to assess NK severity is by using a 3-stage system, as seen in Table 1.5,13 Stage 1 (mild) NK is characterized by punctate keratopathy, epithelial hyperplasia, stromal scarring, and corneal neovascularization. Stage 2 (moderate) NK is characterized by recurrent or persistent epithelial defects (PED), usually in the paracentral area and with an oval shape. Stage 3 (severe) NK is characterized by stromal involvement that appears as stromal ulcer, stromal edema, and infiltrates, which may result in perforation and/or corneal thinning due to stromal melting.5,13 A cross-sectional image of the cornea depicting the 3 stages of NK according to the depth of the layers affected is shown in Figure 1. Some degree of vision loss can occur at all stages of the disease, and, if left untreated, moderate NK progresses to severe disease with associated risk of vision loss resulting from scarring and corneal perforation.1
Table 1. NK Staging\textsuperscript{5,13}

<table>
<thead>
<tr>
<th>Stage</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1 (mild)</td>
<td>Punctate keratopathy, epithelial hyperplasia, stromal scarring, and corneal neovascularization</td>
</tr>
<tr>
<td>Stage 2 (moderate)</td>
<td>Persistent epithelial defects (PED), usually in the paracentral area and with an oval shape</td>
</tr>
<tr>
<td>Stage 3 (severe)</td>
<td>Stromal involvement that appears as stromal corneal ulcer, stromal edema, and infiltrates, which may result in perforation and/or corneal thinning due to stromal melting</td>
</tr>
</tbody>
</table>

Figure 1. Cross-sectional image of the cornea depicting the 3 stages of NK according to the depth of the layers affected: stage 1 (mild), stage 2 (moderate), and stage 3 (severe).
Neurotrophic Keratitis Treatment

NK has traditionally been a highly challenging disease to treat effectively. There is no international consensus regarding the management of NK, and no international or national guidelines specific for NK treatment have been published.7 Prior to the introduction of OXERVATE, no treatment has been approved by regulatory agencies specifically for the indication of NK.1,2,7 Conventional therapies are palliative in nature and do not address the underlying pathogenesis of NK (ie, they do not stimulate corneal nerve regeneration or restore corneal nerve function).2,3,7 Furthermore, few of these therapies have been evaluated in prospective, randomized, controlled clinical trials in NK patients.7 Even in cases where complete corneal healing is achieved using conventional therapies, NK patients still face the risk of disease relapse.7 However, the introduction of OXERVATE has now made it possible to effectively manage NK by addressing the underlying pathogenesis of the disease. The main goals of conventional NK treatment have been to preserve epithelial integrity, promote epithelial healing, and prevent corneal damage progression.2 The roundtable participants emphasized healing/normalizing the epithelium as the most important goal of NK therapy. Treatment for NK varies according to the stage of the disease, with less invasive, pharmacological options employed for early-stage NK and more invasive, nonpharmacological treatments for refractory patients and those with more advanced disease at the time of diagnosis (Table 2).3,6,7 In clinical practice, NK treatment is often tailored to individual needs, with multiple treatments used either sequentially in a stepwise approach and/or concurrently.7

Conventional therapy for stage 1 NK aims to prevent epithelial breakdown through the use of preservative-free artificial tears and discontinuation of toxic topical medications.1 The participants cautioned that corneal toxicity in NK patients can be exacerbated by the use of topical antiviral and intraocular pressure (IOP)-lowering glaucoma medications, which

Table 2. Conventional Approaches to NK Treatment Prior to the Introduction of OXERVATE*3,6,7

<table>
<thead>
<tr>
<th>Stage</th>
<th>Therapy/Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>Preservative-free artificial tears</td>
</tr>
<tr>
<td>(mild)</td>
<td>Ocular lubricants</td>
</tr>
<tr>
<td></td>
<td>Discontinuation of topical/systemic medications associated with corneal toxicity</td>
</tr>
<tr>
<td></td>
<td>Punctal plugs</td>
</tr>
<tr>
<td></td>
<td>Oral omega-3 fatty acid supplementation</td>
</tr>
<tr>
<td>Stage 2</td>
<td>Topical antibiotics (eg, doxycycline, fluoroquinolone)</td>
</tr>
<tr>
<td>(moderate)</td>
<td>Topical steroids</td>
</tr>
<tr>
<td></td>
<td>Autologous serum eye drops</td>
</tr>
<tr>
<td></td>
<td>Therapeutic bandage contact lenses</td>
</tr>
<tr>
<td>Stage 3</td>
<td>Conjunctival flap</td>
</tr>
<tr>
<td>(severe)</td>
<td>Tarsorrhaphy</td>
</tr>
<tr>
<td></td>
<td>Amniotic membrane transplantation</td>
</tr>
<tr>
<td></td>
<td>Cyanoacrylate glue</td>
</tr>
<tr>
<td></td>
<td>Lamellar/penetrating keratoplasty</td>
</tr>
<tr>
<td></td>
<td>Corneal transplantation</td>
</tr>
</tbody>
</table>

*Treatment options are considered in a step-ladder approach according to NK stage/severity and are not exclusive.
can damage the limbal stem cell architecture, and by the use of multiple therapies administered concurrently. Therapy for DED such as punctal plugs may also be used, along with oral omega-3 supplementation.5 Therapies for stage 2 or 3 NK aim to facilitate corneal healing and to prevent the corneal thinning that can lead to perforation. These treatments include steroids and other invasive procedures such as tarsorrhaphy, botulinum-induced ptosis, conjunctival flap, and amniotic membrane transplantation, which can restore ocular surface integrity, but some treatments can pose a potential risk of impacting vision and cosmesis.¹³

As highlighted by the roundtable participants, other treatments commonly used for late-stage/refractory NK include steroids and doxycycline to treat corneal haze, autologous serum eye drops, bandage contact lenses, prophylactic antibiotics such as topical fluoroquinolone, ocular tissue glue, and, as a last resort, corneal transplantation. For glaucoma patients with a failing ocular surface, the participants noted that consideration should be given to IOP-lowering surgical procedures as an alternative to topical drops.

**OXERVATE™**

OXERVATE (cenegermin-bkbj) 0.002% (20 µg/mL) ophthalmic solution is a first-in-class medication indicated for the treatment of NK. Its active ingredient, cenegermin-bkbj, a recombinant human NGF (rhNGF) protein structurally identical to the NGF protein found in human ocular tissues.² It is formulated as a preservative-free topical medication and supplied in multiple-dose vials.³ The recommended dose is 1 drop instilled in the affected eye(s) 6 times a day at 2-hour intervals for 8 weeks.³

OXERVATE became the first FDA-approved treatment for NK in August 2018 and is the first topical biologic medication ever to be approved for ophthalmologic use. It is the first treatment for NK that targets the underlying pathogenesis of the disease to support corneal integrity.⁴,⁵

To receive FDA approval, the safety and efficacy of OXERVATE for the treatment of NK was evaluated in 2 pivotal clinical trials. NGF0212 (REPARO; NCT01756456) was a phase 2 randomized, double-masked, multicenter, vehicle-controlled, parallel-group trial involving 32 sites in 6 countries in Europe.⁴ A total of 156 adult patients with stage 2 (moderate) or stage 3 (severe) NK in 1 eye were randomized 1:1 to treatment with 6 drops per day of either cenegermin-bkbj 10 µg/mL, OXERVATE 20 µg/mL, or vehicle for 8 weeks. The patients in the REPARO trial were then followed for 48 or 56 weeks after completing treatment.³ The formulation that was tested in the REPARO trial did not include the antioxidant methionine (an excipient added to the commercial formulation to improve its stability) and is not the final formulation that is marketed as OXERVATE. More than 1 study was conducted with the final commercial formulation, and no difference in safety was seen in either of the trials.

NGF0214 (NCT02227147) was a US phase 2 study in which 48 patients with NK were randomized 1:1 to treatment with either OXERVATE 20 µg/mL or vehicle.³ The enrollment criteria and treatment protocol were the same as in the REPARO trial; however, patients with bilateral NK were included and treated bilaterally, and the primary endpoint (percentage of patients with complete corneal healing, defined as absence of staining of the corneal lesion and no persistent staining in the rest of the cornea) was examined at 8 weeks vs 4 weeks in REPARO. Across the trials, the mean age of the patients was 61 to 65 years (range, 18-95 years) and the majority (approximately 61%) were female.¹³

In the REPARO trial, 72% of patients treated with OXERVATE vs 33% with vehicle (P <.01) experienced complete corneal healing.⁹

“NK has been terribly neglected because we didn’t have good diagnostics, and until now, we lacked effective therapies. So instead, we borrowed treatments for dry eye to try and get our NK patients better.”

— Jay Pepose, MD, PhD

“We need to shift the NK treatment paradigm and not wait for a defect to develop before starting therapy. If we wait until a persistent defect develops before treating, the patient will suffer visual loss from chronic epitheliopathy.”

— Edward Holland, MD
In the US trial, 65% of patients experienced complete corneal healing with OXERVATE vs 17% with vehicle (P < .01). Representative staining images illustrating improvement of a neurotrophic corneal lesion from baseline through week 8 in a patient treated with OXERVATE 20 μg/mL in the REPARO trial are shown in Figure 2. Approximately 96% of patients who healed after 8 weeks of treatment with OXERVATE in the REPARO trial remained recurrence free (recurrence defined as return to baseline), and 80% remained completely healed 1 year after treatment initiation.1

Most adverse events (AEs) reported in patients treated with OXERVATE were ocular, mild, and transient and did not necessitate discontinuation or corrective treatments.1 The most common AE in the trials was eye pain following instillation, which was reported in approximately 16% of patients. Other adverse reactions occurring in 1% to 10% of OXERVATE-treated patients and more frequently than in the vehicle-treated patients included corneal deposits, foreign body sensation, ocular hyperemia, ocular inflammation, and tearing.1

The OXERVATE clinical trials included a diverse pool of patients representative of NK. For example, consistent with published literature, the most common underlying causes of NK in the REPARO study population (N=156) were herpetic eye disease (44 patients) and ocular or neurologic surgery (21 patients each). Prior treatments used most frequently were artificial tears, gels/ointments, and topical antibiotics.1

Figure 2. Improvement of neurotrophic corneal lesion from baseline through week 8 in a patient treated with OXERVATE in the REPARO trial.1

Images showing assessment of corneal lesion size on clinical pictures. Representative images showing the progression of a typical oval, paracentral, neurotrophic corneal lesion from baseline through week 8 in a patient treated with OXERVATE. Top row: Photographs of the cornea illuminated with diffuse white light. Bottom row: Corneal lesion healed at week 8 as assessed by the central reading center on fluorescein staining (green) photographs obtained under cobalt-blue light illumination.
Patient Selection for OXERVATE

OXERVATE, a recombinant human NGF, is the first FDA-approved pharmacologic treatment that targets the root pathogenesis of NK. Supreme OXERVATE represents a fundamentally new approach to NK therapy. It is the only topical treatment for NK that targets the underlying pathogenesis of the disease to promote corneal healing. OXERVATE is approved as a treatment for all stages of NK disease to promote corneal healing. OXERVATE targets the root pathogenesis of NK. It is the only topical treatment for NK representing a fundamentally new approach to NK.

The roundtable participants emphasized the importance of early NK diagnosis and treatment when considering treatment with OXERVATE. For patients who have chronic epitheliopathy/ superficial punctate keratitis (SPK; stage 1 NK) with decreased sensation (as measured by a tool such as the Cochet-Bonnet aesthesiometer), treatment should be started before an epithelial defect develops, since NK is a degenerative disorder.\(^1\) Patients who have an epithelial defect and reduced corneal sensitivity due to various causes (eg, herpetic infection, neurosurgical and ocular surgery, trauma, diabetes, penetrating keratoplasty, LASIK/photorefractive keratectomy) are also candidates for therapy with OXERVATE (Figure 3).

NK patients with active ocular infections should first be treated to control the infection, and then if the NK remains, treatment with OXERVATE can be initiated. It should be noted that the REPARO trial excluded patients with active ocular infection or inflammation unrelated to NK, as well as those with severe blepharitis and/or severe Meibomian gland disease.\(^1\) Patients who have evaporative DED/Meibomian gland dysfunction in the absence of reduced corneal sensitivity are not suitable candidates for OXERVATE and instead should receive appropriate treatment for those conditions. Patients with late-stage NK who present with stromal involvement in the posterior third, corneal melting, or perforation have already progressed beyond the point where OXERVATE would be recommended and should instead be considered for other therapeutic or surgical procedures.

![Figure 3. Neurotrophic keratitis patient algorithm](image)

**Figure 3. Neurotrophic keratitis patient algorithm**

**Assessment**
- Evaluate medical history and risk factors: eg, herpetic infections, corneal surgeries, trauma, systemic diseases (eg, MS, diabetes), topical anesthetics, contact lens use, etc
- Test corneal sensitivity: using cotton swab method or Cochet-Bonnet aesthesiometer, Belmonte aesthesiometer, dental floss, etc
- Perform additional tests to confirm or rule out NK: eg, routine tests such as general slit lamp exam, corneal staining, Schirmer test, blink pattern and reflex tearing, or more complex exams (microbiological examination, confocal microscopy, anterior OCT, impression cytology)
- Assess for infectious etiology: if active infection exists, treat underlying infection
- Discontinue ocular treatments causing toxicity

**Neurotrophic Keratitis Diagnosis**

**Staging**

**Stage 1 (Mild)**
- Punctate keratitis, epithelial hyperplasia, stromal scarring, and corneal neovascularization

**Stage 2 (Moderate)**
- Persistent epithelial defect (PED), usually in the paracentral area and with an oval shape

**Stage 3 (Severe)**
- Stromal melting
- Corneal thinning and perforation

**Treatment**

**Stage 1 (Mild)**
- Preservative-free artificial tears
- Ocular lubricants
- Discontinuation of topical/systemic medications associated with corneal toxicity
- Punctal plugs
- Oral omega-3 fatty acid supplementation

**Stage 2 (Moderate)**
- Topical antibiotics (eg, doxycycline, fluorquinolone)
- Topical steroids
- Autologous serum eye drops
- Therapeutic bandage contact lenses

**Stage 3 (Severe)**
- Pharmacological treatments
- Conjunctival flap
- Tarsorrhaphy
- Amniotic membrane transplantation

**OXERVATE™ (cenergermin-bkb) ophthalmic solution 0.002% (20 mcg/mL)**

OXERVATE is a recombinant human nerve growth factor indicated for the treatment of neurotrophic keratitis.
Important Safety Information

INDICATION
OXERVATE™ (cenegermin-bkbj) ophthalmic solution 0.002% is indicated for the treatment of neurotrophic keratitis.

DOSAGE FORMS AND STRENGTHS
Ophthalmic solution for topical use in the eye: cenegermin-bkbj 0.002% (20 mcg/mL) is a clear, colorless solution in a multiple-dose vial.

CONTRAINDICATIONS
None.

WARNINGS AND PRECAUTIONS
Use With Contact Lenses
Contact lenses should be removed before applying OXERVATE because the presence of a contact lens (either therapeutic or corrective) could theoretically limit the distribution of cenegermin-bkbj onto the area of the corneal lesion. Lenses may be reinserted 15 minutes after administration.

Eye Discomfort
OXERVATE may cause mild to moderate eye discomfort such as eye pain during treatment. The patient should be advised to contact their doctor if a more serious eye reaction occurs.

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 compared directly to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

In 2 clinical trials of patients with neurotrophic keratitis, a total of 101 patients received cenegermin-bkbj eye drops at 20 mcg/mL at a frequency of 6 times daily in the affected eye(s) for a duration of 8 weeks. The mean age of the population was 61 to 65 years of age (18 to 95). The most common adverse reaction in clinical trials that occurred more frequently with OXERVATE was eye pain (16% of patients). Other adverse reactions included corneal deposits, foreign body sensation in the eye, ocular hyperemia (enlarged blood vessels in the white of the eye), swelling (inflammation) of the eye, and increase in tears (1%-10% of patients).

USE IN SPECIFIC POPULATIONS
Pregnancy
Risk Summary
There are no data from the use of OXERVATE in pregnant women to inform any drug-associated risks. Administration of cenegermin-bkbj to pregnant rats or rabbits during the period of organogenesis did not produce adverse fetal effects at clinically relevant doses. In a pre- and postnatal development study, administration of cenegermin-bkbj to pregnant rats throughout gestation and lactation did not produce adverse effects in offspring at clinically relevant doses.
Data

Animal Data

In embryofetal development studies, daily subcutaneous administration of cenegermin-bkbj to pregnant rats and rabbits throughout the period of organogenesis produced a slight increase in postimplantation loss at doses greater than or equal to 42 mcg/kg/day (267 times the maximum recommended human ophthalmic dose [MRHOD]). A no-observed-adverse-effect level (NOAEL) was not established for postimplantation loss in either species. In rats, hydrocephaly and ureter anomalies were observed once each in fetuses at 267 mcg/kg/day (1709 times the MRHOD). In rabbits, cardiovascular malformations, including ventricular and atrial septal defects, enlarged heart, and aortic arch dilation, were observed once each in fetuses at 83 mcg/kg/day (534 times the MRHOD). No fetal malformations were observed in rats and rabbits at doses of 133 mcg/kg/day and 42 mcg/kg/day, respectively.

In a pre- and postnatal development study, daily subcutaneous administration of cenegermin-bkbj to pregnant rats during the period of organogenesis and lactation did not affect parturition and was not associated with adverse toxicity in offspring at doses up to 267 mcg/kg/day.

In parental rats and rabbits, an immunogenic response to cenegermin-bkbj was observed. Given that cenegermin-bkbj is a heterologous protein in animals, this response may not be relevant to humans.

Lactation

Risk Summary

There are no data on the presence of OXERVATE in human milk, the effects on breastfed infants, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for OXERVATE and with any potential adverse effects on the breastfed infant.

Pediatric Use

The safety and effectiveness of OXERVATE have been established in the pediatric population. Use of OXERVATE in this population is supported by evidence from adequate and well-controlled trials of OXERVATE in adults with additional safety data in pediatric patients from 2 years of age and older.

Geriatric Use

Of the total number of subjects in clinical studies of OXERVATE, 43.5% were 65 years old and older. No overall differences in safety or effectiveness were observed between elderly and younger adult patients.

Please see full Prescribing Information at www.OXERVATE.com.

• The FDA-approved product labeling can be found at www.OXERVATE.com
• You may report side effects to FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. You may also report side effects to Dompé at USDrugSafety@dompe.com or 1-833-366-7387
References


