AN EXPANDED indication for aflibercept injection (Eylea, Regeneron) is now approved by the FDA to treat all stages of diabetic retinopathy (DR).

The approval is significant in that for the first time, an anti-vascular endothelial growth factor (VEGF) agent has been evaluated and approved in patients with moderately severe to severe non-proliferative diabetic retinopathy (NPDR).

“The PANORAMA trial marks the first time we have a prospective, multicenter, double-masked, randomized, controlled trial evaluating these high-risk NPDR eyes without diabetic macular edema (DME),” said Charles C. Wykoff, MD, PhD, Retina Consultants of Houston.

The study showed that not only can clinicians improve the Diabetic Retinopathy Severity Scale (DRSS) score, but they also can prevent sight-threatening complications.
Brief Summary of Prescribing Information for XELPROS™ (latanoprost ophthalmic emulsion) 0.005%, for topical ophthalmic use

See package insert for Full Prescribing Information.

INDICATIONS AND USAGE
XELPROS is indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

CONTRAINDICATIONS
Known hypersensitivity to latanoprost, or any other ingredients in this product.

WARNINGS AND PRECAUTIONS
Pigmentation
XELPROS may cause changes to pigmented tissues. The most frequently reported changes are increased pigmentation of the iris, periorbital tissue (eyelid), and eyelashes. Pigmentation is expected to increase as long as XELPROS is administered. After discontinuation of XELPROS, iris pigmentation is likely to be permanent. Patients who receive treatment should be informed of the possibility of increased pigmentation. The long-term effects of increased pigmentation are not known.

Eyelash Changes
XELPROS may gradually change eyelashes and vellus hair in the treated eye, including increased length, thickness, pigmentation, and number of lashes. The changes are usually reversible upon discontinuation of treatment.

Intraocular Inflammation
XELPROS should be used with caution in patients with a history of intraocular inflammation (iritis/uveitis) and should generally not be used in patients with active intraocular inflammation.

Macular Edema
XELPROS 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
XELPROS should be used with caution in patients with a history of herpetic keratitis. XELPROS should be avoided in cases of active herpes simplex keratitis because inflammation may be exacerbated.

Bacterial Keratitis
There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products.

Use with Contact Lenses
Contact lenses should be removed prior to administration of XELPROS and may be reinserted 15 minutes following administration.

ADVERSE REACTIONS
Clinical Trials Experience
Because clinical trials 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 clinical practice.

Across multiple clinical trials conducted with XELPROS, the most frequently reported ocular adverse reactions were eye pain/stinging upon instillation and ocular hyperemia, reported in 55% and 41% of patients treated with XELPROS, respectively. Other adverse reactions reported (incidence ≥5%) were conjunctival hyperemia, eye discharge, growth of eyelashes, and eyelash thickening. Less than 1% of patients discontinued therapy because of intolerance to the eye pain/stinging or to the ocular hyperemia.
DRUG INTERACTIONS
Precipitation may occur if drugs containing thimerosal are used concomitantly with XELPROS. If such drugs are used, they should be administered at least 5 minutes apart.

USE IN SPECIFIC POPULATIONS
Pregnancy
Pregnancy Category C
Reproduction studies have been performed in rats and rabbits. In rabbits, an incidence of 4 of 16 dams had no viable fetuses at a dose that was approximately 80 times the maximum human dose, and the highest nonembryocidal dose in rabbits was approximately 15 times the maximum human dose. There are no adequate and well-controlled studies in pregnant women. XELPROS should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers
It is not known whether latanoprost or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when XELPROS is administered to a nursing woman.

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

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

PATIENT COUNSELING INFORMATION
Potential for Pigmentation
Advise patients about the potential for increased brown pigmentation of the iris, which may be permanent. Patients should also be informed about the possibility of eyelid skin darkening, which may be reversible after discontinuation of XELPROS.

Potential for Eyelash Changes
Inform patients of the possibility of eyelash and vellus hair changes in the treated eye during treatment with XELPROS. These changes may result in a disparity between eyes in length, thickness, pigmentation, number of eyelashes or vellus hairs, and/or direction of eyelash growth. Eyelash changes are usually reversible upon discontinuation of treatment.

Handling the Container
Instruct patients to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures because this could cause the tip to become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated emulsions.

When to Seek Physician Advice
Advise patients that if they develop an intercurrent ocular condition (eg, trauma or infection) or have ocular surgery, or develop any ocular reactions, particularly conjunctivitis and eyelid reactions, they should immediately seek their physician’s advice concerning the continued use of the multiple-dose container.

Use with Contact Lenses
Advise patients that contact lenses should be removed prior to administration of the emulsion. Lenses may be reinserted 15 minutes following administration of XELPROS.

Use with Other Ophthalmic Drugs
Advise patients that if more than one topical ophthalmic drug is being used, the drugs should be administered at least 5 minutes apart.

Rx Only
Distributed by: Sun Pharmaceutical Industries, Inc. Cranbury, NJ 08512

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INDICATIONS AND USAGE
XELPROS™ (latanoprost ophthalmic emulsion) 0.005% is indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

IMPORTANT SAFETY INFORMATION
CONTRAINDICATIONS
XELPROS is contraindicated in patients with a known hypersensitivity to latanoprost, or any other ingredients in this product.

WARNINGS AND PRECAUTIONS
Pigmentation: XELPROS may cause changes to pigmented tissues. The most frequently reported changes are increased pigmentation of the iris, periorbital tissue (eyelid), and eyelashes. Pigmentation is expected to increase as long as XELPROS is administered. After discontinuation of XELPROS, iris pigmentation is likely to be permanent. Patients who receive treatment should be informed of the possibility of increased pigmentation. The long-term effects of increased pigmentation are not known.

Eyelash Changes: XELPROS may gradually change eyelashes and vellus hair in the treated eye, including increased length, thickness, pigmentation, and number of lashes. The changes are usually reversible upon discontinuation of treatment.

Intraocular Inflammation: XELPROS should be used with caution in patients with a history of intraocular inflammation (iritis/uveitis) and should generally not be used in patients with active intraocular inflammation.

Macular Edema: XELPROS 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: XELPROS should be used with caution in patients with a history of herpetic keratitis. XELPROS should be avoided in cases of active herpes simplex keratitis because inflammation may be exacerbated.

Bacterial Keratitis: There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products.

Use with Contact Lenses: Contact lenses should be removed prior to administration of XELPROS and may be reinserted 15 minutes following administration.

ADVERSE REACTIONS
The most common ocular adverse reactions in clinical trials (incidence ≥5%) for XELPROS were eye pain/stinging, ocular hyperemia, conjunctival hyperemia, eye discharge, growth of eyelashes, and eyelash thickening.

DRUG INTERACTIONS
Precipitation may occur if drugs containing thimerosal are used concomitantly with XELPROS. If such drugs are used, they should be administered at least 5 minutes apart.

Please see brief summary of Full Prescribing Information on the reverse side.

BAK=benzalkonium chloride.

Anti-VEGF expansion treats all DR stages

Afiblercept, two dosing options allow clinicians to customize treatment to patients’ needs

By Michelle Dalton, ELS;
Reviewed by Charles C. Wykoff, MD, PhD

An expanded indication for aflibercept injection (Eylea, Regeneron) is now approved by the FDA to treat all stages of diabetic retinopathy (DR).

“The PANORAMA trial marks the first time we have a prospective, multicenter, double-masked, randomized, controlled trial evaluating these high-risk NPDR eyes without diabetic macular edema (DME),” said Charles C. Wykoff, MD, PhD, Retina Consultants of Houston.

The study showed that not only can clinicians improve the Diabetic Retinopathy Severity Scale (DRSS) score, but they also can prevent sight-threatening complications.
THE STARS HAVE ALIGNED.
DISTANCE AND STABILITY.

ACTIVEFOCUS™ Optical Design:

Only one **presbyopia-correcting** IOL design delivers a full range of vision with **uncompromised distance** and **unrivaled stability**.

Please see next page for Important Product Information and supporting references.
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.
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.

The data are compelling and consistent—OMIDRIA makes cataract surgery better for you and your patients

Published and presented clinical studies and manuscripts in press and/or in preparation report that in post-launch (i.e., not included in current labeling), prospective and retrospective, double-masked and open-label, cohort and case-controlled, single- and multi-center analyses, the use of OMIDRIA, compared to the surgeons’ standard of care, statistically significantly:

• Prevents Intraoperative Floppy Iris Syndrome (IFIS)1
• Reduces complication rates (epinephrine comparator)3
• Decreases use of pupil-expanding devices (epinephrine comparator)2,3,4
• Reduces surgical times (epinephrine comparator)3,4,5,7,8
• Prevents miosis during femtosecond laser-assisted surgery (epinephrine comparator)2,3,4
• Improves uncorrected visual acuity on day after surgery (epinephrine comparator)2
• Delivers NSAID to the anterior chamber and related structures better than routine preoperative topical drug administration, resulting in effectively complete postoperative inhibition of COX-1 and COX-29,10
• Reduces the incidence of rebound iritis, postoperative pain/photophobia, and cystoid macular edema (CME) in patients without preoperative vitreomacular traction (VMT), when used with a postoperative topical NSAID (compared to postoperative topical NSAID + corticosteroid without OMIDRIA)2,3

OMIDRIA inhibits prostaglandin release, reducing intraoperative inflammation, to prevent miosis and reduce postoperative pain13

OMIDRIA is separately reimbursed under Medicare Part B and by many Medicare Advantage and commercial payers.*

Contact your OMIDRIA representative today or visit omidria.com to learn more.

*Based on currently available information and subject to change without notice. Individual plan coverage, policies, and procedures may vary and should be confirmed. Omeros does not guarantee coverage or payment.

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.


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Seeing the future
Real-world experience can bring fresh insight

A YOUNG OPHTHALMOLOGIST and I strolled into the convention center at an event in another country. We found ourselves among booths exhibiting the wares from a wide range of ophthalmic device and pharmaceutical companies. It was the first such international meeting for this junior colleague.

“What is particularly fun about these exhibits is seeing what they have for sale in other countries, including medicines and devices that might not be approved for marketing in the United States until years from now,” I told this young person as we walked along the exhibit floor. “It is like seeing into the future.”

MEETING MEMORIES
This recent experience reminded me of something that I had learned many years ago while attending a meeting. I was a young assistant professor with much to learn, and the meeting was in the tropical paradise of Hawaii.

The Aloha State became the 50th state in 1959, and while it may not be an international venue, this particular meeting had attracted speakers from countries around the world.

The daily routine during the meeting was a few hours of lectures followed by relaxation, including floating in the swimming pool, body surfing at the beach, or trying to hit a little white ball into a succession of 18 holes.

On this particular day, I had listened to one of my fellow American speakers describe the results of a clinical trial with a new multifocal IOL.

IMPRESSIVE ... INITIALLY
The data were impressive and the speaker, a consultant to the manufacturer, was enthusiastic that this device would be a big success in the United States.

Distance and near uncorrected visual acuities were quite good, and contrast sensitivity testing showed very little loss of contrast compared with standard monofocal lenses.

A few hours later, I found myself in the pool with a senior ophthalmology department chairman from Europe. We found that we could beat the afternoon heat and humidity by standing in the pool near the edge, with our maîtai within easy reach to maintain proper hydration. I brought up the subject of the multifocal IOL.

“When I get back to Los Angeles, I am going to have to get ready to start implanting a lot of those IOLs,” I told my friend.

“Why?” he asked.

“You heard the talk this morning,” I said. “The data he showed seemed quite impressive to me.”

“Don’t waste your time,” he responded. “That lens is no good.”

“No good?” I asked. “But the data he presented seemed wonderful. Why do you say the lens is no good?”

My senior colleague explained that it had been available in his country for two years, and everyone was quick to try it when it first entered the market.

“We quickly learned that a very high percentage of patients complained bitterly of problems with night driving, and we were soon dealing with angry patients and explanting the lenses,” he explained. “No one uses them anymore. You definitely don’t want to be putting those lenses in your patients.”

LEARNING THE TRUTH
I recall being stunned by his statements. The “hot-off-the-press” information from the clinical trial that seemed so exciting was rendered moot by two years of practical real-world experience of excellent clinicians.

Time then proved my colleague to be absolutely correct. Within a period of about two years, the limitations of the device became evident to all and the lens never was marketed in the United States.

“Wow,” I thought. “You can learn an awful lot about what will happen in the future in the United States by hanging around in the pool with intelligent ophthalmologists from other countries.”

Instead of continuing to plan my use of this new multifocal IOL, I took another sip on my maîtai and focused on perfecting my floatation technique.
XIIDRA MAY INTERRUPT THE CYCLE OF INFLAMMATION CENTRAL TO DRY EYE DISEASE\textsuperscript{1,2}

The exact mechanism of action of Xiidra in Dry Eye Disease is not known.\textsuperscript{1}

**Indication**

Xiidra\textsuperscript{®} (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.

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**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:**


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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 omphalocele 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 omphalocele 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.

Manufactured for: Shire US Inc., 300 Shire Way, Lexington, MA 02421. For more information, go to www.Xiidra.com or call 1-800-828-2088. Marks designated ® and ™ are owned by Shire or an affiliated company. ©2018 Shire US Inc. SHIRE and the Shire Logo are trademarks or registered trademarks of Shire Pharmaceutical Holdings Ireland Limited or its affiliates. Patented: please see https://www.shire.com/legal-notice/product-patents Last Modified: 01/2018 533769
Engage faculty members in program expectations from the start

Communication is key to optimizing potential of every instructor

By Lynda Charters; Reviewed by Vivek R. Patel, MD

In an ideal world, all faculty members are equally motivated. They all want to teach, and teaching is a clear part of the job description. In the real world, however, faculty members are not motivated by the same things.

The reasons for being in academia vary widely, and expectations and feedback are not always clearly communicated, according to Vivek R. Patel, MD, associate professor of ophthalmology, director of the Neuro-Ophthalmology Service, and director of education at the University of Southern California Roski Eye Institute, Keck School of Medicine, Los Angeles.

“Faculty members are not born challenging,” he said.

**CHALLENGE BORN**

This can occur as a result of competing demands of the institution and the individual.

Program expectations include good supervisory coverage for all sites, dedicated teachers, didactic curriculum champions, help with surgical curricula, mentors (research, clinical and personal) for residents, managing residents’ expectations, and satisfying Graduate Medical Education and the Accreditation Council for Graduate Medical Education requirements, Dr. Patel explained.

**CLEARLY, OPENLY COMMUNICATE**

Communication is key to optimizing potential of every instructor

Dr. Patel emphasized that faculty members feel stretched to their limits balancing competing responsibilities.

“No one role is equally interesting to everyone, and a lack of incentive is an important problem to address as medical school educators,” he said.

To deal with the challenges that can arise today, there are several principles to live by.

**LEARN ABOUT THE DEPARTMENT**

Dr. Patel advised that faculty members should try to learn the identity or mission of their department and program.

“We need to work within our departmental mission; departments differ in that respect,” he said. “Some are research-heavy, others are more clinical.”

**GET HELP WITHOUT DRAMA**

This can happen by asking colleagues about which areas of the program mission they believe they can contribute to most.

Dr. Patel added that the teaching faculty must reflect the identity of the program to some degree.

“Besides knowing the program, it is also important to know the individuals in the program and their strengths and interests,” he said. “We can all contribute to the program but not necessarily in the same way.”

**TAKE-HOME**

Clear and effective communication can go a long way to satisfy both the medical program’s needs, and those of the faculty members, who need support from the chairman, and medical school.

**NOT EVERYONE FEELS LIKE THEY ARE GETTING SUFFICIENT FEEDBACK**

“Not everyone feels like they are getting sufficient feedback,” Dr. Patel explained. “Faculty generally never get feedback about how they are teaching and how they are received by residents and other faculty members. This should be done before they become alienated.”

Rather than mandated improvement engagement, faculty members need support from the chairman, and medical school to help foster the vision for a well-rounded, and balanced program.

“Ultimately, we must establish a culture of recognizing and acknowledging education as a contribution worthy of compensation and promotion that includes clinical educator promotions.”

—Vivek R. Patel, MD

**‘Ultimately, we must establish a culture of recognizing and acknowledging education as a contribution worthy of compensation and promotion that includes clinical educator promotions.’** - Vivek R. Patel, MD

In contrast, faculty members have their own set of needs, including clinical demands, financial productivity, research goals, managing patients’ expectations, and academic development. Barriers to successfully meshing the program are too great, looking elsewhere is an option, and there are some possible solutions.

This can include getting assistance from volunteers or adjunct faculty, the latter of which can be hired for perhaps one day a week to provide support.

Another creative option, if the institution is lacking a particular area of experience, “away” rotations can afford residents the needed training at another facility.

**ULTIMATELY, WE MUST ESTABLISH A CULTURE OF RECOGNIZING AND ACKNOWLEDGING EDUCATION AS A CONTRIBUTION WORTHY OF COMPENSATION AND PROMOTION THAT INCLUDES CLINICAL EDUCATOR PROMOTIONS.”** —Vivek R. Patel, MD

Dr. Patel has no financial interest in any aspect of this report.

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Dr. Patel has no financial interest in any aspect of this report.
Fighting fire with fire: Combating burnout among medical educators

Physicians report emotional exhaustion, depersonalization, decreased accomplishment

By Lynda Charters; Reviewed by Joan M. O’Brien, MD

BURNOUT AMONG EDUCATORS occurs in 40% to 45% of physicians who report emotional exhaustion, depersonalization, or a decreased sense of accomplishment. However, these feelings do not exist in a vacuum. Medical errors, physician suicide, and depression are serious consequences.

Joan M. O’Brien, MD, advised that physicians start by taking a look inward.

Dr. O’Brien is the William F. Norris and George E. de Schweinitz professor, chair of ophthalmology, University of Pennsylvania, and director, Scheie Eye Institute, Philadelphia.

Dr. O’Brien advised that physicians should live in the moment, which can be achieved both by leaving their work in the office and not bringing it home to the family. This can start by putting down the phone or computer. Disconnect for a time from email, and patient charts.

JUST SAY NO

Sometimes, physicians have to consider themselves, and another step in caring for oneself is learning that sometimes you have to say “no.”

Another option is to create a caring work environment by supporting colleagues, and students. “Giving more results in receiving more,” she noted.

LEARN ABOUT YOURSELF

Dr. O’Brien recounted her personal experience with mitigating burnout as an oncology intern early in her medical career.

In her close relationships with an educator and a student, Dr. O’Brien explained that she was able to learn her limitations in caring for seriously ill patients.

Dr. O’Brien ultimately decided to switch her specialty from oncology to ophthalmology.

“I needed to change course,” she explained. “As leaders and faculty, when we feel burned out there comes a moment when we need to talk with our chairman, and change direction.”

Physicians should be able to recognize the signs of burnout among students and residents, and support the promotion of a positive, open learning environment.

TAKE-HOME

Physicians can take steps to avoid burnout, including leaving their work in the office, not bringing it home to the family, and disconnecting for a time from email and patient charts.

WHAT TO AVOID AND WHAT TO DO

For Dr. O’Brien, there are some “never” actions that she takes care to avoid because they commodify physicians. Specifically, she never uses the word “provider” in place of the word “physician.” While it is a small thing, it can go a long way in valuing physicians.

Dr. O’Brien said she also avoids physician performance measures, such as work relative value units, avoids metrics for performance, and de-emphasizes patient satisfaction survey scores.

SHOW APPRECIATION

On the flip side of the coin, she has pursued actions that include always appreciating individuals around her, particularly educators.

Dr. O’Brien also makes an effort to recognize and call out noteworthy educational comments during grand rounds.

It also is important to provide financial incentives for teaching and citizenship from medical centers, and philanthropists, apply for teaching awards for faculty members through societies and universities among others, and support the Academy of Master Clinicians and Educators by advising faculty members to join.

Dr. O’Brien also advocates running frequent team building events promoting transparency of expectations about teaching. She also suggests identifying physician educators.

Openly value their work in academia to ensure that they become role models, and mentors. They will be positioned to educate the next generation of ophthalmologists well, and with enthusiasm.

‘Fostering an environment of belonging can result in reduced rates of attrition in a surgical residency setting. By securing our own well-being, we can ensure that trainees are not experiencing burnout.’

- Joan M. O’Brien, MD

“Success does not mean accepting every request,” Dr. O’Brien pointed out. “Learn to selectively say ‘yes.’”

SHARE YOUR THOUGHTS

Further, she pointed out, by sharing thoughts, burnout and exhaustion can be destigmatized, and physicians can receive the support that they may need.

“We need supportive mentors in all aspects of our lives,” Dr. O’Brien said. “Learn to ask for help, advice, or resources, when needed.”

“Fostering an environment of belonging can result in reduced rates of attrition in a surgical residency program,” Dr. O’Brien said.

EARLY CAREER ISSUES

Higher rates of burnout have been reported in residents, fellows, and physicians early in their careers. Medical students have also been shown to have higher rates of depression than students in other disciplines. Solving the issues in many instances can start at the top.
Indication

LOTEMAX® SM (loteprednol etabonate ophthalmic gel) 0.38% is a corticosteroid indicated for the treatment of post-operative inflammation and pain following ocular surgery.

Important Safety Information

- LOTEMAX® SM, as with other ophthalmic corticosteroids, is contraindicated in most viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal diseases of ocular structures.
- Prolonged use of corticosteroids may result in posterior subcapsular cataract formation.
- Use of corticosteroids may result in posterior subcapsular cataract formation.
- LOTEMAX® SM patients had complete ACC resolution vs vehicle (15%) at Day 8 (N=371, P<0.0001)1.3†
- 74% of LOTEMAX® SM patients were completely pain-free vs vehicle (49%) at Day 8 (N=371, P<0.0001)1.3†
- 30% of LOTEMAX® SM patients had complete ACC resolution vs vehicle (15%) at Day 8 (N=371, P<0.0001)1.3†
- 74% of LOTEMAX® SM patients were completely pain-free vs vehicle (49%) at Day 8 (N=371, P<0.0001)1.3†

†Pooled analysis of Phase 3 clinical studies. Study 1: 29% LOTEMAX® SM (N=171) vs 9% vehicle (N=172). Study 2: 31% LOTEMAX® SM (N=200) vs 20% vehicle (N=199); P<0.05 for all.
‡Pooled analysis of Phase 3 clinical studies. Study 1: 73% LOTEMAX® SM (N=171) vs 48% vehicle (N=172). Study 2: 76% LOTEMAX® SM (N=200) vs 50% vehicle (N=199); P<0.05 for all.

Important Safety Information (cont.)

- The use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation. In those with diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical steroids. The initial prescription and renewal of the medication order should be made by a physician only after examination of the patient with the aid of magnification such as slit lamp biomicroscopy and, where appropriate, fluorescein staining.
- 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 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 of the cornea are particularly prone to develop coincidentally with long-term local steroid application. Fungus invasion must be considered in any persistent corneal ulceration where a steroid has been used or is in use. Fungal cultures should be taken when appropriate.
- Contact lenses should not be worn when the eyes are inflamed.
- There were no treatment-emergent adverse drug reactions that occurred in more than 1% of subjects in the three times daily group compared to vehicle.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit [www.fda.gov/medwatch](http://www.fda.gov/medwatch) or call 1-800-FDA-1088.

Please see brief summary of Prescribing Information on adjacent page.

BRIEF SUMMARY OF PRESCRIBING INFORMATION

This Brief Summary does not include all the information needed to use LOTEMAX® SM safely and effectively. See full prescribing information for LOTEMAX® SM.

LOTEMAX® SM (loteprednol etabonate ophthalmic gel) 0.38%

For topical ophthalmic use

Initial U.S. Approval: 1998

INDICATIONS AND USAGE

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

DOSEAGE AND ADMINISTRATION

Invert closed bottle and shake once to fill tip before instilling drops. Apply one drop of LOTEMAX® SM into the conjunctival sac of the affected eye three times daily beginning the day after surgery and continuing throughout the first 2 weeks of the post-operative period.

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

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

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

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

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

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

Contact Lens Wear: Contact lenses should not be worn when the eyes are inflamed.

ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials 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. Adverse reactions associated with ophthalmic steroids include elevated intraocular pressure, which may be associated with infrequent optic nerve damage, visual acuity and field defects, posterior subcapsular cataract formation, delayed wound healing and secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera. There were no treatment-emergent adverse drug reactions that occurred in more than 1% of subjects in the three times daily group compared to vehicle.

USE IN SPECIAL POPULATIONS

Pregnancy: Risk Summary: There are no adequate and well controlled studies with loteprednol etabonate in pregnant women. Loteprednol etabonate produced teratogenicity at clinically relevant doses in the rabbit and rat when administered orally during pregnancy. Loteprednol etabonate produced malformations when administered orally to pregnant rabbits at doses 4.2 times the recommended human ophthalmic dose (RHOD) and to pregnant rats at doses 106 times the RHOD. In pregnant rats receiving oral doses of loteprednol etabonate during the period equivalent to the last trimester of pregnancy through lactation in humans, survival of offspring was reduced at doses 10.6 times the RHOD. Maternal toxicity was observed in rats at doses 1066 times the RHOD, and a maternal no observed adverse effect level (NOAEL) was established at 106 times the RHOD. The background and risk of major birth defects and miscarriage in the human population is unknown. However, the background risk in the U.S. general population of major birth defects is 2 to 4%, and of miscarriage is 15 to 20%, of clinically recognized pregnancies. Data Animal Data. Embryofetal studies were conducted in pregnant rabbits administered loteprednol etabonate by oral gavage on gestation days 6 to 18, to target the period of organogenesis. Loteprednol etabonate produced fetal malformations at 0.1 mg/kg (4.2 times the recommended human ophthalmic dose (RHOD) based on body surface area, assuming 100% absorption). Spina bifida (including meningocele) was observed at 0.1 mg/kg, and exencephaly and craniofacial malformations were observed at 0.4 mg/kg (17 times the RHOD). At 3 mg/kg (128 times the RHOD), loteprednol etabonate was associated with increased incidences of abnormal left common carotid artery, limb flexures, umbilical hernia, scoliosis, and delayed ossification. Abortion and embryofetal lethality (resorption) occurred at 6 mg/kg (256 times the RHOD). A NOAEL for developmental toxicity was not established in this study. The NOAEL for maternal toxicity in rabbits was 3 mg/kg/day. Embryofetal studies were conducted in pregnant rats administered loteprednol etabonate by oral gavage on gestation days 6 to 15, to target the period of organogenesis. Loteprednol etabonate produced fetal malformations, including absent innominate artery at 5 mg/kg (106 times the RHOD); and cleft palate, agnathia, cardiovascular defects, umbilical hernia, decreased fetal body weight and decreased skeletal ossification at 50 mg/kg (1066 times the RHOD). Embryofetal lethality (resorption) was observed at 100 mg/kg (2133 times the RHOD). The NOAEL for developmental toxicity in rats was 0.5 mg/kg (10.6 times the RHOD). Loteprednol etabonate was maternally toxic (reduced body weight gain) at 50 mg/kg/day. The NOAEL for maternal toxicity was 5 mg/kg. A peri-/postnatal study was conducted in rats administered loteprednol etabonate by oral gavage from gestation day 15 (start of fetal period) to postnatal day 21 (end of lactation period). At 0.5 mg/kg (10.6 times the clinical dose), reduced survival was observed in live-born offspring. Doses ≥ 5 mg/kg (106 times the RHOD) caused umbilical hernia/incomplete gastrointestinal tract. Doses ≥ 50 mg/kg (1066 times the RHOD) produced maternal toxicity (reduced body weight gain, death), decreased number of live-born offspring, decreased birth weight, and delays in postnatal development. A developmental NOAEL was not established in this study. The NOAEL for maternal toxicity was 5 mg/kg.

Lactation: There are no data on the presence of loteprednol etabonate in human milk, the effects on the 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 LOTEMAX® SM and any potential adverse effects on the breastfed infant from LOTEMAX® SM.

Pediatric Use: Safety and effectiveness of LOTEMAX® SM in pediatric patients have not been established.

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

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term animal studies have not been conducted to evaluate the carcinogenic potential of loteprednol etabonate. Loteprednol etabonate was not genotoxic in vitro in the Ames test, the mouse lymphoma tk assay, or in the chromosomal aberration test in human lymphocytes, or in vivo in the mouse micronucleus assay. Treatment of male and female rats with 25 mg/kg/day of loteprednol etabonate (533 times the RHOD based on body surface area, assuming 100% absorption) prior to and during mating caused preimplantation losses and decreased the number of live fetuses/live births. The NOAEL for fertility in rats was 5 mg/kg/day (106 times the RHOD).

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IV PGE1 infusion for acute CRAO

Study finds treatment resulted in significant visual improvement

By Brett Malbin, MD, with Xihui Lin, MD; Special to Ophthalmology Times

PURPOSE

In this abstract, we evaluate the efficacy of intravenous (IV) prostaglandin E1 (PGE1) infusion within the first 24 hours of acute central retinal artery occlusion (CRAO).

CRAO is a blockage in the main artery of the retina, often resulting in severe vision loss. CRAO tends to have a poor outcome, no matter what we do.

I’d like to say that we came up with this idea all by ourselves, but there was a 2013 study in Japan that looked at 10 eyes in 10 patients.

The results were promising. We took the data and became, to my knowledge, the first U.S. institution to publish the data and became, to my knowledge, a 2013 study in Japan that looked at 10 eyes in 10 patients.

METHODS

The study included the retrospective analysis of six eyes from six patients. It included analysis of the best corrected visual acuity (mean age: 69.33 years) with acute CRAO who were treated with twice-daily intravenous infusion of 40 μg PGE1.

The therapy continued until the patient no longer experienced visual acuity improvements for 24 hours.

RESULTS

The average time to presentation was 8.33 hours, with a range from two to 12 hours. The average age at presentation was 69.33 years old.

In the study, 66.67% of patients were African American, and 33.33% were Caucasian. The best-corrected visual acuity (BCVA) logMAR at presentation was 2.73 and found to be 1.48 (p = 0.025) at one-month follow up.

There was essentially no correlation between time to presentation and amount of visual recovery (R² = 0.036). Six out of six eyes in the study showed improved visual acuity. We would like to expand the study to include more patients.

CONCLUSION

The study found that IV PGE1 infusion resulted in a significant visual improvement in patients presenting with acute CRAO. Therapy at 40 μg BID was well tolerated and no patients experienced significant or mild side effects.

The study also found that six of six eyes demonstrated visual improvement compared with 16% of patients as previously described.

In summary, CRAO can present in all ophthalmology settings ranging from primary clinics to tertiary academic centers.

To date, there have been no studies which were able to demonstrate reproducible significant visual acuity recovery.

Our data suggest PGE1 IV infusion may represent a safe and effective treatment for CRAO, resulting in statistically significant visual acuity recovery in patients.

This study is limited by its retrospective nature. Future randomly selected prospective studies can further determine the effectiveness of therapy.

REFERENCES


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INNOVATIVE PROCEDURES IN
Special Report
CORNEA SURGERY
ADVANCES CONTINUE TO PROGRESS FOR CORNEAL SURGEONS AND THEIR PATIENTS

Corresponding with the evolution in techniques for endothelial keratoplasty (EK), there has been a debate over which procedure corneal surgeons should perform. Going forward, the discussion will be about the battle between Descemet’s membrane endothelial keratoplasty (DMEK) and nano-thin Descemet’s stripping automated endothelial keratoplasty (NT-DSAEK), said Clara C. Chan, MD.

Surgeons performing DSAEK first migrated to ultrathin (UT) DSAEK, and now we will see migration to NT-DSAEK,” Dr. Chan said. “The use of thinner graft tissue has benefits of a lower rejection rate, more predictable tissue handling, fewer detachments, and lower rebubbling rates.”

“We know that, when compared with DSAEK using thicker grafts, DMEK seems to be associated with lower higher-order aberrations (HOAs) and faster visual recovery,” she said. “Studies are needed to compare long-term outcomes of DMEK with UT- and NT-DSAEK.”

Dr. Chan reviewed published literature comparing outcomes with different EK techniques. She cited the 2008 American Academy of Ophthalmology (AAO) Ophthalmic Technology Assessment report on Descemet’s stripping endothelial keratoplasty (DSEK), noting that the first outcomes study on DSEK appeared in the peer-reviewed literature in 2005.

In 2006, the first report of DMEK appeared in the peer-reviewed literature. Thin DSAEK, using a graft with a thickness <130 μm was first reported in 2011. By 2018, authors of an AAO Ophthalmic Technology Assessment concluded that DMEK was superior to DSEK/DSAEK in terms of providing faster vision recovery, better overall visual outcomes, a lower rejection rate, and less refractive error.

Authors of a systematic review and meta-analysis of DMEK and DSEK/DSAEK came to similar conclusions regarding the relative advantages and similarities of the two procedures, Dr. Chan noted.

UT-DSAEK (graft thickness <100 μm) was described in 2011, and the first randomly selected controlled trial comparing DMEK and UT-DSAEK (average central graft thickness 73 microns) was reported this year. Patients included in the study had Fuch’s endothelial dystrophy or pseudophakic bullous keratopathy and were followed for 12 months after surgery.

The study found DMEK was associated with better BSCVA at three, six, and 12 months, but also that later during the available follow-up, there was a trend for increased endothelial cell loss after DMEK compared with UT-DSAEK. There were no statistically significant differences between the two surgeries in rates of rebubbling, graft rejection or graft survival, although the study only included 50 eyes, and may have been underpowered to evaluate these outcomes.

Analyses of posterior corneal HOAs showed a decrease from baseline in eyes that underwent DMEK, and an increase in the UT-DSAEK group.

The only published comparison of NT-DSAEK and DMEK is a prospective case series that includes 28 eyes with Fuch’s endothelial dystrophy. The surgeons evaluated BSCVA as the primary outcome and found it was better after DMEK at one month postoperatively, but similar for the two procedures at three, six, and 12 months. In addition, the percentage of eyes achieving BSCVA of 20/25 or better was similar in the two groups at six and 12 months.

Rebubbling was needed in one eye that had NT-DSAEK. There were no cases of graft rejection or failure.

DMEK VS DSAEK: DEBATE GOES ON
Question of which technique is superior remains unanswered amid shift to thinner grafts
By Cheryl Guttman Krader; Reviewed by Clara C. Chan, MD

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Dextenza®
(dexamethasone ophthalmic insert) 0.4 mg
for intracanalicular use

BIG TIME INNOVATION

DEXTENZA is an advancement in steroid treatment
- Resorbable, so no need for removal²
- Insert can be removed via saline irrigation or manual expression, if necessary²
- Physicians rated DEXTENZA as easy to insert³*
- Designed to deliver a tapered dose¹
- Contains fluorescein for visualization²
- No additional components or assembly required²

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 (9%); intraocular pressure increased (5%); visual acuity reduced (2%); eye pain (1%); cystoid macular edema (1%); corneal edema (1%); and conjunctival hyperemia (1%).

ADVERSE REACTIONS

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


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Dextenza®
(dexamethasone ophthalmic insert) 0.4 mg
for intracanalicular use

BRIEF SUMMARY: Please see the DEXTENZA Package Insert for full prescribing information for DEXTENZA (11/2018)

1 INDICATIONS AND USAGE

DEXTENZA® (dexamethasone ophthalmic insert) is a corticosteroid indicated for the treatment of ocular pain following ophthalmic surgery (1).

2 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 dacyrocystitis.

3 WARNINGS AND PRECAUTIONS

3.1 Intraocular Pressure 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. Intraocular pressure should be monitored during the course of the treatment.

3.2 Bacterial Infection

Corticosteroids may suppress the host response and thus increase the hazard from secondary ocular infections. In acute purulent conditions, steroids may mask infection and enhance existing infection [see Contraindications (4)].

3.3 Viral Infections

Use of ocular steroids may prolong the course and may exacerbate the severity of many viral infections of the eye (including herpes simplex) [see Contraindications (4)].

3.4 Fungal Infections

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 [see Contraindications (4)].

3.5 Delayed Healing

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

4 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling:

- Intraocular Pressure Increase [see Warnings and Precautions (5.1)]
- Bacterial Infection [see Warnings and Precautions (5.2)]
- Viral Infection [see Warnings and Precautions (5.3)]
- Fungal Infection [see Warnings and Precautions (5.4)]
- Delayed Healing [see Warnings and Precautions (5.5)]

5.1 Intraocular Pressure Increase

5.2 Bacterial Infection

5.3 Viral Infections

5.4 Fungal Infections

5.5 Delayed Healing

6 CLINICAL TRIAL

In a recent clinical trial, only 81% of the viruses causing EKC were species D viruses, while about 10% were species E4, and most of the remainder were species B viruses, led by B3.

“Species D was more likely associated with subepithelial infiltrates and more severe disease, so the paradigm holds,” Dr. Chodosh said.

Understanding the structure of the adenovirus is essential to making progress toward a treatment. The protein capsid of the adenovirus is an icosahedron whose faces are composed of 240 hexons that form the serum neutralization determinant. It is interrupted by 12 rings of penton base proteins—five proteins forming each ring—from which project the fiber and the fiber knob.

“It is the binding of the fiber knob to a host cell receptor that starts the infectious process, but it is the subsequent interaction with an amino acid motif on the penton base called the RGD loop that—and because there are five proteins—aggregates five alpha-v integrins that cause conformational changes in those integrins, which leads to phosphorylation and intracellular signaling,” Dr. Chodosh said. “And it is that intracellular signaling pathway that pulls the virus into the cell.”

The same pathway that mediates internalization is also responsible for host-cell immune response—innate immune expression of chemokines—and also stabilizes the cell so that it remains alive long enough for the virus to replicate.

Dr. Chodosh referred to the work of the late Prof. Barrie Jones of Moorfields Eye Hospital, who postulated that the adenovirus grows in the epithelial cells alone, and in killing them, liberates antigens, which soak into the underlying stroma to become fixed in the surface of fiber and cell membranes.

No damage occurs until antibodies arrive from the bloodstream or are produced locally.

There is evidence for such a stromal signal, Dr. Chodosh said, but not an antigen-antibody reaction due to subepithelial infiltration formation.

“The data are most consistent with a different kind of signal, a chemotactic signal caused by a chemotactic protein in the anterior cornea,” he said.

Much has been learned about epidemic keratoconjunctivitis (EKC) since it was first described in 1869, yet aspects of the viral pathogenesis of adenovirus keratitis have remained an enigma, according to James Chodosh, MD, MPH, the David Glendenning Cogan Professor of Ophthalmology in the field of cornea and external disease, Massachusetts Eye and Ear, Harvard Medical School.

However, persistent researchers armed with the latest technology are following clues that one day may crack the code of this severe form of conjunctivitis.

EKC is the only ocular adenovirus infection with corneal involvement and is caused principally by the human adenovirus species D (HADV-D), types 8, 37, 53, 54, 56, and 64 (formerly type 19a).

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PATHOGENESIS MODEL

He described a proposed pathogenesis model for adenoviral keratitis:

- Infection of the corneal epithelium
- Interaction between the viral capsid and molecular pattern receptors on corneal cells
- Intracellular signaling
- Chemokine expression
- Binding of chemokine protein to epithelial basement membrane
- Migration of limbal leukocytes to chemokine reservoirs at corneal epithelial basement membrane, forming infiltrates within corneal subepithelial stroma

Based on this model, Dr. Chodosh Continues on page 17: EKC

Adenovirus keratitis challenge
Researchers target form of conjunctivitis

By Nancy Groves; Reviewed by James Chodosh, MD, MPH

MUCH HAS BEEN learned about epidemic keratoconjunctivitis (EKC) since it was first described in 1869, yet aspects of the viral pathogenesis of adenovirus keratitis have remained an enigma, according to James Chodosh, MD, MPH, the David Glendenning Cogan Professor of Ophthalmology in the field of cornea and external disease, Massachusetts Eye and Ear, Harvard Medical School.

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Bringing DALK application to forefront for corneal surgeons

Innovations in procedure may overcome current technical difficulty

By Cheryl Guttman Krader; Reviewed by Marjan Farid, MD

**DEEP ANTERIOR** lamellar keratoplasty (DALK) has recognized advantages compared with penetrating keratoplasty when transplantation is needed in eyes with anterior corneal disease. However, the difficulty of baring the 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 dissection 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 eliminating the need for the big-bubble, said Marjan Farid, MD, professor of ophthalmology, and director of Cornea, Cataract and Refractive Surgery, Gavin Herbert Eye Institute, University of California, Irvine, by Roger Steinert, MD.

"Further exploration and advocacy is needed to bring these innovations in technology into the hands of every corneal surgeon," Dr. Farid said.

Dr. Farid noted that application of the femtosecond laser to keratoplasty was pioneered at the University of California, Irvine, by Roger Steinert, MD.

**EKC**

(Continued from page 16)

would rewrite Jones’ statement to say: “I postulate that the virus grows on the surface, initiating the expression of chemokine-activants which soak into the stroma to become fixed in the underlying basement membrane. Infiltration results only when leucocytes arrive from limbal blood vessels.”

Dr. Chodosh also noted important work on viral evolution performed by the adenovirus research community, which has completed whole genome sequencing on all human adenoviruses.

"Anecdotal evidence from clinicians around the world suggests to me that there are new viruses emerging and more severe, more virulent pathogens," he said, adding that as the database grows, the scope of research will also expand.

Species D is the largest and most rapidly growing adenovirus species, comprising almost two-thirds of all human adenoviruses in GenBank (the National Institute of Health’s genetic sequence database) that have been typed, Dr. Chodosh said. In the last decade, almost 40 new viruses have been added, more than 20 are in the pipeline, and three that have been newly typed are associated with EKC.

Dr. Chodosh, along with his collaborators, has shown that adenoviruses evolved through homologous recombination of specific genomic regions, and that every species D virus to date has at least 2 prior recombinations accounting for its existence. This recombination may be triggered by the frequency and duration of co-infection in humans by different HAdVs with homologous genome parts.

Despite advances in understanding how adenoviruses cause keratitis, why some are more likely to trigger the disease, and how they evolve, there is still no effective, adenovirus-specific therapy for EKC, although ongoing clinical trials show promise, Dr. Chodosh said.

Given the relatively large and still growing number of whole genome sequences for adenoviruses, Dr. Chodosh said the focus now in the laboratory is on connecting studies of genomics and pathogenesis.

"The audacious goal is to be able to take a viral genome, predict what tissues it would infect, and how virulent it would be," he concluded. “From that, we may eventually be able to develop specific therapies that are geared towards the virus instead of solely at the inflammation.”

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This article was adapted from the Jones/Smolin Lecture, which Dr. Chodosh presented at the 2018 meeting of the American Academy of Ophthalmology. Dr. Chodosh receives grant support from the National Eye Institute and is a consultant/advisor to Shire.
CXL adoption involves planning, training, professional rewards

Treatment slows or halts the progression of keratoconus, corneal ectasia

By Cheryl Guttman Krader; Reviewed by Kathryn M. Hatch, MD

OFFICE IMPLEMENTATION OF corneal collagen crosslinking (CXL) requires space and a full staff effort, but it does not compromise practice efficiency and is worthwhile due to its benefits of preserving vision in patients, said Kathryn M. Hatch, MD.

Dr. Hatch has been involved with CXL since 2011 as a clinical trial investigator and has been performing it in her practice since its commercial launch in 2016. She is director, Refractive Surgery Service, Massachusetts Eye and Ear, assistant professor of ophthalmology, Harvard Medical School, Boston.

“CXL is the only treatment available that is able to slow or halt the progression of keratoconus, and corneal ectasia following refractive surgery,” she said.

LOGISTICS

CXL is performed in a clean room and can be done as an in-office procedure, but the practice needs to have a room available where the patient can undergo the riboflavin loading procedure (riboflavin 5’-phosphate in 20% dextran ophthalmic solution, Photorex Viscous; riboflavin 5’-phosphate ophthalmic solution, Photorex T; both from Avedro), and the light treatment (KXL System, Avedro).

Dr. Hatch emphasized the need for an educated support staff to assist with patient scheduling, counseling, care, and reimbursement. She advised designating one staff as a “CXL champion” to serve as the administrative expert and handle scheduling. The staff member can talk to patients preoperatively, reviewing the steps, and obtaining informed consent.

Dr. Hatch suggested having at least two technicians who are trained to administer the riboflavin, comfortable staying with the patient during the light treatment, and able to review the details about postoperative care.

“I explain to patients that I am in charge of their care, but that they will see me during key steps of their procedure,” she said. “It is important to provide that information because some patients expect that the ophthalmologist will be with them throughout.”

On the day of the procedure, patients are given oral lorazepam when they arrive, about 40 minutes prior to surgery. After epithelial preparation and instillation of the riboflavin solution is completed, Dr. Hatch checks that the loading is adequate, measures the pachymetry, and begins the light treatment. After the irradiation is done, she returns to see the patient, answer any questions, and discharges the patient.

POSTOPERATIVE MANAGEMENT

The follow-up schedule for patients who have undergone CXL includes a return visit at 1 day and about a week after the procedure. Thereafter, patients are seen at 4 to 6 weeks post-CXL, after 3 to 4 months, and after 6 to 9 months. Younger patients, however, are seen more regularly in the first years because they are at high risk for keratoconus progression.

CXL is performed in a clean room and can be done as an in-office procedure, but the practice needs to have a room available where the patient can undergo the riboflavin loading procedure (riboflavin 5’-phosphate in 20% dextran ophthalmic solution, Photorex Viscous; riboflavin 5’-phosphate ophthalmic solution, Photorex T; both from Avedro), and the light treatment (KXL System, Avedro). The following schedule for patients who have undergone CXL includes a return visit at 1 day and about a week after the procedure. Thereafter, patients are seen at 4 to 6 weeks post-CXL, after 3 to 4 months, and after 6 to 9 months. Younger patients, however, are seen more regularly in the first years because they are at high risk for keratoconus progression.

Dr. Hatch added that collaboration is needed with diagnosing providers, who can refer patients for CXL and set postop expectations.

REIMBURSEMENT

Insurance coverage for CXL has come a long way since 2016. As of April 2019, the procedure was covered by six national and 59 regional health plans, which encompass more than 95% of commercial lives. In 29 states, CXL is covered by eight or more plans.

With the availability of the Avedro Reimbursement Custom Hub (ARCH) patient assistance program, cost should not be a barrier to any patient getting treated with CXL. Offices enrolled in ARCH can call a hotline for help with predetermination and appeals processes, and they have access to field-based reimbursement specialists.

If an insurance claim is denied, ARCH will continue to appeal the claim for up to 6 months, and if coverage is still denied, the office receives a credit from Avedro for the riboflavin.

Through its indigent program, ARCH also covers the cost of the riboflavin treatment for patients who have Medicaid.

TAKE-HOME

Corneal collagen crosslinking can be done as an in-office procedure. One clinician describes the process and the logistics.

TAKE-HOME

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

PreCISE DEPTH

Although the femtosecond laser can cut to a precise depth, the quality of the cut achieved using the laser for deep lamellar 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 initial 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. Audrey Talley-Rostov, MD, Seattle, has teamed up with Dr. Farid to work on overcoming this problem by adjusting the laser energy, spot size, and spot separation on newer generation lasers.

Dr. Farid presented evidence showing that a smooth cut was created using the technique in a human cadaver eye.

DALK

(Continued from page 17)

Intraoperative OCT guidance offers another approach for enabling accurate needle placement when creating the big-bubble.

Dr. Farid demonstrated its application with a video provided by Namrata Sharma, MD, Delhi, India.

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

Intraoperative OCT guidance offers another approach for enabling accurate needle placement when creating the big-bubble. Dr. Farid demonstrated its application with a video provided by Namrata Sharma, MD, Delhi, India. "With intraoperative OCT, the surgeon is able to visualize Descemet’s membrane through the entire process, which decreases the risk of perforation, and also help with placement of viscoelastic and positioning of the scissors for the final cut," she said.

Dr. Farid presented evidence showing that a smooth cut was created using the technique in a human cadaver eye.
ACUTE HIGH-DOSE ANTIVIRAL treatment is recommended for herpes zoster ophthalmicus (HZO), but an initiative is under way to evaluate a new treatment protocol for HZO utilizing a lower dose of medication administered over a longer period, according to Elisabeth J. Cohen, MD, professor of ophthalmology, New York University School of Medicine, New York.

The Zoster Eye Disease Study (ZEDS) is a randomly selected, multicenter, five-year, 60-center clinical trial to investigate the effectiveness of longer-term suppressive antiviral medication to reduce the complications of HZO.

The treatment protocol currently recommended for HZO is a seven- to 10-day course of antiviral medication started within 72 hours of the onset of rash: acyclovir 800 mg five times a day, valacyclovir 1,000 mg three times a day, or famciclovir 500 mg three times a day for one week orally.

There have been no randomly selected, controlled trials or case-controlled or cohort studies involving newer suppressive antiviral treatment protocols, Dr. Cohen said. One retrospective case report series of 241 herpes simplex virus (HSV) and HZO patients found that suppressive antiviral treatment decreased recurrent episodes of inflammation by 35% in HZO patients and 39% in HSV patients.1

The ZEDS trial, begun in 2016 and funded by the National Eye Institute, is led by NYUSoM, NYU Langone Health. Dr. Cohen is the study chair. Bennie H. Jeng, MD, of the University of Maryland School of Medicine, is co-chair.

The two-fold rationale for the study is that first, knowledge of the infectious pathogenesis of complications of herpes zoster and HZO is relatively new, and secondly, that suppressive antiviral treatment offers significant benefits in reducing recurrent HSV eye disease.

ZEDS investigators plan to enroll 1,050 immunocompetent HZO patients 18 years and older who will be randomly selected 1:1 to double-masked valacyclovir 1,000 mg or placebo daily for one year of treatment. They will be stratified by age at onset of HZO (<60 years versus 60 years or more), and duration of disease at the time of enrollment (six months versus six months or more). More than 150 have been enrolled.

The goal is to evaluate whether suppressive valacyclovir treatment compared with placebo will delay time during 12 months of treatment to the occurrence of new or worsening disease manifestations, including dendriform epithelial keratitis, stromal keratitis with and without ulceration, endothelial keratitis, or iritis.

Secondary objectives include evaluating whether the effect of treatment on the key endpoint persists for six months; testing the theory that suppressive valacyclovir treatment reduces the incidence, severity, and duration of postherpetic neuralgia compared to placebo at 12 and 18 months; the development of disease manifestations of HZO, including primary endpoint diagnoses, neurotrophic keratopathy, scleritis, and glaucoma.

“ZEDS is an opportunity to do a randomized clinical trial to develop evidence-based recommendations regarding the role of suppressive antiviral treatment in the management of HZO,” Dr. Cohen said, adding physicians can refer HZO patients or contact the team if they are interested in becoming a study investigator.

REFERENCE

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This article was adapted from Dr. Cohen’s presentation at the 2018 meeting of the American Academy of Ophthalmology. Dr. Cohen has no financial interests or relationships to disclose.
Phaco effective approach for angle-closure glaucoma

Clinical evidence, hands-on experience yields pearls for physicians

By Vanessa Caceres; Reviewed by Reay H. Brown, MD

It may seem unconventional to tell patients with angle-closure glaucoma that they need cataract surgery, but that sometimes can be the most effective glaucoma treatment, according to Reay H. Brown, MD, Atlanta Ophthalmology Associates, Atlanta.

Phacoemulsification is an evidence-based approach to assist many of these patients, Dr. Brown explained. 

“Although cataract surgery in some patients with angle closure may take all of our skills, the surgery is usually routine,” he said. “The main challenge is not how, but why and when.”

SECONDARY CHOICES

Trabeculectomy and tube shunts should be secondary choices, he said.

Dr. Brown shared the example of a 47-year-old woman he treated for five years who had chronic angle closure in both eyes. The hyperopic patient had closed angles for at least six years and was on maximum medications. Her average right-eye IOP over two years was 23 mm Hg, with one spike of 31 mm Hg. The optic nerve was showing progressive cupping and an early visual field defect.

Her left eye had a normal IOP on medication. “I sweated over this case,” he said.

After he sent her to someone he respected who would perform trabeculectomy, the patient ultimately had cataract surgery with Dr. Brown. The treatment went well.

“I now have 11 years of follow up and she is 20/20 with no meds,” he said. “It is like she does not even have glaucoma. She is much better off without a trab or tube.”

Although trabeculectomy or tubes may have been the more common choice before (and still may be the right choice for some patients), Dr. Brown said the pendulum has swung in a different direction.

Dr. Brown also shared the case of a 64-year-old male with a clear lens and a right eye visual acuity of 20/25. He was using five medications in his right eye, including pilocarpine that started a year previously after a dangerous IOP spike. The patient’s cup-to-disc ratio in both eyes was 0.5.

“Just like in poker, chronic pilocarpine is a tell,” Dr. Brown said. “It is nature’s way of ‘telling’ you that you need to perform cataract surgery.”

Surgeons should consider performing phacoemulsification earlier and sometimes as initial treatment in angle-closure glaucoma patients.

‘Although cataract surgery in some patients with angle closure may take all of our skills, the surgery is usually routine. The main challenge is not how, but why and when.’

— Reay H. Brown, MD

Changes

Although trabeculectomy or tubes may have been the more common choice before (and still may be the right choice for some patients), Dr. Brown said the pendulum has swung in a different direction.
Managing cataracts in glaucoma patients: A rock-hard case

Challenging procedures often require a deft approach by surgeons

By Vanessa Caceres; Reviewed by Garry P. Condon, MD

A ROCK-HARD CATARACT in a glaucoma patient requires plenty of patience, according to Garry P. Condon, MD, Allegheny Ophthalmic and Orbital Associates, PC, Pittsburgh.

“We’ve all been there,” he said. “Despite our best efforts, you can end up with a chewy, chunky piece of leather that is frustrating to deal with.”

OFFERING UP PEARLS

Dr. Condon shared a few pearls—what he called his “secret sauce”—that can help surgeons better manage these cases.

First, Dr. Condon recommends surgeons do what they can to make the pupil larger. As a result, surgeons will want to have pupil expanders and hooks close on hand.

Surgeons also will want to create a large capsulorhexis.

Dr. Condon also suggests that cataract surgeons take a divide-and-conquer approach, which can prove to be a great decision during a challenging procedure.

“Good old divide-and-conquer results in the vast majority of phaco energy being expended in the capsular bag, as far away from the corneal endothelium as possible,” he said.

GOING WIDE, DEEP

Another tried-and-true tip is to go wide and deep.

“Big, wide, and deep grooves are key to being able to fracture the posterior nuclear plate,” Dr. Condon said.

This results in smaller quadrants that will be emulsified closer to the endothelium at or above the iris plane—so ultimately, there is less energy exposure to the endothelium.

Surgeons also should give little attention to cumulative dispersed energy (CDE).

Dr. Condon does not pay attention to the CDE. When it comes to expending phaco energy, the capsular bag is a “free phaco zone,” he said.

Surgeons also should take advantage of an adherent dispersive viscoelastic material.

“This can be replenished during the case and is the best protector of the endothelium,” he said.

Another pearl offered up by Dr. Condon is to phaco as much as possible in the bag.

A lens fragmentation device (miLoop, Carl Zeiss Meditec) offers an effective way to prechop the lens, can help divide. However, if it is used at the outset, it still results in large, dense quadrants brought above the iris plane, where more energy and time is spent closer to the endothelium, Dr. Condon explained.

FINAL PEARLS

Immediately after surgery, surgeons should use a single-drop of IOP-lowering medication.

This provides the best protection in controlling the IOP postoperatively. Dr. Condon learned this from friend and colleague Luther Fry, MD.

“It has changed my postop life,” he said.

The final pearl, Dr. Condon noted, is to resume IOP medications following surgery, and consider using a nonsteroidal medication.

REVIEWED BY GARRY P. CONDON, MD

This article was adapted from Dr. Condon’s presentation at the 2019 meeting of the American Glaucoma Society. Dr. Condon is a consultant for Akita Laboratories and Glaukos and is an employee of Sight Sciences Inc.

REFERENCE


PHACO

(Continued from page 20)

Cataract surgery was performed, followed by DSEK six months later. Although the results were favorable, the patient did not return to the office for three years, when the same problem occurred in the fellow eye.

Fortunately, she only needed cataract surgery.

Now, one year after cataract surgery in her second eye, she has excellent visual acuity in both eyes and is doing well on no medications.

Dr. Brown shared journal reports that support clear lens extraction as an effective treatment for angle closure.1,2

Phaco is an effective glaucoma treatment in all stages of angle closure—early and late, with a high or normal IOP, Dr. Brown said. It is also effective when the angle has been closed for many years.

Some surgeons also might consider performing goniosynechialysis, but there is only weak evidence that this alone will lower IOP, Dr. Brown pointed out.

Perform it if needed, but do not push it if there is bleeding, and limit it to no more than 180°, Dr. Brown cautioned.

REFERENCE


REAY M. BROWN, MD

This article was adapted from Dr. Brown’s presentation at the 2019 meeting of the American Glaucoma Society. Dr. Brown is a consultant for Aerie Pharmaceuticals and Glaukos and is an employee of Sight Sciences Inc.
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WHEN IT’S CLOUDY AS CAN BE, YOUR CHOICE COULDN’T BE MORE CLEAR.

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Battling obstructed duct remains challenging for physicians
Managing issue with endoscopic DCR preferred by experienced surgeons

By Nancy Groves; Reviewed by Roger A. Dailey, MD, FACS

DACRYOCYSTITIS with nasolacrimal duct obstruction is commonly encountered in the ocularplastic surgeon’s office. It can be managed with external dacryocystorhinostomy (DCR) or endoscopic DCR, which most experienced surgeons now prefer.

Roger A. Dailey, MD, FACS, professor and Lester T. Jones Endowed Chair of Oculofacial Plastic Surgery, Casey Eye Institute, Oregon Health and Sciences University, Portland, said that external DCR has been viewed as the gold standard for a long time.

“I’ve probably done eight or 10 external DCRs in the last 20 years,” he said. “For me, the endoscopic DCR is really the gold standard. My success rate is much higher. I’ve had much better results over the last 20 years.”

Dr. Dailey said he prefers to obtain an ENT consult if the patient has significant narrowing, and a deviated septum. At the time of surgery, the septal deviation should be addressed first to create enough room to do the DCR procedure intranasally.

Dr. Dailey also recommends using a self-retaining nasal speculum to improve visualization, and a large forward-biting rongeur for a bone that requires removal more superiorly. Minimal bleeding that occurs postoperatively can be controlled with various products, including a hemostat dressing, and intranasal splint (PosiSep, Hemostasis LLC).

An advantage of endoscopic DCR is that patients recover more quickly, Dr. Dailey said, adding that they can typically go back to work within a day or two after undergoing the procedure.

When an obstruction is severe and the canaliculi cannot be reconstructed, conjunctivodacryocystorhinostomy (CDCR) is performed, and a Pyrex tube known as the Jones tube comes into play to connect the surface of the eye directly to the nasal cavity.

Endoscopic CDDR is similar to regular endoscopic DCR, Dr. Dailey said, except that the Pyrex Jones tubes are permanently left in place to prevent future blockage, and completely bypass the upper drainage system (canaliculi).

The objective is to position the tube so that the soft tissue can surround and hold it in place. To achieve this, Dr. Dailey inserts a pair of sharp iris scissors in the medical canthus just anterior to the caruncle.

The scissors should be at a 45° angle—and slightly posterior—to allow for proper positioning of the tube, which is inserted into place with a probe. It can be sutured if necessary.

“These tubes rarely migrate out anywhere else to cause any problems, although sometimes they migrate in,” he said.

Dr. Dailey added that he uses frosted Jones tubes, primarily those with a 4-mm collar, and recommends that surgeons err on the long side when selecting the tube so that there is no chance the intranasal mucosa can scar over the distal opening of the tube. A shorter one can be inserted later, if needed.

If inward migration is detected, a tube with a 4.5-mm collar is inserted, and if migration continues, it can be replaced by a tube with a 5-mm collar. In one case so far, Dr. Dailey has used a tube with a 5.5-mm collar.

GETTING RESULTS
With the strategy of replacing tubes with those having a large collar size as needed, Dr. Dailey has achieved 100% anatomic success, a 97% symptomatic patient cure rate, and a loss or migration rate of about 3%.

Patients are seen at one week and six months postoperatively, and asked to return once a year for a tube cleaning.

“I also want them to monitor the tube position every morning and call if it looks like it is coming out or migrating in, or if they have persistent tearing,” Dr. Dailey concluded.

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This article was adapted from Dr. Dailey’s presentation during Oculofacial Plastic Surgery Subspecialty Day at the 2018 meeting of the American Academy of Ophthalmology. Dr. Dailey is an equity owner in Nature’s Tears Biologic Aquea.
THERE IS no longer any reason to dread cataract surgery in eyes with uveitic glaucoma, according to Mark A. Werner, MD, Delray Eye Associates, Delray Beach, FL.

Although there was a time when performing cataract surgery in these patients was a frightening prospect, the prognosis has improved, Dr. Werner said.

“They can do quite well,” he said.

Dr. Werner points to more and better options for steroid delivery and systemic immunosuppression, as well as better knowledge of the importance of aggressively managing inflammation in these patients. In addition to those factors, modern surgical techniques are less traumatic to the eye, he added.

“If patients have poor outcomes now, it is more likely due to posterior segment complications of the underlying uveitis,” Dr. Werner said.

PROBLEMS ARISE
Potential problems in uveitic glaucoma patients often are linked to their specific disease. For example, a patient with pars planitis is more likely to have cystoid macular edema. A patient with Behçet’s disease may have even more significant posterior segment disease that could limit the visual prognosis.

“It is important to counsel patients on that,” Dr. Werner said.

In patients with juvenile idiopathic arthritis, surgeons can improve outcomes with aggressive suppression of inflammation. Glaucoma and hypotony are both concerns, Dr. Werner added. Anecdotally, Dr. Werner said he has noticed that patients with rheumatoid arthritis may have decreased encapsulation of glaucoma drainage implants.

“I would advocate for the use of a nonabsorbable suture and to secure your plate well if you are doing a tube shunt,” he said.

TAKE-HOME

Patients with uveitic glaucoma have diverse presentations. Carefully planned cataract surgery can be successful.

WATCH INFLAMMATION
Surgeons should also consider how long a patient has gone without inflammation.

Dr. Werner said a patient should experience three months with no inflammation before a good outcome is backed by evidence.

“In Behçet’s disease, six months may even be better,” he said.

It also is preferable that the systemic disease is quiet. Postoperatively, focus on the control of inflammation first, and treat IOP secondarily.

“For anterior intraocular lens opacity or membranes, you can use a YAG laser beam, turn off the retrofocus, avoid the central lens and the iris, and turn the laser energy down, once the eye is quiet,” Dr. Werner said.

Dr. Werner shared information on a patient he treated with rheumatoid arthritis that was reasonably controlled with low-potency steroids. The patient had visually significantly cataracts, posterior synechiae, and IOP that was not well controlled.

When evaluating the patient’s optic nerve, Dr. Werner saw that she had pre-perimetric glaucoma. He performed cataract surgery along with Ahmed tube insertion, a 7-0 Vicryl suture ligation, and an orphan trabeculectomy. Triamcinolone (20 mg sub-Tenon’s) also was used. She has done quite well with four years of follow up, he said.

‘If patients have poor outcomes now, it is more likely due to posterior segment complications of the underlying uveitis.’ — Mark A. Werner, MD

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This article was adapted from Dr. Werner’s presentation at the American Glaucoma Society annual meeting. Dr. Werner is a speaker for Bausch + Lomb.
Micropulse laser may increase aqueous outflow

Studies have shown changes in outflow system structures mimic effects of pilocarpine

By Lynda Charters; Reviewed by Murray A. Johnstone, MD

INVESTIGATION INTO THE effects of the micropulse laser suggests it may act in a manner that opens conventional and uveoscleral outflow channels. A laboratory study in monkey eyes documented changes in outflow system structures that mimic the effects of pilocarpine, an agent known to enhance pulsatile aqueous outflow.

Murray Johnstone, MD, a clinical professor, department of Ophthalmology, University of Washington, Seattle, WA, explained that the trabecular meshwork and the aqueous outflow system act like a pump that functions by trabecular meshwork motion.

“The motion depends on the meshwork being highly mobile,” he said. “The ciliary body is a big factor because it provides tension pulling the trabecular meshwork away from Schlemm’s canal external wall, thus allowing full excursions that permit it to function normally.”

Previous studies have shown that pulsatile aqueous outflow decreases and eventually stops as glaucoma worsens. Pilocarpine temporarily restores pulsatile flow, followed by a reduction in pressure during its brief duration of action. This raises the question about what exactly pilocarpine does that facilitates this effect.

Dr. Johnstone and his colleagues conducted a study to determine how the micropulse laser affects the sclera, ciliary body, and aqueous outflow pathways. A secondary goal was to see if the laser acts like pilocarpine.

The investigators used real-time video, histology, and high-resolution optical coherence tomography (OCT) to evaluate freshly enucleated non-human primate eyes. The study was carried out in radial sections of the limbus.

Dr. Johnstone explained that the laser energy was delivered through the sclera to the ciliary body just as it is clinically. Videomicroscopy captured the tissue effects in real time. His videomicroscopy demonstrated immediate changes at the sclera-ciliary body interface. At the same time, there was inward and posterior movement of the ciliary body, and the trabecular meshwork mimicking the known effects of pilocarpine.

The trabecular meshwork movement caused Schlemm’s canal to dilate. Dr. Johnstone pointed out that connections linking the trabecular meshwork and hinged flaps at collector channel entrances were placed under tension.

The stretched connecting bonds pulled on hinged collector channel flaps, which he reported, enlarged the collector channels themselves.

When the outlines of the pre- and post-laser appearance were superimposed, differences were readily apparent. The most reliable means of assessing effects on the outflow system was found to be the scleral spur. After analyzing a series of experiments, they found that the mean change in the position of the scleral spur was about 100 microns, a statistically significant difference.

Dr. Johnstone described changes of that magnitude as likely to be “quite significant” in terms of a modifying outflow system dynamics, but that the ability to retain the change in position requires further study.

Real-time video of the ocular structures was evaluated and compared to those from histology, and high-resolution OCT.

The three approaches showed tissue shrinkage, and damage primarily at the sclera-ciliary body interface. Scleral-ciliary body interface shrinkage created a gap in the suprachoroidal space. The ciliary muscle effects were generally limited to the region of the longitudinal portion of the muscle.

A lack of damage to the area of the pars plicata was a consistent finding of each of the modalities. Dr. Johnstone noted that the round probe tip acts as a converging lens focused at the scleral-ciliary body interface that may partially explain the localization, and limited depth of penetration of the laser beam.

“The micropulse laser causes significant changes in the ciliary muscle configuration, similar to the effects of pilocarpine indicating that the procedure may be capable of enhancing conventional outflow,” Dr. Johnstone said. “Our findings of enlargement of the suprachoroidal space may increase aqueous flow through uveoscleral pathways.”

Dr. Johnstone did note that in the study, the effects of the procedure did not reach the region of the epithelium of the pars plicata, a primary source of aqueous secretion.

“Although inflammation and cytokine release may affect inflow, in our study, effects leading to enlargement of outflow pathways provide another way to explain intraocular pressure reduction,” he concluded.
INDICATIONS AND USAGE

XELPROS™ (latanoprost ophthalmic emulsion) 0.005% is indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

IMPORTANT SAFETY INFORMATION

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XELPROS is contraindicated in patients with a known hypersensitivity to latanoprost, or any other ingredients in this product.

WARNINGS AND PRECAUTIONS

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Intraocular Inflammation:

XELPROS should be used with caution in patients with a history of intraocular inflammation (iritis/uveitis) and should generally not be used in patients with active intraocular inflammation.

Macular Edema:

XELPROS 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:

XELPROS should be used with caution in patients with a history of herpetic keratitis. XELPROS should be avoided in cases of active herpes simplex keratitis because inflammation may be exacerbated.

Bacterial Keratitis:

There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products.

Use with Contact Lenses:

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

ADVERSE REACTIONS

The most common ocular adverse reactions in clinical trials (incidence ≥5%) for XELPROS were eye pain/stinging, ocular hyperemia, conjunctival hyperemia, eye discharge, growth of eyelashes, and eyelash thickening.

DRUG INTERACTIONS

Precipitation may occur if drugs containing thimerosal are used concomitantly with XELPROS. If such drugs are used, they should be administered at least 5 minutes apart.

Please see brief summary of Full Prescribing Information on the adjacent page.

BAK=benzalkonium chloride.

Use with Contact Lenses

XELPROS™ (latanoprost ophthalmic emulsion) 0.005%

Use with Contact Lenses

Brief Summary of Prescribing Information for XELPROS™ (latanoprost ophthalmic emulsion) 0.005%, for topical ophthalmic use

XELPROS™ (latanoprost ophthalmic emulsion) 0.005%
See package insert for Full Prescribing Information.

INDICATIONS AND USAGE

XELPROS is indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

CONTRAINDICATIONS

Known hypersensitivity to latanoprost, or any other ingredients in this product.

WARNINGS AND PRECAUTIONS

Pigmentation

XELPROS may cause changes to pigmented tissues. The most frequently reported changes are increased pigmentation of the iris, periorbital tissue (eyelid), and eyelashes. Pigmentation is expected to increase as long as XELPROS is administered. After discontinuation of XELPROS, iris pigmentation is likely to be permanent. Patients who receive treatment should be informed of the possibility of increased pigmentation. The long-term effects of increased pigmentation are not known.

Eyelash Changes

XELPROS may gradually change eyelashes and vellus hair in the treated eye, including increased length, thickness, pigmentation, and number of lashes. The changes are usually reversible upon discontinuation of treatment.

Intraocular Inflammation

XELPROS should be used with caution in patients with a history of intraocular inflammation (iritis/uveitis) and should generally not be used in patients with active intraocular inflammation.

Macular Edema

XELPROS 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

XELPROS should be used with caution in patients with a history of herpetic keratitis. XELPROS should be avoided in cases of active herpes simplex keratitis because inflammation may be exacerbated.

Bacterial Keratitis

There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products.

Use with Contact Lenses

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

ADVERSE REACTIONS

Clinical Trials Experience

Because clinical trials 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 clinical practice.

Across multiple clinical trials conducted with XELPROS, the most frequently reported ocular adverse reactions were eye pain/stinging upon instillation and ocular hyperemia, reported in 55% and 41% of patients treated with XELPROS, respectively. Other adverse reactions reported (incidence ≥5%) were conjunctival hyperemia, eye discharge, growth of eyelashes, and eyelash thickening. Less than 1% of patients discontinued therapy because of intolerance to the eye pain/stinging or to the ocular hyperemia.

DRUG INTERACTIONS

Precipitation may occur if drugs containing thimerosal are used concomitantly with XELPROS. If such drugs are used, they should be administered at least 5 minutes apart.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category C

Reproduction studies have been performed in rats and rabbits. In rabbits, an incidence of 4 of 16 dams had no viable fetuses at a dose that was approximately 80 times the maximum human dose, and the highest nonembryocidal dose in rabbits was approximately 15 times the maximum human dose. There are no adequate and well-controlled studies in pregnant women. XELPROS should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether latanoprost or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when XELPROS is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

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

PATIENT COUNSELING INFORMATION

Potential for Pigmentation

Advise patients about the potential for increased brown pigmentation of the iris, which may be permanent. Patients should also be informed about the possibility of eyelid skin darkening, which may be reversible after discontinuation of XELPROS.

Potential for Eyelash Changes

Inform patients of the possibility of eyelash and vellus hair changes in the treated eye during treatment with XELPROS. These changes may result in a disparity between eyes in length, thickness, pigmentation, number of eyelashes or vellus hairs, and/or direction of eyelash growth. Eyelash changes are usually reversible upon discontinuation of treatment.

Handling the Container

Instruct patients to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures because this could cause the tip to become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated emulsions.

When to Seek Physician Advice

Advise patients that if they develop an intercurrent ocular condition (eg, trauma or infection) or have ocular surgery, or develop any ocular reactions, particularly conjunctivitis and eyelid reactions, they should immediately seek their physician’s advice concerning the continued use of the multiple-dose container.

Use with Contact Lenses

Advise patients that contact lenses should be removed prior to administration of XELPROS and may be reinserted 15 minutes following administration.

Use with Other Ophthalmic Drugs

Advise patients that if more than one topical ophthalmic drug is being used, the drugs should be administered at least 5 minutes apart.

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Focusing on xerophthalmia, vitamin A deficiency

Centuries of research show treating deficiencies can have dramatic impact

By Lynda Charters; Reviewed by Alfred Sommer, MD, MHS

Xerophthalmia, a form of dry eye that results from vitamin A deficiency, was recognized medically as far back as 1520 BC. A treatment was devised that involved cooking beef liver, and then squeezing the “juice” of the liver on the affected eyes, according to Alfred Sommer, MD, MHS.

In 1977, George Wald theorized that the juice from the liver trickled down through the lacrimal sac and was absorbed, entered the blood stream, and ultimately reached the back of the eye.

Dr. Sommer, professor of ophthalmology, Johns Hopkins University, Baltimore, recounted his experience in 1978 in an Indonesian village during which he witnessed a similar ceremony performed on a child with nightblindness who was treated with goat’s liver and then given the liver to eat, which may be how the vitamin A entered the child’s circulation in the first place.

IN THE DARK

A 19th-century treatment that was less humane advised keeping the affected person in a dark room for at least a month, which works temporarily because the retinal pigments have a chance to regrow. Dr. Sommer explained.

Nightblindness is diagnosed currently by observing a patient’s response to various levels of light, a method that grew out of an observation in a malnourished Confederate soldier during the American Civil War. The soldiers refused to take night watch because they could not see in the dark, which was confirmed by the lack of a pupillary response when a candle was waved in front of their eyes, Dr. Sommer noted.

Another manifestation of xerophthalmia is the presence of Bitot’s spots on conjunctiva, which are comprised of keratin.

“Vitamin A is necessary for development of normal, mucous-secreting conjunctival epithelium,” he explained.

The spots usually develop temporally, but severe cases involve the entire conjunctiva. In the late 19th century, cod liver oil, which is rich in vitamins A and D, was determined to be an effective cure for night blindness and Bitot’s spots.

This manifestation often begins with a small ulcerative area that is hard to differentiate from an infection until the clinician realizes that nothing can be cultured from it and it is refractory to antibiotic treatment,” Dr. Sommer said.

Slit-lamp examination revealed the presence of liquefied corneal stroma over an intact epithelium.

The World Health Organization recommended treatment of the necrosis with water-miscible vitamin A, which was unavailable and required formulation. Dr. Sommer instead administered an oily preparation of vitamin A orally (it was known that it did not work when injected, as had long been taught) until the water-miscible formulation became available.

The new formulation worked well when given intra-muscularly, but no better than the less expensive oily preparation given by mouth. Studies of locally necrotic corneal ulcers in children who died showed them to be strictly demarcated, absent of inflammatory cells, under an intact epithelium, and bordered by normal tissue.

“It did not fit any of the suggestions we had about the mechanism by which sterile corneal melting would develop,” Dr. Sommer said.

Because of the good results Dr. Sommer achieved with the cheap, available orally administered oily vitamin A, he compared it with the more expensive, less readily available water-miscible form administered intramuscularly.

“The rates at which corneal healing occurred were very similar in the two groups,” he said. “We confirmed in 1980 that both the clinical and biochemical responses were identical in the two groups.”

At six to eight days after administration, the improved/cure rates were 94% and 97%.

Early treatment of xerophthalmia is essential before the cornea is completely necrotic. The disease is associated with a mortality rate of about 25% despite hospital care.

THE PATH TO VITAMIN A

Keratomalacia is the most severe form of xerophthalmia. The association between the corneal deterioration and Bitot’s spot was not recognized until the early 1900s, about the same time as the discovery of vitamin A. This was a period when it was found that the so-called essential nutrients, i.e., fat, carbohydrates, and protein, were insufficient by themselves to sustain life, but, according to Dr. Sommer, life required “accessory factors,” as they were called by Hopkins, or “vital amines” by Funk, and fat-soluble A by McCollum and Davis.

It was not until 1917, that McCollum reported, “We
Exploring stem cells as neurologic treatment: Not a closed case

While some results have proved to be less than promising, potential remains intact

By Lynda Charters; Reviewed by Alfredo A. Sadun, MD, PhD

RESEARCH INTO THE use of stem cells as a treatment of neurologic disorders is in its infancy, and maybe, more wishful thinking than reality.

Alfredo A. Sadun, MD, PhD, uses the eye to access the brain, and he pointed out a few other researchers have taken the same approach, to push the envelope with stem cell treatments of neurologic diseases.

MIXED RESULTS

So far, the results are more frightening than promising. One company, Beike Biotech in Shenzhen, China, is focused on optic nerve hypoplasia, a congenital condition that is mostly bilateral and characterized by a small optic nerve(s) and profound visual loss in at least one eye. The company uses autologous stem cells from the bone marrow, venous blood, and umbilical cord, the last of which provides stem cells from the blood and mesenchymal cells.

Dr. Sadun, the F. Thornton Chair and Professor, Department of Ophthalmology, Doheny Eye Institute, University of California at Los Angeles, noted a key factor is that optic nerve hypoplasia is a midline structure disease.

“The septum pellucidum and corpus callosum are affected but sometimes the hypothalamus is also, and this is a major clinical issue because of the association of the hypothalamus and serious endocrine problems,” he said.

Beike Biotech performed a study of 48 patients with optic nerve hypoplasia, for which the outcome measure was determined by the responses to a patient questionnaire completed 16 days after the procedure. The company reported that 60% of patients improved immediately, and 77% at one year. They did not do any visual outcome studies.

INDEPENDENT REVIEW

However, as Dr. Sadun pointed out, an independent review of this study was performed at Children’s Hospital in Los Angeles, and they confirmed that there was no evidence that the treatment was beneficial for the optic nerve hypoplasia.

In that study, patients received six intravenous infusions over 16 days, using mesenchymal cells from the umbilical cord.

The optic nerve head size was evaluated at one, three, and nine months postoperatively. The visual acuity, and contrast sensitivity were assessed.

The findings of the study (Fink et al. AAPOS 2013;5) indicated that nothing improved, Dr. Sadun recounted.

TAKE-HOME

» The role that stem cells can play in ophthalmology may be akin to science fiction, but stem cells can be useful to develop a better model of brain diseases.

OCULAR STEM CELL RESEARCH

This research is exciting to Dr. Sadun, who said he believes that stem cells may be beneficial for treating the corneal endothelium, trabecular meshwork, and retinal pigment epithelium. However, the retinal ganglion cells may be another story.

“I am not sanguine that stem cells will work for diseases of retinal ganglion cells because there are no endogenous stem cells for retinal ganglion cells; the mesenchymal cells may be helpful because they secrete neuroprotective factors in the vitreous,” he explained.

Dr. Sadun noted that replacement of the retinal ganglion cells requires consideration of the problem of specificity.

“The cells are attached to specific parts of the brain to exactly the right cell, and interfering with this circuitry is likely to be very problematic,” he said.

CONCLUSION

Dr. Sadun provided two take-home messages. First, regarding research, if it is about treatment today with stem cells, neurons have circuitry while stem cells are clonal.

Stem cells are not going to work when dealing with precise circuitry issues.

“At the moment, the use of stem cells for optic neuropathies is nonsense,” he said.

Second is the idea of using stem cells to develop a better model of brain diseases. Dr. Sadun said he believes this is where the promise lies.

DEFICIENCY

(Continued from page 29)

feel confident that these cases of xerophthalmia … should be looked upon as a deficiency disease not hitherto recognized in its true relationship to diet.”

Dr. Sommer described a rat study in which pregnant rats were made vitamin A deficient and the pups were born severely deficient, to facilitate development of xerophthalmia and other manifestations of vitamin A deficiency. The deaths among the pups were charted. The results showed that xerophthalmia developed much later, after a number had died.

This death rate was evident when Dr. Sommer and colleagues studied xerophthalmia in Indonesia and found that children with mild vitamin A deficiency, but with normal looking eyes, died at a third of the rate of those with nightblindness, which was one-sixth the rate of the children with Bitot’s spots.

Further studies, and randomized trials, showed that by giving vitamin A by mouth twice a year to children in the developing world, would reduce childhood mortality by one-third.

“This changed the paradigm,” he noted. “Instead of vitamin A deficiency equaling xerophthalmia, as the vitamin A status declines other systemic functions are seriously impacted.”

The ocular manifestations, which had been considered the primary outcomes of vitamin A deficiency, develop relatively late. This recognition led to a program in 50 countries in which large-dose vitamin A capsules are distributed twice annually to all children younger than 5 years. This has been estimated to save about 350,000 lives annually.

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Dr. Sommer has no financial interest in any aspect of this report.
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Adjunct Professor of Ophthalmology, Singapore
**STAGES**

(Continued from page 1)

The FDA approval was based on 6-month and 1-year results from PANORAMA, a randomized, multicenter, controlled phase III trial that enrolled 402 patients and was designed to investigate the improvement of moderately severe to severe NPDR without DME, compared to sham injection.

PANORAMA is the first prospective trial to study whether an anti-VEGF can also help prevent worsening disease in patients with NPDR without DME. Though there was improvement in visual acuity scores, these were not statistically different between the two aflibercept arms, and neither of the groups improved by more than 1.5 letters. Clinical signs of high-risk NPDR, such as intraretinal microvascular abnormalities and venous bleeding, indicate Level 53 on the DRSS scoring—and about 40% of these patients will develop proliferative disease within a year, Dr. Brown said.

With the new approval, however, “we’re going to be treating patients before they get into trouble as opposed to waiting until the plane’s nose-diving to be treating patients before they get into trouble,” Dr. Wykoff said. “Both arms were highly statistically significantly better than sham. In the real world, monthly and even every-other-month dosing is impractical for many patients, and the q6m arm speaks to that.”

The safety outcomes in PANORAMA were similar to what was found in the pivotal phase III studies on aflibercept for DME. Though there was improvement in visual acuity scores, these were not statistically different between the two aflibercept arms, and neither of the groups improved by more than 1.5 letters.

Clinical signs of high-risk NPDR, such as intraretinal microvascular abnormalities and venous bleeding, indicate Level 53 on the DRSS scoring—and about 40% of these patients will develop proliferative disease within a year, Dr. Brown said.

With the new approval, however, “we’re going to be treating patients before they get into trouble as opposed to waiting until the plane’s nose-diving and you’re dumping fuel,” he said. “Even if you treat with just the loading dose, we’ll be able to knock them down to the low-level 53 and out of high-risk NPDR and a moderate or mild NPDR in almost all of them,” Dr. Brown said. “Those are the patients that make the most sense to treat.”

Dr. Wykoff said that anatomically, there is strong evidence that anti-VEGF therapy provides “dramatic benefit, both through improving DR severity levels and decreasing the development of PDR and center-involved DME.”

“Through 1 year, we have seen that the hemorrhages get better and that fewer eyes develop PDR and DME, but we have not yet seen functional data,” he noted. “That is, does earlier treatment, before eyes develop PDR or DME, result in better long-term functional outcomes or a decrease in treatment burden? Such data would be valuable.”

The q6m arm pushed the envelope to see how much dosing frequency was necessary to maintain DR severity improvements, and the hope is “less-frequent dosing will allow improved compliance,” Dr. Wykoff said.

“Fortunately, PANORAMA is a 2-year trial, and visual field is one of the endpoints. I look forward to collecting more functional endpoints evaluating the value of earlier intervention,” said Dr. Wykoff, who added the Diabetic Retinopathy Clinical Trial Retina Network is also evaluating anatomic and functional endpoints in the ongoing Protocol W.

Including this expanded approval, aflibercept is indicated for the treatment of wet age-related macular degeneration (AMD), macular edema following retinal vein occlusion (RVO), DME, and DR.

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**Diabetic Retinopathy Severity SCALE (DRSS)**

**TAKE-HOME**

- The PANORAMA study shows aflibercept can improve diabetic retinopathy scores and prevent sight-threatening complications.

Since it remains unknown how often clinicians ideally should be treating patients, the data set from PANORAMA is likely to be a starting point.

For more information, see the full article in Ophthalmology Times. For the next issue of Ophthalmology Times, subscribe now at www.ophthalmologytimes.com.
INTRODUCED NEARLY 30 years ago as a noninvasive technique for viewing the retina, optical coherence tomography (OCT) has established a definitive niche in the diagnosis and management of glaucoma.

“We are relying more and more on OCT to try to determine progression because, one it shows changes sooner than visual fields, and two, it is an objective measure, rather than a visual field, which is a semi-objective measure,” said Sanjay G. Asrani, MD, glaucoma specialist, Duke Eye Center, and professor of ophthalmology, Duke University, Durham, NC.

There are a number of steps clinicians can take to obtain the most accurate data and draw appropriate conclusions from the scans, Dr. Asrani explained. Just as with visual fields, an important step is following a reliability checklist: make sure that the signal strength is good and that there is no tracking error; measure the slope of the retinal nerve fiber layer (RNFL) thickness over time to see if there is any unusual pattern of tissue loss; search for artifacts due to pathology; and determine if the RNFL loss matches the macular loss.

Dr. Asrani cautions clinicians against overreliance on the technology.

“Do not accept the software interpretation of stability of progression,” he said. “Confirm by examining the raw image. It takes time, but we owe it to our patients.”

Macular features to watch for are a change in an arcuate shape and whether it corresponds to the loss on the RNFL. For example, imaging may show RNFL thinning over time and a drop in average thickness of the sector; however, the global average thickness may not be changing.

“That is because there are certain areas where the RNFL appears to be slightly thicker, but that is averaged out and therefore the global average doesn’t change while the sectoral average does,” Dr. Asrani explained.

“Try to confirm changes in the RNFL with macular thickness to be sure that the change is due to glaucoma,” he added. “If you are not sure, repeat the measurement in 4 months to confirm the changes.”

Another OCT pearl he shared is to use caution with coexisting pathologies and be extremely careful about the effects of vitreous on the retinal tissues. The epiretinal membrane can create a hyper-reflective band along the internal limiting membrane, making it seem that the RNFL is thicker than it actually is.

Dr. Asrani pointed out that, in many cases, the vitreous traction pulls on the RNFL, causing it to become thicker.

“That gives you false reassurance that the patient’s glaucoma is not that bad because the nerve fiber layer appears normal in thickness,” he said. “But what happens is as the vitreous relaxes its traction on the nerve fiber layer, the nerve fiber layer thins out, and that appears like glaucoma progression. But when the nerve fiber layer changes do not match up with the macular changes, there is a high chance of an artifact.”

Other misinterpretation artifacts can also arise, and clinicians should consider whether a pattern of change is nonglaucomatous. For example, if RNFL thickness decreases dramatically from one visit to another, it may be due to non-arteritic ischemic optic neuropathy having developed in the interim, which can be identified if the thickness loss is only in one sector.
Assessing quality of OCT scans impacts clinical-decision process

With imaging artifacts common, clinicians must be focused on key points

By Nancy Groves; Reviewed by David S. Greenfield, MD

AN ASSESSMENT OF the quality of optical coherence tomography (OCT) scans can impact clinical decisions related to the diagnosis of glaucoma and its progression, according to David S. Greenfield, MD.

Because imaging artifacts are common, found in as many as 20% of nerve fiber layer scans and almost 30% of scans involving the macular region, particularly in those patients that have coexisting macular pucker, clinicians should pay careful attention to all aspects of their scans, said Dr. Greenfield, Douglas R. Anderson distinguished professor of Ophthalmology and vice chair for academic affairs at the Bascom Palmer Eye Institute, University of Miami Miller School of Medicine.

A number of ocular factors contribute to the incidence of artifacts, a frequent one being that highly myopic patients are not represented in the normative database despite the fact that high myopia is known to be an important cause of errors or misinterpretation, Dr. Greenfield said. Other factors to watch for include significant ocular surface disease, opacification in the lens or vitreous, and peripapillary atrophy.

Four parts of the scan to study closely are signal strength (refer to the manufacturer's specifications); the thickness map (look for the presence or absence of shadowing artifacts); the deviation map (has the optic disk been automatically and accurately delineated, and can any subtle features related to motion artifacts be detected); and individual tomograms (search for signs of segmentation failure).

Monitoring the recommended individual signal-to-noise ratios is clinically relevant because a reduction in the signal strength will not only affect the estimation of retinal fiber layer (RNFL) thickness, but is also highly associated with an increase in the measurement's variability and failure of the measurement algorithm (as demonstrated in the figure).

DETAILS IN THE IMAGING RNFL imaging artifacts can be very subtle, arising from causes such as a horizontal translation of the blood vessels due to eye movement during imaging acquisition. Other common problems are blink artifacts and shadowing artifacts from vitreous opacities.

Eyes with severe pathologic myopia often have what Dr. Greenfield refers to as the “trifecta,” an incorrect axial alignment with shadowing artifacts, poor delineation of the optic disc border, and clear evidence of segmentation failure, all contributing to RNFL measurements that are “off the chart.”

Macular artifacts are even more common than RNFL artifacts and can be found in eyes with pathology on the surface of the macula, intraretinal edema, and even associated with subretinal pathology such as choroidal neovascularization, confounding the GCIPL measurement algorithm. Extremely large regions of macular pathology can also adversely affect the RNFL thickness algorithm and resemble glaucomatous RNFL atrophy.

“But that does not mean that eyes with comorbid conditions should not also undergo testing in other anatomic regions,” Dr. Greenfield added, referring to the case of a patient with cystoid macular edema due to a macular pucker.

The GCIPL thickness had been increasing over time due to worsening CME, masking the ability to detect progressive glaucoma. Serial examination of the RNFL images showed progressive atrophy in the average, superior, and inferior RNFL thickness that was

Continues on page 36: CME detection

AXONAL LOSS

(Continued from page 33)

Misinterpretation is also possible when the RNFL is hollow because the axonal bundles have degenerated, leaving their sheaths intact and making the RNFL thickness seem normal. But when the structures collapse, the thickness drops dramatically.

However, this is not a “real” change, because the axonal loss was pre-existing, which is a very subtle difference to detect.

Co-existing uveitis and glaucoma requires extra vigilance in interpreting OCT scans, Dr. Asrani noted.

“Because the RNFL is swollen, it appears thicker than it actually is, giving you a false sense of reassurance that the glaucoma is not bad,” he concluded.

“As the inflammation is treated, the thickness of the RNFL significantly decreases, resulting in thinning that appears as if the glaucoma is getting worse. OCT must be used with extreme caution in patients with uveitis.”

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This article was adapted from Dr. Asrani’s presentation at the 2019 meeting of the American Glaucoma Society. Dr. Asrani receives lecture honoraria from Heidelberg Engineering.
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OCT and OCTA: Seeing deeper into sickle cell retinopathy

Imaging provides ophthalmologists with additional valuable information

By Lynda Charters; Reviewed by Jennifer Irene Lim, MD

SPECTRAL-DOMAIN OPTICAL coherence tomography (SD-OTC), an interferometric technique that provides depth-resolved tissue structure information encoded in the magnitude and delay of the back-scattered light by spectral analysis of the interference fringe pattern, is offering ophthalmologists another way to battle the wide range of issues patients can present on a daily basis, including sickle cell retinopathy.

AD-OTC and microperimetry offer new options for physicians.

“The era of advances in retinal imaging allows observation of subclinical sickle cell retinopathy even when no findings are visible clinically,” said Jennifer Irene Lim, the Marion H. Schenk Chair Professor of Ophthalmology, and director of the Retina Service, University of Illinois at Chicago, Illinois Eye and Ear Infirmary, Chicago. “These findings add to the clinical staging system described by Mort Goldberg, MD.”

The value of SD-OCT is clear in the case of a 26-year-old patient with sickle cell disease. A fundus photograph showed retinal whitening, and five weeks later OCT showed retinal thinning corresponding to the areas of retinal infarction.

In 2011, Dr. Lim and her colleagues reported sickle cell thinning in the maculas of 42 patients who had excellent vision. The foveal depression sign was observed in some patients, while others had no clinical findings.

‘The era of advances in retinal imaging allows observation of subclinical sickle cell retinopathy even when no findings are visible clinically.’

— Jennifer Irene Lim, MD

In patients with sickle cell disease, the central macular thickness was 220 μm in contrast to the controls in whom the central macular thickness was 240 μm, a difference that reached significance (p < 0.0001).

The parafoveal areas in patients with sickle cell disease also were significantly thinner compared with controls (189 versus 330 μm, respectively; p < 0.02), Dr. Lim noted.

CME DETECTION

(Continued from page 34)

not detectable in the macular region because of the presence of CME.

“Poor quality scans with some measures may not preclude high quality scans with other measures in different anatomic regions,” Dr. Greenfield said.

In terms of disease detection, many normal eyes with high axial myopia have anomalous tilted discs making it difficult to clinically establish the presence of glaucomatous damage, he noted.

Close examination may show that the neural rim of the optic disc is intact, and the visual field may show a characteristic enlargement of the physiologic blind spot, he added.

The false identification of glaucoma using OCT in such eyes has been referred to as “red disease” (RNFL thickness values outside of the normal range that are displayed in red lettering or boxes). The thickness values in such eyes are flagged as statistically abnormal simply because they are poorly represented in the normative database. Some eyes may have early glaucomatous damage despite normal RNFL imaging, often referred to as “green disease.”

Dr. Greenfield managed the case of a glaucoma patient with a reproducible paracentral visual field scotoma, normal RNFL thickness, and localized atrophy in GCIPL thickness due to centralized glaucoma damage in the macular region.

Such cases remind clinicians of the importance of examining the central 10-2 visual field and GCIPL thickness in addition to performing RNFL imaging in eyes with glaucoma, he said.

A final factor that must be considered when analyzing OCT scans over time is the impact of the aging process, Dr. Greenfield said, adding that serial imaging over an extended period of time may demonstrate slow changes in the RNFL thickness due to normal aging. He urged caution when interpreting eyes with very slowly progressive, isolated changes in RNFL thickness with stable IOP and stable visual function.

Microperimetry showed that the sensitivity in eyes with focal thinning was less than in eyes without focal thinning (14.2 versus 16.5 decibels (dB), respectively, p = 0.00005). The eyes without focal thinning did not differ in sensitivity from normal controls (16.5 versus 16.7 dB).

Dr. Lim also pointed out that eyes with sickle cell retinopathy can have different patterns of thinning despite being classified in the same Goldberg stage.

“The thinning ranges from focal thinning in the fovea and temporally to more confluent temporal thinning to actual confluent temporal and foveal thinning,” she said.

‘The era of advances in retinal imaging allows observation of subclinical sickle cell retinopathy even when no findings are visible clinically.’

— Jennifer Irene Lim, MD

TAKE-HOME

Many ocular factors contribute to the incidence of artifacts. Myopic patients are not represented in the normative database even though it is an important cause of errors or misinterpretation.
REGENXBIO completes dosing for phase I/IIa clinical trial of RGX-314

REGENXBIO INC. announced it completed dosing across all five cohorts in the phase I/IIa clinical trial of RGX-314 for the treatment of wet age-related macular degeneration (AMD).

“We are excited to announce this important clinical milestone as we continue to drive the development of RGX-314 as a potential one-time gene therapy for patients with wet AMD,” said Steve Pakola, MD, chief medical officer, REGENXBIO, in a prepared statement. “Patients with wet AMD require intravitreal injections every four to 12 weeks, on average, with the current standard of care.

“We were pleased to report durable treatment response from Cohort 3 of the RGX-314 phase I/IIa trial for wet AMD at one year after a single administration of RGX-314 in a heavily pre-treated patient population in our interim trial update earlier this month,” Dr. Pakola said. “We look forward to providing top-line data, including from Cohorts 4 and 5, in the phase I/IIa trial by the end of the year.”

Eight leading retinal surgery centers across the United States are participating in the phase I/IIa trial of RGX-314, designed to evaluate the safety and tolerability of RGX-314 as a one-time therapy for patients with wet AMD who were previously treated with anti-vascular endothelial growth factor (VEGF) injections. The trial includes 42 dosed subjects across five escalating dose cohorts. Each subject received a single dose of RGX-314 administered by subretinal delivery.

“The sustained clinical durability of effect seen one year after one-time administration of RGX-314 in Cohort 3 demonstrates the potential of RGX-314 to provide foundational anti-VEGF therapy that may sustain vision gains and alleviate treatment burden for millions of patients suffering from wet AMD,” added Robert Avery, MD, trial investigator and retina surgeon from California Retina Consultants.

REGENXBIO is planning to initiate a phase Ib trial in wet AMD by the end of 2019 based on the phase I/IIa trial data and expand clinical development of RGX-314 by filing an Investigational New Drug (IND) application for diabetic retinopathy (DR) in the second half of 2019.

RGX-314 is being evaluated in a phase I/IIa, multicenter, open-label, multiple-cohort, dose-escalation study in adult subjects with wet AMD in the United States, according to the company.

The study includes subjects previously treated for wet AMD who are responsive to anti-VEGF therapy.

The study is designed to evaluate five escalating doses of RGX-314, with six subjects in the first three dose cohorts and 12 subjects in the fourth and fifth dose cohorts.

Secondary endpoints include visual acuity, retinal thickness on spectral domain optical coherence tomography (SD-OCT), ocular RGX-314 protein expression, and the need for additional anti-VEGF therapy.

Following completion of the primary study period, subjects enter a follow-up period and will continue to be assessed until week 106 for long-term safety and durability of effect, according to the company.
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Narrow your candidate search to the best.
Sound fiscal knowledge vital to harmony, practice success

Working with accountant, knowing the numbers can create order in office

By David Hutton; Reviewed by Gregory S. Brinton, MD

For a practice with multiple physicians to find success and profitability, everyone must be on the same page, particularly when it comes to the finances of the office. Gregory S. Brinton, MD, clinical professor, University of Utah School of Medicine, Salt Lake City, discussed the value of benchmarking of office finances along with his son, Eric P. Brinton, MD, who also practices with his father at Retina Associates of Utah.

The elder Dr. Brinton said participation in the AAO-AAOE benchmarking survey, while time-consuming, can prove to be rewarding.

“It takes a lot of work because they want very specific things and it may not be what you have,” he said. “You are really comparing yourself to other practices on an accurate basis.”

Dr. Gregory Brinton said benchmarking can be an invaluable tool that could allow you to track your performance and compare your practice to others.

Benchmarking also can help you identify embezzlement and determine proper staffing levels, and outline collections and other trends. It is important for physicians or practice managers understand the finances of the office. Dr. Gregory Brinton said rather than accepting the numbers your accountant offers, you should get numbers that are relevant and that tell you something about your practice.

He also noted that accountants speak a “different” language, so it is important to ensure you are getting information in a format that you can understand.

“Too often, the information an accountant may provide will not provide the sort of answers that you may be looking for,” he said. “You need to negotiate to get the numbers you need to know.”

Once you are getting the right numbers, a quick review each month will take a minute or less.

For example, knowing operations expenses percentage (operations over collections), can tell you what your overhead percentage is.

**RATIOS TO KNOW**

Dr. Eric Brinton noted that there are several ratios that are important to know, including the operating expense percentage as it relates to collections.

“This ratio tells you how efficient your practice is,” he said. “The lower the number is, the more efficient you are.”

However, Dr. Eric Brinton noted that if the percentage, generally in the 35% to 70% range, is too low, you may be hurting patient volume because you either aren't paying for enough help or don't have enough office space, or both.

Another key metric is operating expenses per relative value unit (RVU), a measure of value used in U.S. Medicare reimbursement formula for physician services.

“If the number is high, your overhead is high relative to the number of services you are providing,” Dr. Eric Brinton said, noting the figure usually is $11 to $20.

Knowing the non-physician payroll percentage can help you gauge your staff's efficiency. If you have an optometrist on staff, you may want to determine this percentage twice, with and without the optometrist wages included in the non-physician payroll.

You also can put your finger on the pulse of collections with the gross collection percentage, relative to gross charges. This will offer an efficiency measure of your collections. The average in today's practices is 65.7%, with a range of 43% to 96%, depending on what your recorded charges are compared to Medicare or other insurance allowables.

“If you write off a lot of money because your charges are higher than Medicare allows or more than insurance pays, this number may be artificially low,” Dr. Eric Brinton said.

Another metric to consider is collections per RVU per contract with low-paying insurance companies or if your AR people don't collect well.

“This is a valuable number that allows you to compare different procedures,” Dr. Gregory Brinton said. Another figure that will help you gauge staff efficiency is collections per full-time equivalent (FTE) employee, which Dr. Eric Brinton said is usually $100,000 to $150,000 for ophthalmologists.

“For a retina specialist, that number may be a little higher,” he said. “You aren't doing refractions, which requires more skill from your employees.”

The number of FTEs per physician also can vary, depending on how much work physicians like to do themselves. The average, according to the presentation, is 6, with a range of three to 13.

“In some practices, this number may be 1:1, and they look very efficient,” Dr. Gregory Brinton said. “But they may be losing work because they can’t take on more patients.”

You also can get numbers, such as accounts receivable ratios, that tell you how efficient your collections staff is. It also can help tell if staff is just writing collections off because it is easier.

Ultimately, all of the figures should be reviewed monthly, or at least quarterly. You can track the figures over time to measure the performance of various aspects of your business. You also can set goals at the start of the year and track your progress toward meeting those goals.

**COMPENSATION CONFLICTS**

One source of conflict in many offices is the method of splitting physician compensation. Physicians are faced with gross income and overhead.

Ultimately, physicians can have an office-sharing relationship where they compete against each other, or a total partnership, which encourages referrals and cooperation. Gross income can be divided equally or divided by production.

“This is the one issue that has caused partnerships to split up,” Dr. Gregory Brinton explained.

Calculating income can be done from charges or collections, and overhead can be fixed and split equally. Staff and equipment can be variable and divided according to production.

The line between fixed and variable can be a hard one to draw. Ultimately, all of the figures should be reviewed monthly, or at least quarterly. You can track the figures over time to measure the performance of various aspects of your business. You also can set goals at the start of the year and track your progress toward meeting those goals.

**TAKE-HOME**

- It is important for physicians or practice managers to understand the financials of the office to ensure efficiency and productivity while thwarting mismanagement.

CONTINUES ON PAGE 41: Fair compensation
Physicians often are faced with walking a tight rope of providing services without placing undue financial burdens on their patients.

Yvonne Ou, MD, is an associate professor, co-director of the Glaucoma Service, and Vice Chair for Postgraduate Education in the Department of Ophthalmology, UCSF. She specializes in treating glaucoma with medical, laser and surgical therapies. During the recent American Glaucoma Society annual meeting, she presented “Practical Tips and Tricks to Ease Your Patients’ Financial Burdens.”

She shared ways a physician can help his or her patients with the cost of medications.

“We must talk to our patients and consider switching medication class,” she stated.

Virtually every practice must deal with prescription issues. Prescription drug costs are a pressing concern for both physicians and patients. Rising drug prices affect patients’ out-of-pocket costs as well as the budgets of private and public payers, though the challenges can vary by payer.

Physicians are the front line of treatment and you can encourage patients to shop around and talk to their pharmacists.

“I think the take home message is that we need to be the ones initiating these discussions,” she said, noting that about half of patients facing financial issues with prescription costs will not broach the subject with their physician.

If a patient is not getting the needed medications, treatment of an ongoing condition can be impeded. Glaucoma is a lifelong disease, and physicians must work with their patients to create a treatment plan that is sustainable over the long term.

COPING WITH COSTS

This can lead to a search for more affordable options, including the large retailers. However, lists of $4 per month eye drops at places like Walmart can change from year to year.

She urged physicians to encourage patients to shop around. They can use websites to compare prices. They also can print coupons.

“There is a little caveat to that and that is the coupons overall may not be helping costs within our health care system, but at least at the time that the patient purchases the medication, coupons will help them,” she said.

Some independent pharmacies can sometimes offer good deals to patients who pay cash.

Patients can often buy their medications online, for example patients might want to go to Canada or abroad. It is important that they determine which online pharmacies are reputable.

Encourage patients to talk to the pharmacists, since pharmacists can now discuss how to reduce their medication costs, she said.

A recent study examined the frequency and magnitude of copayments and prescription drug costs. It analyzed prices of 1.6 million people paying for 9.5 million prescriptions.

“They found that patients would have been better off paying cash 23% of the time,” she said. “And the average overpayment is $8.”

Special programs are another area where you can help your patients. Drug manufacturers also provide patient assistance programs, although patients often need help with determining eligibility and paperwork.

“In my limited experience, they do not provide patient advocates directly,” she said. “But the folks on the phone are actually quite helpful in helping navigate the system.”

Finally, laser trabeculoplasty is a very effective option as a first-line treatment, as a recent UK study demonstrated.

She also noted that bilateral laser trabeculoplasty was less expensive than a three-year supply of medications in 71% of developing countries.

Fair Compensation

(Continued from page 40)

line to draw. Staff can work more with one partner than another.

“As you look at overhead costs, it is more important to decide how it affects your relationship, that to really decide if they are fixed or variable.” Dr. Gregory Brinton said. “If you want to light a fire under doctors (encourage them to see more patients), consider all of your overhead as fixed, and divide the dollars equally. On the other hand, if you want to encourage cooperation, rather than competition, consider all of your overhead as variable, and charge it to each doctor as a percentage of income. There are, of course, many options in between.”

Money is at the root of many battles, both private and professional, and financial issues can drive a wedge in a practice if caution isn’t used.

“When it comes right down to it, it isn’t how people are paid. It is their perception of how they are paid.” Dr. Gregory Brinton concluded. “People need to feel good at the end of the day when they go home. That is more important than the numbers.”

TAKING HOME

Physicians must be willing to drive financial discussions with their patients.

Too many patients who are struggling financially to pay for medications won’t initiate the conversation.

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This article was adapted from Dr. Ou’s presentation at the 2019 meeting of the American Glaucoma Society. Dr. Ou has no financial disclosures related to this article to release.

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This article was adapted from Dr. Gregory S. Brinton and Dr. Eric P. Brinton’s presentation at the 2018 meeting of the American Academy of Ophthalmic Executives. They have no financial interest in the subject matter.
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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.

DOSEAGE 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.

CONTRAINDICATIONS
None.

WARNINGS AND PRECAUTIONS

Pigmentation
Rocklatan® contains latanoprost which has been reported to cause changes to pigmented tissues. The most frequently reported changes have been increased pigmentation of the iris, pretibial skin, and eyelid margin in patients with unpigmented eyelids. Further, patients with cornual and conjunctival nevi have been reported to have ocular nevi, which were not present at baseline. No data on the presence of netarsudil or latanoprost in human milk, the effects on the breastfed infant, or on 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 tests for unscheduled DNA synthesis in rats. Latanoprost was not mutagenic in bacteria, in mouse lymphoma, or in mouse micronucleus tests. Chromosomal aberrations were observed in vitro with human lymphocytes. In addition, in vitro and in vivo studies on unscheduled DNA synthesis in rats were not performed. 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; 8,934,826; 9,096,569; 9,415,043; 9,931,336; 9,993,470

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 ophthalmic 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 0.005% 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 ophthalmic 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\text{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\text{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\text{max}). Malformations were observed at ≥5 mg/kg/day (1330-fold the plasma exposure at the RHOD, based on C\text{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\text{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.

Pregnancy
Safety and effectiveness in pediatric patients have not been established.

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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 mammalian 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. Chromosomal aberrations were observed in vitro with human lymphocytes. Additional in vitro and in vivo studies on unscheduled DNA synthesis in rats were not performed. 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; 8,934,826; 9,096,569; 9,415,043; 9,931,336; 9,993,470
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

IOP: intraocular pressure; ROCK: rho kinase

IMPORTANT SAFETY INFORMATION

Contraindications
None.

Warnings and Precautions
- Pigmentation changes
- Eyelash changes
- Intraocular 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.

 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.

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References: